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Neural correlates of inhibitory spillover in adolescence: associations with internalizing symptoms

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Abstract

This study used an emotional go/no-go task to explore inhibitory spillover (how intentional cognitive inhibition 'spills over' to inhibit neural responses to affective stimuli) within 23 adolescents. Adolescents were shown emotional faces and asked to press a button depending on the gender of the face. When asked to inhibit with irrelevant affective stimuli present, adolescents recruited prefrontal cognitive control regions (rIFG, ACC) and ventral affective areas (insula, amygdala). In support of the inhibitory spillover hypothesis, increased activation of the rIFG and down-regulation of the amygdala occurred during negative, but not positive, inhibition trials compared with go trials. Functional connectivity analysis revealed coupling of the rIFG *pars opercularis* and ventral affective areas during negative no-go trials. Age was negatively associated with activation in frontal and temporal regions associated with inhibition and sensory integration. Internalizing symptoms were positively associated with increased bilateral IFG, ACC, putamen and pallidum. This is the first study to test the inhibitory spillover emotional go/no-go task within adolescents, who may have difficulties with inhibitory control, and to tie it to internalizing symptoms.

Key words: rIFG; adolescence; inhibition; internalizing; go/no-go

Introduction

Adolescence represents a time of dynamic change and development in social, emotional and cognitive domains. Adolescents are known to show attentional biases to socioemotional cues and may make risky or hasty decisions (Blakemore and Choudhury, 2006; Eaton *et al.*, 2006; Merikangas *et al.*, 2010). Adolescence is also a time of increased risk for psychopathology, with evidence that mental health problems are more prevalent during this time than in childhood or adulthood (Davey *et al.*, 2008). Although many studies have reported on adolescent neural and socioemotional development, relatively few studies have examined brain function, connectivity and behavior simultaneously in adolescents (Pfeifer and Allen, 2012). Measures of 'inhibitory spillover'—how cognitive inhibition is linked with affective inhibition—have not been thoroughly tested within adolescents but may be ideally suited for assessing the complex interplay of neural development, behavior, emotion and cognition.

Recently, researchers have moved toward studying the neural correlates of emotion, cognition and behavior using integrated models rather than treating these as separate constructs. One integrated approach is to investigate executive functioning as it relates to inhibitory control, emotion regulation and behavior (Eisenberg *et al.*, 2005; Norman *et al.*, 2011; Schmeichel and

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Tang, 2015 Berkman et al., 2012). The emotional go/no-go task was designed to assess inhibitory spillover from cognitive neural networks to the ventral affective system, given evidence that intentional inhibition in one domain (i.e. cognitive/motor) may have spillover effects to neural regions associated with other domains of inhibition (i.e. affective) via a common substrate of the right inferior frontal gyrus (rIFG) *pars opercularis* (Berkman *et al.*, 2009; Tabibnia *et al.*, 2011). The emotional go/no-go task uses emotional stimuli, but demands only cognitive inhibition. Participants view photographs of people making emotional facial expressions and are asked to press or withhold a button press in response to the sex of the face. The emotion of the face is irrelevant to the task. When adults completed this task, researchers found spillover of motor/cognitive inhibition to limbic structures: there was decreased amygdala signal change during no-go, negative (hereafter referred to as: no-go$^-$) trials compared with go, negative (go$^-$) and all positive trials (Berkman *et al.*, 2009). In addition, functional connectivity analyses found the activity of the rIFG and amygdala to be inversely correlated, providing evidence for inhibitory spillover, such that more recruitment of the rIFG was coupled with decreased activation in the amygdala (Berkman *et al.*, 2009).

The current study is the first to administer the inhibitory spillover emotional go/no-go task to a sample of adolescents. Studying the interaction of emotional cues and cognitive processes within adolescents can help shed light on the neural underpinnings of emotion regulation and decision-making in adolescence. This study also assessed whether internalizing symptoms were associated with neural correlates of inhibitory spillover. In sum, few studies of adolescents have actually tested both inhibition and emotional interference within one task, while also assessing psychological symptoms, in order to test inhibitory control in a way that maps on to the complexity of real-world experience.

Adolescent brain development and inhibition

Adolescence is characterized by significant developmental changes in the brain that have direct implications for inhibition and emotion regulation (Ernst *et al.*, 2006; Casey *et al.*, 2008; Steinberg, 2010; Mills *et al.*, 2014; Casey, 2015; Schmeichel and Tang, 2015). The dual-systems model of adolescence hypothesizes that adolescents engage in risky behavior because ventral affective neural networks, underlying emotional salience and arousal, develop faster than prefrontal networks involved in inhibition (Steinberg, 2005; Blakemore and Choudhury, 2006; Strang *et al.*, 2013). Another model, the triadic model of motivated behaviors (Ernst *et al.*, 2006), purports that immature prefrontal areas result in ineffective orchestration of approach/avoidance systems and that development of regulatory brain regions lags behind development of affective brain systems, resulting in an increased vulnerability to affective stimuli and internalizing problems (Davey *et al.*, 2008). Other researchers (e.g., Pfeifer and Allen, 2012) have argued that the dual-systems models of adolescent brain development may oversimplify the nuanced and bidirectional findings that are often seen in the literature on coordination of ventral affective and prefrontal function during cognitive control tasks and their relation to adolescent behavior. Adolescents may indeed be capable of successful inhibition, but choose not to exercise this skill in certain contexts, depending on other developmental goals (e.g. forming new peer affiliations).

A common foundation across all of these theories of adolescent development is that prefrontal, cognitive control brain networks and subcortical, affective networks show different developmental trajectories, with complex implications for adolescent inhibition. Inhibition, or the ability to stop a prepotent action, thought, or feeling, requires the coordination of both neural networks and is often studied using go/no-go paradigms (Cohen and Lieberman, 2010; Ogilvie *et al.*, 2011; Tabibnia *et al.*, 2011). Prior research with adults points to the role of the rIFG *pars opercularis* in supporting inhibitory control across affective, cognitive and motor domains (Stevens *et al.*, 2007; Berkman *et al.*, 2009; Cohen *et al.*, 2013; Tabibnia *et al.*, 2015). Studies looking at inhibition separately by domain consistently implicate the rIFG (Miyake *et al.*, 2000; Carlson and Wang, 2007). Furthermore, behavioral studies of inhibition show correlations between motor and cognitive inhibition and affective versus cognitive/motor inhibition (Miyake *et al.*, 2000; Carlson and Wang, 2007).

Inhibition is also intricately intertwined with emotion regulation. Considerable evidence suggests that cognitive ability shapes an individual's emotional experiences, and vice versa, and that the shared biological substrate of the rIFG plays a pivotal role in this process (Casey *et al.*, 1997; Hare *et al.*, 2008; Berkman *et al.*, 2009; Berkman et al., 2012; Cohen and Lieberman, 2010; Tabibnia *et al.*, 2011; Schmeichel and Tang, 2015). Behavioral studies in adults have found better performance on inhibitory control tasks to be linked with individual differences in the ability to halt facial affect expression (von Hippel and Gonsalkorale, 2005), decreased emotional reactivity to recalling of negative events (Tang and Schmeichel, 2014) and successful emotion regulation on a daily basis (Stawski *et al.*, 2010). Review articles comparing animal and human studies of inhibition show evidence for specific recruitment of the rIFG in both humans and animals (Aron *et al.*, 2004; Cohen *et al.*, 2013) and gray matter structural integrity of the rIFG *pars opercularis* was found to be linked with performance on motor and affective inhibition tasks (Tabibnia *et al.*, 2011).

Neural correlates of internalizing in adolescence

Given that adolescents have complex and bidirectional communication between still-maturing prefrontal cognitive and ventral affective networks, adolescence is a unique window in which to study inhibitory spillover, which requires the coordination of both systems. Adolescence is also a time of heightened vulnerability to internalizing disorders, including onset of depressive and anxious symptoms and risky behaviors, which may be linked with individual differences in the coordination of subcortical and prefrontal regions.

Internalizing symptoms are characterized by compromised emotion regulation and executive functioning skills, including inhibitory control. Neuroimaging studies investigating inhibition and affective processing in youths with internalizing symptoms find associations with prefrontal, cognitive control regions such as the anterior cingulate cortex (ACC) and the ventrolateral prefrontal cortex which encapsulates the rIFG (Anderson and Teicher, 2008; Davey *et al.*, 2008; Kerestes *et al.*, 2014). Reviews of inhibition fMRI studies on adolescents with depression report that youth exhibit increased activation in subcortical regions, such as the amygdala and striatum, and in inhibitory control regions (IFG, ACC) in comparison to healthy controls (Anderson and Teicher, 2008; Davey *et al.*, 2008; Kerestes *et al.*, 2014). The amygdala and striatum overlap with brain regions involved in emotion regulation, which may involve the down-regulation of these subcortical, emotion-processing regions via top-down cognitive-control. However, it

is still unclear how adolescent internalizing symptoms are tied with neurodevelopment and the developing coordination of prefrontal regions with subcortical affective processing regions necessary for inhibition.

This study

This study is the first to study the neural correlates of inhibitory spillover in adolescence by administering the inhibitory spillover emotional go/no-go fMRI task. This study also aims to tie brain function and connectivity with behavior by studying self-reported internalizing symptoms and fMRI performance.

We tested five hypotheses:

1. We expected no-go trials compared with baseline to recruit ACC and rIFG, given previous literature suggesting that inhibition requires effortful cognitive control. We expected a main effect of condition such that no-go trials would recruit more rIFG and ACC than go trials. We expected that both negative and positive trials, compared with baseline, would recruit amygdala, ACC, striatum and anterior insula activity, but that negative trials would recruit more BOLD signal in these regions than positive trials, given that these regions respond more strongly to potentially threatening stimuli (Ohman, 2005).
2. We expected to find a negative association between age and signal recruitment to the rIFG and cognitive control regions during inhibition (i.e. no-go) trials, given the aforementioned developmental literature. We planned to test age effects for both the main effect of inhibition (no-go > baseline) and for the inhibitory spillover contrast (no-go$^-$ > go$^-$ trials) specifically.
3. We expected to find inhibitory spillover in the form of an interaction between task condition and valence. We also expected to see greater prefrontal activation and decreased subcortical activation in our main inhibitory spillover contrast of interest (no-go$^-$ > go$^-$ trials).
4. We hypothesized there would be increased functional connectivity between the rIFG and amygdala during the no-go$^-$ trials compared with go$^-$ trials, given the inhibitory spillover hypothesis finding incidental down-regulation of ventral affective regions during inhibition (Berkman *et al.*, 2009).
5. We hypothesized that internalizing symptoms would be associated with greater BOLD signal recruitment in ventral affective regions (amygdala, insula) and the rIFG during no-go$^-$ trials compared with go$^-$ trials.

Methods

Participants

Participants were recruited for a longitudinal study of youth development (Margolin *et al.*, 2010) from a large U.S. West Coast City via flyers, word-of-mouth and radio/newspaper advertisements. Inclusion criteria included that the youth were in early adolescence, proficient in English and that the youth's family had been living together for the past 3 years. Exclusion criteria for the MRI substudy included contraindications to MRI scanning (e.g. metal implants, braces, tic disorder) and daily use of psychoactive medications.

MRI scanning was completed after youths' second visit of the larger longitudinal study. For the MRI study, 43 families who had participated in the second visit were recruited when the youth were between 15 and 19 years old. Of the 43 families contacted, 24 youth were eligible and willing to participate in scanning. Of the 24 youth eligible for scanning, 23 were right-handed and 21 also participated in the third visit of the larger longitudinal study and completed the Youth Self-Report (YSR) measure of internalizing symptoms (Achenbach and Rescorla, 2001). The 23 right-handed youths' MRI data were used for whole-brain and gPPI analyses. Separate whole-brain analyses, using internalizing scores as regressors, were conducted with the 21 youth with YSR data. Twelve youth (52.2%) identified as Caucasian, two youth (8.7%) as Asian-American, three youth (13%) as African-American and six youth (26.1%) as multiracial. Eight (34.8%) youths also identified as Hispanic or Latino. At the time of the MRI scan, youth were an average of 16.97 years old (range 15.47–18.67, s.d. = 0.79). All participants provided informed assent and parents provided informed consent as approved by the university's Institutional Review Board.

Procedures

During the MRI visit, participants completed functional, structural and resting state neuroimaging. Participants completed self-report measures, including the YSR, at their third visit of the larger longitudinal study when youth were an average of 16.70 years old (range 14.93–18.63, s.d. = .94 years). Between the third visit behavioral data collection and the MRI visit there was an average of 0.08 years (about 1 month; range = −0.74 to +1.79 years, s.d. = 0.58). Most data collection for the third visit happened within 6 months of the MRI, except for one participant who completed this visit 21 months after the scan; we controlled for lag time between the visit and scan when examining internalizing symptoms.

Behavioral measures and analysis

Internalizing symptoms. The 112-item YSR (Achenbach and Rescorla, 2001), which assesses behavioral and emotional problems in adolescents over the previous 6 months, has two scales: the internalizing and externalizing behavior scales. The internalizing behavior scale sums the anxious/depressed, withdrawn/depressed and somatic complaints subscales. Raw scores were transformed into *T*-scores normalized for age and sex. The average *T*-score on the internalizing scale was 50.05 (s.d. = 10.26; range 26–68) and only one participant reported clinical-range internalizing symptoms ($T = 68$). We used the internalizing scores as continuous measures in analyses because we focused on a community sample of adolescents without severe psychopathology.

Inhibitory spillover emotional go/no-go fMRI task. The fMRI task was adapted from Berkman *et al.* (2009). The mixed block- and event-related fMRI task consisted of two functional runs; each run had three blocks, each with 50 emotional facial expressions (positive: happy; negative: fear, anger; Tottenham *et al.*, 2009). We optimized stimulus presentation order using the genetic algorithm program, OptimizeDesign (Wager and Nichols, 2003). For half of the blocks, the participants were asked to press a button each time a male face was shown (go condition) and to inhibit a button press each time a female face was shown (no-go condition; Figure 1). The go sex was counterbalanced within participants. The positive faces were primarily presented to prevent habituation to the negative faces. The go sex was presented on 80% of the trials and the no-go sex was presented on 20% of the trials, consistent with prior go/no-go paradigms designed to activate inhibitory mechanisms (Stevens *et al.*, 2007; Berkman *et al.*, 2009). Task performance was measured via

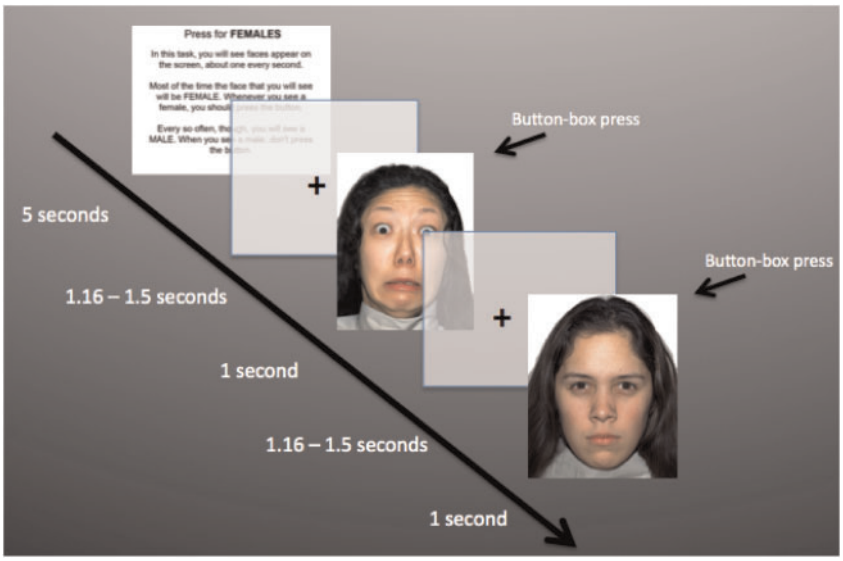

Fig. 1. Emotional go, no-go fMRI task design. This figure depicts an example of the fMRI emotional go/no-go task administered to adolescents who were instructed to inhibit based off of the sex of the face; the emotion of the stimulus was irrelevant to the instructed task. In this image, the 'go' condition was female, and the 'no-go' condition was male. Facial stimuli were taken from the NimStim (Tottenham *et al.*, 2009) dataset.

average reaction time to button press and percent accuracy. Average reaction times and percent accuracy scores were examined by condition and valence. Paired *t*-tests were used to examine mean differences between performance scores.

fMRI data acquisition. Whole-brain images were acquired using a Siemens 3 Tesla MAGNETOM TIM Trio Scanner with a 12-channel phased-array head coil. High-resolution, T1-weighted anatomical images were acquired (3D Magnetization Prepared Rapid Acquisition Gradient Echo; T1 = 900 ms; repetition time, 1950 ms; echo time, 2.26 ms; flip angle, 7°), with an isotropic voxel resolution of 1 mm. Functional data were collected using a T2*-weighted echo-planar imaging interleaved sequence (forty 2.5 mm transversal slices; repetition time, 2000 ms; echo time, 25 ms; field of view, 192 mm^2; $3.0 \times 3.0 \times 2.5\ mm^3$ voxels).

fMRI data analysis. Functional data were preprocessed and analyzed according to the general linear model (GLM) in FSL (FMRIB, Oxford, UK). We ran first level preprocessing on each run, which were then combined using a fixed effects analysis at the subject level. Both runs were despiked, motion-corrected and spatially smoothed using an 8.0-mm full-width half-maximum Gaussian filter. Data were aligned to the anatomical grid, transformed to a standardized atlas and masked to account for motion artifacts and to exclude voxels without valid data at every TR for every run. The GLM had four explanatory variables (go^+, go^-, no-go^+ and no-go^-) to account for each condition while minimizing multicollinearity. Contrasts of interest were created as linear combinations of the explanatory variables to look at overall task effects (e.g. no-go > baseline; no-go^- > go^-). The train of stimulus events was convolved with a gamma-variate hemodynamic response function resulting in a normalized time series with a percent signal change from the mean represented by amplitude and regression coefficients. This produced beta-coefficients and associated *t*- and *z*-statistics for each voxel and explanatory variable. To account for multiple comparisons, cluster thresholding using Gaussian Random Field theory was applied at a z threshold of 2.3 ($P < 0.05$), as this type of correction is more sensitive than voxel-based methods. All coordinates reported are from the Montreal Neurological Institute (MNI) standard brains in radiological view.

Whole-brain analyses and a priori hypothesized region-of-interest analyses (ROIs) were conducted to examine the overall effect of the task (H1), age effects with inhibition trials (H2) and task effects with internalizing scores as regressors (H5). Whole-brain paired *t*-tests were used to examine mean differences between contrasts (H1, H3). This study focused on negative, rather than positive, faces because negative faces have been associated with greater activation in key neural regions (Berkman *et al.*, 2009) and because down regulation of limbic activity during inhibition tasks primarily happens in the presence of negative, not positive, stimuli (Lieberman *et al.*, 2007; Tabibnia *et al.*, 2011). To test H3, we performed an anatomically-defined (Harvard-Oxford Cortical Atlas) ROI paired *t*-test ([no-go^- > go^{--}]–[no-go^+ > go^+]) analysis of the left and right amygdalae and also used FSL's Featquery tool to extract parameter estimates from each amygdalae for each of the four explanatory variables modeled. These parameter estimates were converted to percent signal change and entered into SPSS to compute a 2 (condition: no-go, go)×2 (valence: negative, positive) repeated measures analysis of variance (RM ANOVA) to directly test the interaction effect.

We conducted a context-dependent psychophysiological interaction analysis (gPPI; McLaren *et al.*, 2012) to test H4. A gPPI analysis is used to look at task-specific changes in the relationship between activity in an identified seed region and other areas of the brain (O'Reilly *et al.*, 2012). Given prior literature on the role of the rIFG *pars opercularis* (Tabibnia *et al.*, 2011) in inhibitory spillover (Berkman *et al.*, 2009), we created an anatomically defined (Harvard-Oxford Cortical Atlas) ROI mask of the rIFG *pars opercularis* and used this as the seed region. The no-go^- trials compared with go^- trials were used as the psychological regressors (task-specific). Then the PPI regressors were created using linear combinations of the psychological regressors and seed region regressor (McLaren *et al.*, 2012; O'Reilly *et al.*, 2012).

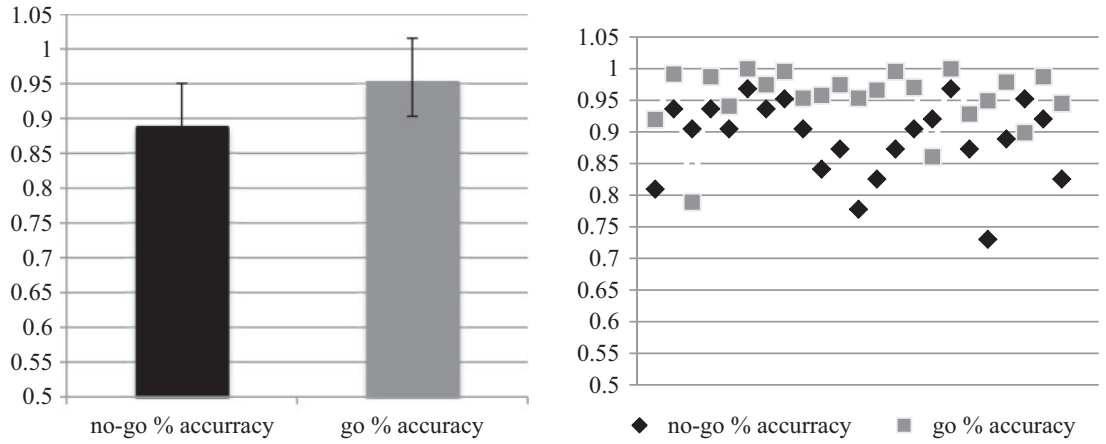

Fig. 2. Percent accuracy in button press during fMRI task. There was a significant difference between percent accuracy in button press during go trials ($M = 95.3\%$, s.d. $=0.05$) and inhibition of button press during no-go trials ($M = 88.82\%$, s.d. $=0.06$), $t(23) = 4.22$, $P < 0.001$.

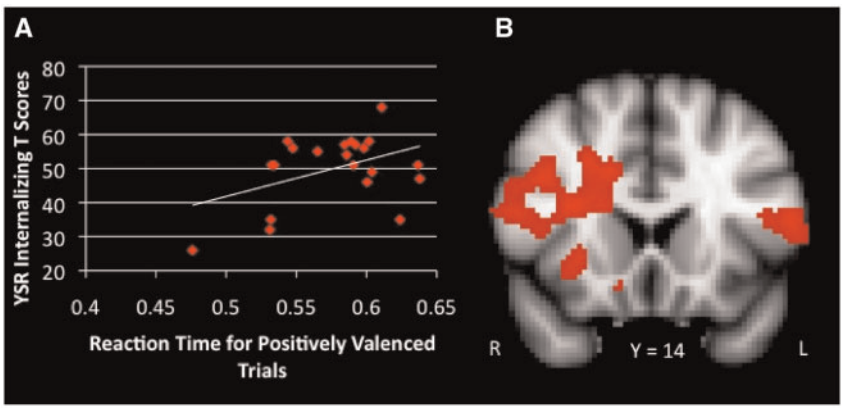

Fig. 3. Positive association between internalizing scores and fMRI task performance. (A) There was an association between average reaction time to positive faces and YSR internalizing symptom scores, $r = 0.429$, $P = 0.05$, such that the higher the reported internalizing symptoms, the faster the average reaction time to button press in the presence of positive faces during task performance. (B) The bilateral IFG ($x = 56$, $y = 18$, $z = 14$; $x = -56$, $y = 18$, $z = 14$) and insula ($x = 30$, $y = 18$, $z = -4$) were positively correlated with internalizing symptoms in adolescents, such that the higher the youth's symptoms, the more activation in inhibitory control regions.

Results

Behavioral results

Percent accuracy of button press on no-go ($M = 88.8\%$, s.d. $= 0.06$) differed from go ($M = 95.3\%$, s.d. $= 0.05$) trials, $t(22) = -4.17$, $P < 0.001$, such that participants responded less accurately to no-go trials (Figure 2). There were no differences on percent accuracy of button press by valence or in reaction times between positive ($M = 0.58$, s.d. $= 0.04$) and negative trials ($M = 0.59$, s.d. $= 0.04$), $t(22) = -1.75$, $P = 0.09$. Higher internalizing symptoms were associated with faster average reaction times to button press in the presence of positive faces, $r = 0.43$, $P = 0.05$ (Figure 3A). No other associations emerged between internalizing scores and task performance. There were no associations between age and task performance.

fMRI data analysis

H1: Neural activation during main effects of task (Tables 1 and 2). As hypothesized, no-go trials, compared with go trials, activated superior frontal gyrus, supplementary motor area (SMA) and the ACC. An ROI of bilateral IFG yielded significant activation in the right, but not left, IFG. Contrary to H1, ROI's of the left and right amygdala yielded no significant results. When looking at neural activation in response to negative faces compared with baseline, inhibition-related regions were activated, specifically the rIFG *pars triangularis* and *pars opercularis*, right SMA, bilateral frontal pole and right superior frontal gyrus. In addition, limbic structures were activated including the right insula, hippocampus and amygdala. There was a negative correlation with the intracalcarine cortex, lateral occipital cortex and precuneus. When viewing positive faces compared with baseline, participants showed activation in the right SMA, superior frontal gyrus and bilateral frontal poles. The posterior cingulate cortex and lateral occipital cortex were negatively associated with this contrast. When directly contrasting negative to positive trials there were no significant clusters of activation. Contrary to H1, there was no main effect of valence: there were no significant differences in activation of the insula, amygdala, or ACC when directly comparing negative to positive trials.

H2: Age effects. As hypothesized, in the main contrast of no-go$^-$ > go$^-$ trials, there was a negative association between age and the central opercular cortex reaching into the insula and rIFG *pars opercularis*, parahippocampal gyrus, posterior superior temporal sulcus reaching to the temporal pole and middle

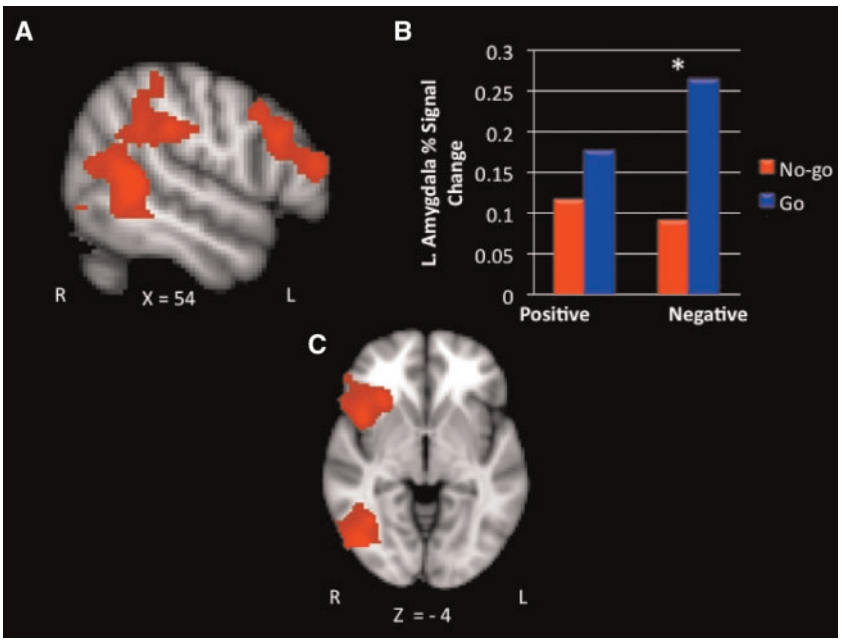

Fig. 4. Support for the inhibitory spillover hypothesis. (A) Blood oxygenation level dependent signal in the rIFG ($x = 54$, $y = 20$, $z = 26$) and middle temporal gyrus ($x = 54$, $y = -46$, $z = 4$) during the main inhibitory spillover contrast-of-interest: no-go$^-$ > go$^-$. (B) Percent signal change values for an anatomically defined amygdala ROI during no-go$^+$, go$^+$, no-go$^-$ and go$^-$ trials. There was a significant reduction in amygdala signal change from go$^-$ ($M = 0.276$) trials to no-go$^-$ ($M = 0.088$) trials, $t(22) = -2.733$, $P = 0.001$, such that intentional motor inhibition led to incidental down-regulation of the amygdala. (C) gPPI connectivity results: neural regions correlated with rIFG *pars opercularis* during negative inhibition trials. There was greater communication between the rIFG *pars opercularis* (anatomically defined seed region) and the insula: $x = 44$, $y = 12$, $z = -4$) during no-go$^-$ > go$^-$ trials. All activations reported are cluster thresholded with a minimum z-statistic of 2.3 and $P < 0.05$. MNI Coordinates reported with images in radiological view.

temporal gyrus. Contrary to H2, there was no significant effect of age on neural signal during no-go > go.

H3: Neural activation during negative and positive inhibition trials (Table 3). As hypothesized, a paired *t*-test analysis revealed differences between no-go$^-$ trials and go$^-$ trials, such that no-go$^-$ trials recruited more cognitive control network regions (right middle frontal gyrus, frontal pole, rIFG *pars opercularis* and middle temporal gyrus), as well as more activation in the precuneus and lingual gyrus reaching the occipital fusiform (Figure 4A). Contrary to our hypothesis, we did not find significantly greater activation in the ACC during no-go$^-$ trials compared with go$^-$ trials. In addition, in support of the inhibitory spillover hypothesis, our small volume ROI analysis found a significant reduction in both left, $t(21) = 2.54$, $P = 0.02$, and right, $t(21) = 2.286$, $P = 0.03$, amygdala activation when comparing go$^-$ trials to no-go$^-$ trials (Figure 4B). When we ran an RM ANOVA in SPSS using percent signal change extracted from both left and right amygdalae, a main effect of condition emerged for both left $F(1, 22) = 8.55$, $P = 0.008$ and right $F(1, 22) = 8.90$, $P = 0.007$ amygdalae, such that there was less activation in both left ($M = 0.103$) and right ($M = 0.131$) amygdalae during inhibition trials than during go trials ($M_{\text{left.amyg}} = 0.229$; $M_{\text{right.amyg}} = 0.258$). There was no main effect of valence or condition × valence interaction. Also, as expected, we did not find any significant clusters of activation or deactivation when comparing positive inhibition trials to positive go trials.

H4: Functional connectivity during negative inhibition trials. Task performance on no-go$^-$ trials compared to go$^-$ trials was coupled with increased functional connectivity between the rIFG *pars opercularis* and the frontal pole ($x = 52$, $y = 36$, $z = 6$), lateral occipital cortex ($x = 44$, $y = -80$, $z = -2$), fusiform gyrus ($x = 38$, $y = -52$, $z = 10$) and anterior insula ($x = 44$, $y = 12$, $z = -4$; Figure 4C).

H5: Associations between youth symptoms and inhibitory spillover. As shown in Table 4, internalizing scores were used as regressors in a whole-brain analysis using the no-go$^-$ > go$^-$ contrast and controlling for lag time between scan time and YSR self-report data collection. As hypothesized, internalizing symptoms were positively associated with BOLD signal recruitment in a frontal cluster reaching to the ACC and bilateral IFG *pars opercularis* and *pars triangularis*. Contrary to H5, there were no significant associations with ventral affective areas of the insula and amygdala; however, there was a positive association with the temporal pole, right putamen and right pallidum. Therefore, higher self-reported internalizing symptoms were associated with more signal recruitment in regions involved in inhibition, reward processing and automatic motor movements, but not affective saliency regions.

Discussion

This is the first article to examine inhibitory spillover within a sample of adolescents using Berkman *et al.*'s (2009) emotional go/no-go task, and also the first article to explore associations between inhibitory spillover and internalizing symptoms. As hypothesized, when asked to inhibit in the face of irrelevant affective stimuli, adolescents recruited the rIFG *pars opercularis* and prefrontal cognitive control regions along with ventral affective areas. Age was negatively associated with activation of regions including the rIFG, insula and temporal pole during inhibitory spillover, suggesting that older youth showed lower recruitment of regions involved in reconciling complex stimulus input and inhibition. In support of the inhibitory spillover

Table 1. Neural regions activated during inhibition and go trials

Region	x	y	z	Z
NoGo>Baseline				
SMA	8	6	64	4.75
PreSMA	−8	8	46	4.5
Superior Frontal Gyrus	−8	26	62	3.71
ACC	8	20	36	3.42
	12	16	38	3.38
Frontal Pole, Superior Frontal Gyrus	−2	60	12	3.39
Insula	44	12	−4	4.65
	30	22	0	4.29
Frontal Orbital Cortex, Insula	26	14	−14	3.45
	28	24	−14	3.14
IFG *pars triangularis*, Frontal Pole	52	36	4	3.39
Ventral Pallidum	16	6	6	3.23
Baseline > NoGo				
Lateral Occipital Cortex	42	−74	44	5.7
	−34	−76	40	5.08
	−34	−88	32	4.72
Intracalcarine Cortex	18	−76	48	5.02
	−12	−86	8	4.6
Precuneus	16	−60	30	4.61
Go > Baseline				
Frontal Pole	6	62	30	5.19
	−2	64	14	4.32
	4	62	20	4.28
	−6	68	26	3.63
Superior Frontal Gyrus	−2	52	40	4.93
	−12	26	64	4.3
Baseline > Go				
Lingual Gyrus	−10	−62	0	4.95
Precuneus	16	−60	26	4.73
	−6	−88	18	4.71
	−12	−68	22	4.69
Lateral Occipital Cortex	40	−76	40	4.69
Superior Parietal Lobule	22	−44	56	4.54
NoGo > Go				
PreSMA/SMA	4	14	50	4.31
SMA	10	4	66	4.18
ACC	8	20	38	4.16
	−6	8	44	3.78
	−10	24	32	3.5
Superior Frontal Gyrus	4	30	46	2.93

Notes: All activations reported are thresholded to a minimum z-statistic of 2.3 and $P < 0.05$. MNI Coordinates reported. IFG, inferior frontal gyrus; PreSMA, pre-supplementary motor area; SMA, supplementary motor area

Table 2. Neural regions activated during emotion facial perception

Region	x	y	z	Z
Negative > Baseline				
Insula	44	10	−4	4.12
	28	26	−2	3.55
Frontal Pole, IFG *pars triangularis*	52	38	4	3.99
Amygdala	18	−4	−12	3.45
Hippocampus	30	−18	−12	3.48
Frontal Orbital Cortex	40	26	−10	3.4
Frontal Pole	6	62	32	4.27
	−8	58	34	3.5
Superior Frontal Gyrus	−10	26	62	3.57
	−16	28	62	3.48
	−2	64	14	3.41
PreSMA/SMA	8	8	64	4.22
Baseline>Negative				
Lateral Occipital Cortex	42	−74	44	5.92
	10	−74	50	4.69
Intracalcarine Cortex	14	−80	14	5.25
Precuneus Cortex	−12	−70	22	5.06
	16	−60	30	5.04
Cuneal Cortex	−4	−74	22	4.48
Positive>Baseline				
PreSMA/SMA	6	8	68	4.25
	6	8	64	4.18
Frontal Pole	−6	56	36	4.11
	4	62	20	4.04
	−2	62	12	3.96
Superior Frontal Gyrus	−10	26	62	4.19
Baseline>Positive				
Posterior Cingulate Cortex	0	−34	48	4.93
Lateral Occipital Cortex	40	−76	40	4.91
	−34	−88	30	4.9
	18	−74	48	4.76
	16	−60	30	4.66
	12	−76	50	4.52

Notes: All activations reported are thresholded to a minimum z-statistic of 2.3 and $P < 0.05$. MNI coordinates reported. IFG, inferior frontal gyrus; PreSMA, pre-supplementary motor area; SMA, supplementary motor area

hypothesis, adolescents showed less amygdala activation and greater functional connectivity between the rIFG *pars opercularis* and insula during negative inhibition trials compared with negative non-inhibition trials (Figure 4). These results dovetail with the literature identifying the rIFG as a key region involved in inhibition and possible down-regulation of ventral affective regions during inhibition (Berkman *et al.*, 2009). In addition, youth with higher internalizing symptoms responded more quickly to positive faces and showed more activation in prefrontal cognitive control regions (rIFG, ACC) and subcortical motor and reward regions (putamen, pallidum), but not ventral affective regions, during negative inhibition trials (Figure 3).

This study converges with prior evidence that the rIFG *pars opercularis* may be a common neurobiological substrate underlying inhibitory control. Recent literature has cited the rIFG *pars opercularis* as part of a 'stop' network involving the rIFG *pars opercularis*, the preSMA/SMA and the right subthalamic nucleus, which are all linked via white matter tracts (Aron *et al.*, 2007). The subthalamic nucleus can then quickly inhibit motor and affective responses by communicating with the basal ganglia, a network of regions involved in motor output and reward processing (Aron *et al.*, 2007; Tabibnia *et al.*, 2011). Lesion studies and comparative studies of humans and monkeys, which implicate the rIFG *pars opercularis* as pivotal to response inhibition, highlight that the IFG is one of the last areas of the PFC to develop to maturity (Aron *et al.*, 2004). Recent studies also link the rIFG *pars opercularis* to the anterior insula, citing that both are necessary for intricate attentional and working memory tasks (Tops and Boksem, 2011). Indeed, the rIFG *pars opercularis* was recruited in this adolescent sample and appeared to successfully have implicit spillover effects to ventral affective regions that responded to distracting, irrelevant stimuli.

Neurodevelopmentally, the prolonged maturation of the rIFG *pars opercularis* and its white matter tract projections have important implications for inhibitory control in adolescents, whose PFC development lags behind limbic development. Consistent with this, we found age was associated with less activation in the ACC and bilateral IFG, such that the younger the adolescent, the less BOLD signal recruitment to these regions which are pivotal for inhibition. However, there was no

Table 3. Neural regions activated during negatively valenced inhibition trials

Region	x	y	z	Z
NoGo⁻>Go⁻				
Middle temporal gyrus	56	−46	4	4.42
Lateral occipital cortex	−28	−74	24	4.1
Lingual gyrus	−24	−60	4	3.79
	18	−60	2	3.7
Lingual gyrus, fusiform	−12	−66	−4	3.7
Precuneus	12	−76	40	3.72
Precentral, middle frontal gyrus	44	8	34	4.15
	44	12	52	2.71
Frontal pole, middle frontal gyrus	50	40	16	3.88
IFG *pars opercularis*	54	20	26	3.45
IFG *pars triangularis*	42	24	16	2.95
Frontal pole	32	42	16	3.37

Notes: All activations reported are thresholded to a minimum z-statistic of 2.3 and $P < 0.05$. MNI Coordinates reported. IFG, inferior frontal gyrus

Table 4. Neural regions negatively correlated with internalizing symptoms

Region	x	y	z	Z
NoGo⁻ > Go⁻ and internalizing symptoms				
Frontal Pole	40	50	−4	4.17
	24	34	−6	3.6
	24	28	−4	3.54
Putamen	30	6	22	3.59
Frontal Pole, ACC, IFG	14	46	36	3.56
Frontal Pole, IFG	−34	46	2	3.56

Notes: All activations reported are thresholded to a minimum z-statistic of 2.3 and $P < 0.05$. MNI Coordinates reported. IFG, inferior frontal gyrus; ACC, anterior cingulate cortex.

correlation between age and behavioral response inhibition during the fMRI task, indicating that regardless of this differential neural recruitment associated with age, age of the participant did not affect the adolescents' abilities to accurately inhibit behaviorally. This is interesting, given that age was also negatively correlated with activation in the sensory integration and resolution center of the temporal pole and posterior superior temporal sulcus. These age-related neural network differences, in consideration with behavioral accuracy rates, suggest that inhibitory neural networks are continuing to mature and refine in late adolescence (youths were 15–18 years old), but that adolescents are still able to effectively inhibit during ongoing network refinement.

Furthermore, as youths' internalizing symptoms increased, so did their recruitment to the right pallidum (part of the basal ganglia), right putamen (involved in automatic motoric movements) and rIFG *pars opercularis*. Notably, like age, internalizing symptoms were not correlated with inhibitory control percent accuracy, indicating that youths with internalizing symptoms behaviorally performed just as well or better (on positive trials) as youths with fewer symptoms. Fitting with Pfeifer and Allen (2012)'s arguments regarding adolescent neurodevelopment, adolescents in our study who reported more internalizing symptoms did not show increased ventral affective saliency and responding in the amygdala and insula and a protracted recruitment of PFC regions. Rather, youths with behavioral symptoms had increased prefrontal cognitive control and subcortical automatic motoric and reward processing activation in the absence of ventral affective neural recruitment, suggesting that perhaps these adolescents are *capable* of inhibiting successfully and *do* inhibit successfully, but do so via differential neural pathways that actually facilitated faster accurate behavioral responding in some cases. Perhaps, in community youths with subclinical internalizing symptoms, the symptoms may be associated with more of a regulated, top-down inhibitory control process rather than an overactive saliency network and faulty inhibitory control.

Our results replicate Berkman *et al.*'s (2009) earlier finding that the rIFG is pivotal to inhibition and that explicit cognitive and motor inhibition leads to down-regulation of ventral affective areas (i.e. amygdala, insula). Our results diverge from those of Berkman *et al.* in two ways. We found a significant difference in performance accuracy of the fMRI task, such that adolescents were significantly better at engaging in the button press than inhibiting their button press. Adults typically show similar accuracy between no-go and go trials. Second, our gPPI analysis showed different results to the Berkman *et al.*'s (2009) paper. The original paper, using a different PPI analysis that was the gold standard at the time of their publication, found that increased functional activity in the rIFG was linked with decreased activity in the amygdala, thereby supporting the inhibitory spillover hypothesis. We used a different approach, which was introduced in 2012: context-dependent generalized PPI analysis (gPPI; McLaren *et al.*, 2012), which is methodologically different from the original PPI analysis. Using the gPPI method, our results indicated increased coupling between the rIFG *pars opercularis*, insula and occipital fusiform gyrus, and when interpreted with the fMRI results, indicated overall down-regulation of the insula via increased functional coupling. Although our results are not exact replications, they do coincide and both support the inhibitory spillover hypothesis within the constraints of the methodologies used.

This study had some limitations, particularly our small sample size. In addition, we scanned a community rather than clinical sample of adolescents, so most participants did not report clinically significant internalizing symptoms. That said, it is notable that significant associations between internalizing symptoms and neural activation appeared, even within a small, non-clinical sample. Moreover, our sample was socioeconomically and ethnically diverse. Although we focused only on adolescents, future research can continue to explore developmental changes in inhibitory spillover and behavior by comparing children, adolescents across a larger age range and adults.

In conclusion, the current findings support the inhibitory spillover hypothesis and elucidate neurodevelopmental processes in adolescence, both of which have important implications for understanding the interplay of cognitive control, emotion regulation and behavior. Recently, emerging emotion theories suggest that perhaps not all emotion regulation skills are as explicit as initially thought, especially given the overlapping neural substrates involved across affective, cognitive and motor domains (Burklund *et al.*, 2014). The inhibitory spillover hypothesis and current findings support the contention that emotion regulation may involve implicit and explicit processing. The current findings also highlight the complexity of studying the adolescent brain and the importance of contextualizing brain findings with behavioral reports (Pfeifer and Allen, 2012; Del Piero *et al.*, 2016). Lastly, the current findings have important implications for not just assessment of cognition and emotion, but for interventions, suggesting that cognitive control training

may be an effective avenue to improve emotion regulation ability in adolescence.

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