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Guanfacine Modulates the Influence of Emotional Cues on Prefrontal Cortex Activation for Cognitive Control

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Abstract

Rationale—Functional interactions between limbic regions that process emotions and frontal networks that guide response functions provide a substrate for emotional cues to influence behavior. Stimulation of postsynaptic α_2 adrenoceptors enhances the function of prefrontal regions in these networks. However, the impact of this stimulation on the emotional biasing of behavior has not been established.

Objectives—This study tested the effect of the postsynaptic α_2 adrenoceptor agonist guanfacine on the emotional biasing of response execution and inhibition in prefrontal cortex.

Methods—Fifteen healthy young adults were scanned twice with functional magnetic resonance imaging while performing a face emotion go/no-go task following counterbalanced administration of single doses of oral guanfacine (1 mg) and placebo in a double-blind, crossover design.

Results—Lower perceptual sensitivity and less response bias for sad faces resulted in fewer correct responses compared to happy and neutral faces, but had no effect on correct inhibitions. Guanfacine increased the sensitivity and bias selectively for sad faces, resulting in response accuracy comparable to happy and neutral faces, and reversed the valence-dependent variation in response-related activation in left dorsolateral prefrontal cortex (DLPFC), resulting in enhanced

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activation for response execution cued by sad faces relative to happy and neutral faces, in line with other frontoparietal regions.

Conclusions—These results provide evidence that guanfacine stimulation of postsynaptic α_2 adrenoceptors moderates DLPFC activation associated with the emotional biasing of response execution processes. The findings have implications for the α_2 adrenoceptor agonist treatment of attention-deficit hyperactivity disorder (ADHD).

Keywords

Guanfacine; Response execution; Response inhibition; Emotion; fMRI; Go/No-go task; Prefrontal cortex

Introduction

Socially appropriate behavior requires the encoding of context-dependent emotional cues to guide decisions about which actions to perform and which actions to suppress (Haberman and Whitney 2007). The facial expressions and body gestures that convey these emotional cues in social contexts have also been found to influence multiple domains of cognitive function (Phelps and LeDoux 2005), including response selection, execution, and inhibition (Maxwell et al. 2005; Schulz et al. 2007). Thus, the positive affect (Otta et al. 1994) and approach behavior (Johansson and Ronnberg 1996) elicited by facial expressions of happiness resulted in faster responses that were more difficult to suppress (Hare et al. 2005; Schulz et al. 2007), while expressionless (neutral) faces reduced the accuracy of responses to happy and sad faces (Schulz et al. 2009; Lewis et al. 2008). Identifying the neural mechanisms that support the emotional biasing reflected in response functions has important implications for addressing the problems with impulsivity and emotion regulation that characterize a wide array of psychiatric disorders (Lewis et al. 2008; Murphy et al. 1999; Musser et al. 2011; Silbersweig et al. 2007; Walcott and Landau 2004).

Functional interactions between limbic structures that process affective cues and prefrontal cortex regions that guide behavior provide a putative cortical entry point for emotion to bias response functions (Dolan, 2007). The amygdala is a core component of a limbic network for rapidly detecting and encoding the intensity and valence of emotionally salient stimuli (Dolan 2007; LeDoux 1998), and sends extensive projections to orbital aspects of inferior frontal gyrus (Petrides and Pandya 2002). The inferior frontal gyrus pars orbitalis integrates this emotional information with contextual input from inferotemporal cortex to compute the behavioral significance of cue stimuli (Sakagami and Pan 2007), with separate sets of neurons coding for cues that signal behavioral execution and inhibition (Sakagami et al. 2001). In turn, dorsolateral prefrontal cortex (DLPFC) integrates the pars orbitalis output and visuomotor input from parietal association cortices to exert goal-directed control by biasing neural activity in task-related sensorimotor regions (Egner and Hirsch 2005; Miller and Cohen 2001) and releasing frontal operculum from inhibitory control (Stevens et al. 2007, 2009). Right frontal operculum is purportedly a neural effector for both goal-directed hand actions (Iacoboni and Wilson 2006) and the inhibition of such actions (Garavan et al. 2006; Xue et al. 2008), and has been shown to display both context- and valence-dependent variations in activation during response inhibition (Schulz et al. 2009).

Prefrontal cortex function is intricately modulated by ascending noradrenergic projections from the pontine nucleus locus coeruleus (Arnsten and Li 2005). Noradrenaline released from these projections acts at postsynaptic α_2 adrenergic receptors to suppress spontaneous activity (Wang et al. 2011) and increase evoked firing of pyramidal neurons (Carr et al. 2007; Gamo et al. 2010), thereby enhancing the response gain of prefrontal neuronal ensembles to task-relevant inputs (Aston-Jones and Cohen 2005). This increase in response

gain has been shown to boost the cue-evoked activation of DLPFC (Clerkin et al. 2009), and may contribute to improvements in response inhibition and increases in frontal opercular activation produced by the noradrenaline reuptake-inhibitor atomoxetine (Chamberlain et al. 2006; 2009). These α_2 adrenoceptor actions offer a mechanism to enhance the top-down control of the emotional biasing of response functions using α_2 adrenoceptor agonists already approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) (Sallee and Eaton 2010).

This study tested the impact of postsynaptic α_2 adrenoceptor stimulation on the emotional biasing of response functions in healthy adults using event-related functional magnetic resonance imaging (fMRI) together with a pharmacological challenge with the α_2 adrenoceptor agonist guanfacine. The adults were scanned twice while performing a face emotion go/no-go task following single oral doses of guanfacine and placebo in a double-blind, counterbalanced design. It was predicted that guanfacine stimulation of postsynaptic α_{2A} adrenoceptors would be associated with activation gains in inferior frontal gyrus pars orbitalis, DLPFC, and frontal operculum, which reflect enhanced cognitive control to overcome the reported emotional biasing of response functions, and would result in improved accuracy of responses to sad faces and inhibition of responses to happy faces compared to placebo.

Methods

Participants

Fifteen right-handed adults (8 females) with a mean ($\pm$ SEM) age of 25.7 ± 1.2 years (range = 21 – 35 years) were recruited via university and medical center campus postings for the study. All participants provided written informed consent for participation after a complete description of the study was provided to them. Participants were compensated for their time. The study was approved by the Institutional Review Boards of Queens College and The Mount Sinai School of Medicine.

Subjects were screened for contraindications to study participation with physical and mental status exams, and ratings on the Beck Anxiety Inventory (BAI) (Beck et al. 1988), Beck Depression Inventory – II (BDI-II) (Steer et al. 1999), and Conners Adult ADHD Rating Scale (CAARS) (Conners et al. 1999). Full Scale IQ was estimated with the Matrix Reasoning and Vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999). A total score ≥ 15 on the BDI-II or the BAI, a T-score 1 SD above the mean (i.e., > 60) on the CAARS Total ADHD Symptoms index, and an estimated IQ < 80 were exclusionary for the study. Mean BDI-II and BAI total scores were both 1.4 ± 0.5 , mean CAARS Total ADHD Symptoms T-score was 42.9 ± 2.5 , and mean estimated IQ was 113.7 ± 9.6 .

General Experimental Design

Participants completed fMRI scans on two separate days, with a mean of 7.0 ± 2.5 days between scans. Blood pressure was measured and 1 mg oral guanfacine or placebo was administered 90 minutes prior to the scans in a counterbalanced, double-blind design. The 1 mg dose of guanfacine was chosen to minimize sedation in the scanner and for its primarily postsynaptic binding profile (Arnsten et al. 1988; Engberg and Eriksson 1991). Participants completed a training session that tested simple face perception and presented the face emotion go/no-go task. Blood pressure was measured at the end of each scan session.

Face emotion go/no-go task

The face emotion go/no-go task has previously been described (Schulz et al. 2009). The task consisted of six 252-s blocks that each began and ended with a 30-s central fixation-cross. Each block contained 72 (75%) go cues and 24 (25%) no-go cues, yielding a total of 432 go cues and 144 no-go cues across the task. Participants had to respond rapidly with the right index finger to “go” cues and withhold responses to “no-go” cues. Stimuli were presented in the center of the screen for 500 ms with an interstimulus interval that was pseudorandomized from 1250 to 1750 ms (mean per block = 1500 ms). Face stimuli consisted of gray-scaled happy, sad, and neutral facial expressions from 18 individuals (9 female, 9 male) from the MacBrain Face Stimulus Set (Tottenham et al. 2009; available at www.macbrain.org). The images were normalized for size and luminance, morphed to exclude hair, and cropped into a black square, which was presented against a black background. Alternating the valence of the face stimuli used as trial cues resulted in six blocks with the following trials: (1) happy go / sad no-go; (2) sad go / neutral no-go; (3) neutral go / happy no-go; (4) happy go / neutral no-go; (5) sad go / happy no-go; and (6) neutral go / sad no-go. Trial order was determined by counterbalancing across all conditions in the task (e.g., trial type, facial expression, face ethnicity, face gender, face) to ensure that each trial type followed every other trial type equally often.

fMRI image acquisition

All participants were scanned on the same 3.0 Tesla Siemens Allegra (Siemens, Erlangen, Germany) head-dedicated MRI scanner. Functional T2*-weighted images depicting the blood oxygenation level-dependent (BOLD) were obtained every 3 s (TR = 3) using gradient-echo echo-planar imaging. Each functional image comprised a brain volume of 42 axial slices with an in-plane resolution of 3.75×3.75 mm and a thickness of 2.5 mm with a gap of 0.825 mm. The matrix size was 64×64 and the field of view was 210 mm. The TR was a trade-off for whole-brain coverage with thinner slices that minimized distortions and increased sensitivity in regions of interest (e.g., inferior frontal gyrus pars orbitalis). The participants each completed 6 runs of 252 seconds on two separate days. A high-resolution T2-weighted anatomical image was also acquired at the same 42 slice locations with a turbo spin-echo pulse sequence. All images were acquired with slices positioned parallel to the intercommisural line.

Behavioral analysis

Percent correct responses on go trials served as the measure of response execution, while percent correct inhibitions on no-go trials was the primary measure of response inhibition. Reaction time (RT) was also calculated for go trials. The signal detection variables d' and criterion (c) were computed to measure discriminability and response bias, respectively (Macmillan and Creelman 2005). The variables d' and c were calculated from the hit and false alarm rates and thus provided pooled measures of performance on both go and no-go trials. Higher d' values indicate greater discriminability, while negative c values indicate a bias to respond (as opposed to a bias to inhibit), with larger negative values indicating greater bias (Stanislaw and Todorov 1999).

The effects of guanfacine and emotion on performance were tested with repeated measures analyses of variance (ANOVA) with face emotion (happy vs. sad vs. neutral) and drug (guanfacine vs. placebo) as within-subject factors. Separate ANOVA with drug (guanfacine vs. placebo) and time (pre-scan vs. post-scan) as within-subject factors were used to test the effect of guanfacine on blood pressure. Statistical significance was set at the 0.05 level for these analyses. All probabilities were based on two-tailed tests. Partial eta squared (η_p^2) values were calculated to estimate the size of the guanfacine and emotion effects on behavioral performance.

fMRI analysis

Pre-processing and analyses of the fMRI data were conducted using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>). Each participant's placebo and guanfacine time series were separately corrected for the staggered acquisition of slices during echo-planar imaging and realigned to the first volume in each time series to correct for inter-scan motion. Next, the placebo and guanfacine time series were co-registered to their respective T2-weighted anatomical images and then to each other. The time series were subsequently spatially normalized to the Montreal Neurological Institute template using normalization parameters estimated from the first T2-weighted image and were then resampled with a $2 \times 2 \times 2$ mm voxel size. Finally, the time series were spatially smoothed with an 8-mm full width at half-maximum isotropic Gaussian kernel.

Event-related analyses were conducted individually for each participant using a general linear model (GLM) to determine the relationship between the observed event-related BOLD signals and regressors that represented expected neural responses to trial events. Regressors were created by convolving a train of delta functions that represented the individual trial events with the default SPM basis function, which consisted of a synthetic hemodynamic response function (HRF) (Friston et al. 1998). Twelve regressors were entered into the GLM, representing the 2 trial types of interest (correct no-go event vs. correct go event) $\times$ 3 face emotions (happy vs. sad vs. neutral) $\times$ 2 drugs (guanfacine vs. placebo). Go and no-go errors and six motion parameters were entered as covariates of no interest in the GLM (Johnstone et al. 2006). Contrasting the parameter estimates for each regressor versus baseline resulted in 12 contrast maps that each represented the specific BOLD response to a single interaction effect (e.g., happy no-go trials in the guanfacine condition).

The 12 contrast maps for each participant were entered into a second-level group analysis that used a factorial ANOVA model with trial type, face emotion, and drug as within-subjects factors. This statistical model enabled us to test all possible two-way and three-way interactions. The resultant voxel-wise statistical maps were thresholded for significance using a cluster-size algorithm that protects against false-positive results (Hayasaka et al. 2004). The height (intensity) threshold of each activated voxel was set at a p value of 0.005 and the extent (cluster) threshold was fixed at $\kappa > 100$ contiguous voxels. A Monte Carlo simulation that accounted for image resolution and smoothing parameters established that a cluster extent of 100 contiguous resampled voxels (2 mm^3) corrected for multiple voxel comparisons at $p < 0.01$. The simulation is described in Slotnick and Schacter (2004).

Results

Blood pressure

Guanfacine reduced blood pressure during the scan compared to placebo (see Supplementary Table 1). Repeated measures ANOVA revealed a significant main effect of time [$F(1,15) = 8.43$, $p = 0.012$] and drug $\times$ time interaction [$F(1,15) = 5.67$, $p = 0.032$] on pulse rate, and a significant drug $\times$ time interaction on systolic blood pressure [$F(1,15) = 7.17$, $p = 0.018$], but not diastolic blood pressure ($p = 0.88$). Reductions in systolic blood pressure over the scan session were only seen for guanfacine, while decreases in pulse rate were seen for both conditions, but were greater for guanfacine than placebo. There were no significant main effects of drug (all $p > 0.10$).

Behavioral performance

Guanfacine moderated the effect of face emotion on the accuracy of response execution on the go/no-go task, but had no effect on response inhibition (Table 1). Repeated measures

ANOVAs revealed a significant main effect of face emotion [$F(2, 28) = 9.95, p = 0.001, \eta_p^2 = 0.42$] and face emotion $\times$ drug interaction [$F(2, 28) = 14.53, p < 0.001, \eta_p^2 = 0.51$] on the percentage of correct responses on go trials, but not on the percentage of correct inhibitions on no-go trials (face emotion, $p = 0.79, \eta_p^2 < 0.001$; face emotion $\times$ drug, $p = 0.83, \eta_p^2 = 0.16$). Similar effects were found for the signal detection measures d' [face emotion, $F(2, 28) = 6.24, p = 0.006, \eta_p^2 = 0.32$; face emotion $\times$ drug, $F(2, 28) = 10.99, p < 0.001, \eta_p^2 = 0.46$] and c [face emotion, $F(2, 28) = 6.31, p = 0.006, \eta_p^2 = 0.33$; face emotion $\times$ drug, $F(2, 28) = 5.64, p = 0.009, \eta_p^2 = 0.30$]. Post-hoc Bonferroni tests revealed that the accuracy of responses was lower, and consequently, perceptual sensitivity and response bias were reduced for sad faces only in the placebo condition (Figure 1). There was also a significant effect of face emotion on RT on go trials [Table 1; $F(2, 28) = 9.02, p = 0.001, \eta_p^2 = 0.39$]. There were no significant main effects of drug (all $p > 0.10$).

fMRI responses

Face emotion influenced neural activation for response execution and inhibition in prefrontal cortex and other regions. The factorial ANOVA identified significant main effects of trial type in two independent brain networks that have been linked to response execution and inhibition (Table 2). Primary motor, striatal, and cerebellar regions showed greater activation for correct go trials than correct no-go trials, while greater activation for no-go than go trials was seen in frontal, parietal, and temporal regions, including left DLPFC and right frontal operculum extending superiorly to DLPFC. The latter region completely overlapped a separate cluster of activation in right frontal operculum that demonstrated a significant main effect of face emotion (Fig. 2). Post-hoc comparisons revealed that activation in this frontal opercular cluster was greater for sad faces than neutral faces, which in turn was greater than the deactivation for happy faces (Fig. 3a). Further, significant trial type $\times$ face emotion interactions were seen in right inferior frontal gyrus pars orbitalis, left primary motor cortex, and several parietal regions (Table 2). Plotting the inferior frontal activation revealed that sad faces evoked activation for go trials versus deactivation for no-go trials, but happy and neutral faces evoked activation for no-go trials versus deactivation for go trials (Fig. 3b). This pattern of activation was conserved across the motor and parietal clusters.

Guanfacine moderated the effect of face emotion on neural activation for response execution and inhibition selectively in left DLPFC (Table 2). The ANOVA identified a trial type $\times$ face emotion $\times$ drug interaction in a cluster that partially overlapped with the DLPFC region that showed an effect of trial type (Fig. 2). Guanfacine reversed the valence-dependent pattern of activation for go and no-go trials seen in this cluster following placebo. Thus, sad faces evoked activation for no-go trials in the placebo condition and for go trials in the guanfacine condition, whereas happy faces, and to a lesser extent neutral faces, elicited activation for go trials following placebo and for no-go trials following guanfacine (Fig. 3c). In addition, significant main effects of drug and trial type $\times$ drug interactions were found in disparate regions that are not typically engaged for go/no-go tasks (Table 2).

Discussion

The current results provide evidence that the α_2 adrenoceptor agonist guanfacine moderates left DLPFC activation associated with the emotional biasing of response execution in healthy adults. Left DLPFC is part of a wider frontoparietal network that is specialized to use emotional and contextual information to guide response execution and inhibition. Frontal opercular, inferior frontal, DLPFC, and parietal areas of this network all showed variations in activation as a function of face valence that were comparable to that seen in a previous study (Schulz et al. 2009). Guanfacine moderated the effect of face emotion on this activation selectively at the level of DLPFC, by reversing the valence-dependent pattern of

task-related activation, which resulted in activation for response execution and deactivation for response inhibition cued by sad faces relative to happy and neutral faces. These guanfacine actions were associated with selective increases in the relatively low sensitivity and response bias for sad faces seen in the placebo condition, which principally reflected improvements in response execution. In contrast, neither face valence nor guanfacine had an effect on response inhibition. These results offer clues about the emotional biasing of motor functions and the manipulation of this bias by α_2 adrenoceptor stimulation.

The present behavioral findings provide clear evidence that emotional cues bias response execution processes on the go/no-go task. The negative values for the signal detection measure c in the current study indicate a bias to respond rather than inhibit for all three face emotions, with less response bias for sad than happy and neutral faces (Stanislaw and Todorov 1999). The differences in response bias across the face emotions were mainly due to fewer correct responses to sad faces, which is partially consistent with our previous report of less accurate responses to both sad and happy faces (Schulz et al. 2009). Moreover, the enhanced response bias and perceptual sensitivity for sad faces following guanfacine reflected an increase in the percentage of correct responses to sad faces. However, unlike previous studies, our finding of faster responses to happy faces did not seem to reflect a broader emotional bias that interfered with the inhibition of responses to happy faces on no-go trials (i.e., fewer correct inhibitions) (Hare et al. 2005; Schulz et al. 2007). Rather, both findings may reflect the inclusion of neutral faces as trial cues. Neutral expressions tend to be mistakenly evaluated as sad faces (Lee et al. 2008; Russell and Fehr 1987), which may have been further compounded by the use of faces with closed mouths (Calvo and Nummenmaa 2008). These difficulties with face discrimination could account for both the poorer accuracy for sad faces and the slower responses to neutral and sad faces than happy faces in this study. The selective effect of guanfacine on the emotional biasing of accuracy for sad faces confirms that these effects were task-specific rather than a general consequence of the medication.

The selective impact of guanfacine on the valence- and task-dependent activation of left DLPFC is consistent with the model of this region as the apex of a frontoparietal network for the context-dependent control of goal-directed behavior (Fuster 2002; Miller and Cohen 2001). Left DLPFC receives limbic and inferotemporal input indirectly via inferior frontal gyrus pars orbitalis (Petrides and Pandya 2002) and represents this input as distinct patterns of neural activation (Fuster 2002; Miller and Cohen 2001). These context representations form the neural basis for DLPFC to exert top-down control over sensorimotor processors that directly support task performance (Sakagami and Pan 2007; Silton et al. 2010), by amplifying responses to task-relevant signals (Egner and Hirsch 2005), particularly in the presence of competing response options, such as for sad faces in the current study (Hester et al. 2004). The guanfacine reversal of the DLPFC function for response to sad faces, from deactivation to activation relative to responses cued by happy and neutral faces, may thus reflect increases in top-down control to overcome the difficulties with responding to sad faces.

The gain in DLPFC activation associated with improvement in response execution cued by sad faces is consistent with the well-described neural actions of guanfacine. Guanfacine stimulation of postsynaptic α_2 adrenoceptors suppresses an inward cation current (Wang et al. 2007), which raises the excitability of pyramidal neurons (Carr et al. 2007) and strengthens local DLPFC recurrent networks that support top-down attention control (Wang et al. 2007). These α_2 adrenoceptor actions have been shown to increase neuronal firing in DLPFC for the preferred direction in a working memory task in monkeys (Avery et al. 2000; Gamo et al. 2010). Similar mechanisms may have improved response execution for sad faces in the current study.

The valence- and task-dependent activation of the inferior frontal gyrus pars orbitalis seen in the current study provides support for the model of this region as a cortical entry point through which emotional cues influence response functions (Sakagami and Pan 2007). The pars orbitalis purportedly computes the behavioral significance of stimuli by integrating information about the target with affective input from amygdala (Petrides and Pandya 2002) and contextual input from inferotemporal cortex (Ungerleider et al. 1989), and is unique among prefrontal areas in that it contains separate populations of neurons that fire selectively for sensory cues that signal behavioral execution and inhibition (Sakagami et al. 2001). The interactive effect of face valence and trial type on pars orbitalis activation in the current study is consistent with the integration of emotional and contextual cues. The pars orbitalis may influence motor functions through projections to DLPFC (Miyachi et al. 2005) and dense connections with the frontal operculum (Petrides and Pandya 2002).

The frontal operculum on the non-dominant side has been implicated in complex sensory guided motor acts (Iacoboni and Wilson 2006). The current finding of greater frontal operculum activation for no-go relative to go trials is consistent with meta-analyses that have implicated the region as a neural effector for response inhibition (Garavan et al. 2006; Simmonds et al. 2008). The overlapping region of operculum that independently displayed greater activation for sad faces than neutral and happy faces may thus have reflected differences in the difficulty of inhibiting responses to sad faces (Schulz et al. 2009). The lack of an interaction between face valence and trial type points to an exclusive role for frontal operculum in response inhibition. The fact that guanfacine did not influence activation in frontal operculum may explain the lack of effect of the α_2 adrenoceptor agonist on response inhibition in this study and others (e.g., Muller et al. 2005). Gains in frontal opercular activation have previously been associated with improvements in response inhibition in healthy adults (Chamberlain et al 2009).

Limitations

The attribution of the behavioral and neural changes in the current study to the biochemical effects of guanfacine is mitigated by the difficulties with measuring local drug actions in humans. Plasma measures of guanfacine and its metabolites that would have strengthened claims of causality were purposely not obtained to minimize participant risk and burden. However, the depressant effect that guanfacine had on blood pressure recordings in this study confirm that the medication, which was originally developed as an antihypertensive, had the desired biochemical effects, at least peripherally.

The absence of face valence effects in amygdala and other limbic regions in this study was unexpected given the previous reports of such activation using emotional go/no-go tasks (Schulz et al. 2009; Goldstein et al. 2007; Hare et al. 2005). This lack of amygdala activation may reflect the difficulty with successfully imaging this subcortical region (Merboldt et al. 2001) and/or the focus on prefrontal cortex in this study, and the use of an analytic approach that was optimized to detect effects in this large region of interest. The extent or cluster threshold (> 100 voxels) that was needed to correct for the multiple voxel comparisons may have been too large to detect effects in the relatively small amygdala. It must also be noted that the relatively small sample size in this study may have limited the statistical power to detect more subtle effects of guanfacine, especially on the behavioral measures of response execution and inhibition.

Clinical Implications

The current findings have potential implications for the α_2 adrenoceptor agonist treatment of psychiatric disorders characterized by problems with impulsivity and emotion regulation. The specific effect of guanfacine on the response bias for sad faces suggests an application

for α_2 adrenoceptor agonists in the treatment of the mood-congruent biases that characterize major depression (Blaney 1986). However, α_2 adrenoceptor agonists have no reported antidepressant properties, and successful antidepressant treatment does not seem to involve alterations of adrenoceptor function (Charney et al. 1984; Price et al. 1986). The lack of antidepressant effects may in part reflect the selective action of guanfacine on executive functions mediated by DLPFC (Jakala et al. 1999), rather than on the limbic affective mechanisms that have been implicated in both mood-congruent biases (Elliott et al. 2000, 2002) and the pathophysiology of major depression (Elliott et al. 2011).

The guanfacine modulation of DLPFC activation associated with emotional biasing of response execution may offer a possible mechanism to address the emotional reactivity and dysregulation that are common to ADHD (Musser et al. 2011; Walcott and Landau 2004). Clinical experience and the few available studies suggest that these emotion regulation problems are not necessarily well served by the psychostimulant medications used to treat ADHD (Manos et al. 2011; Pelham et al. 1991). The finding that guanfacine enhanced response-related DLPFC activation to increase the reduced bias and sensitivity for sad faces suggests that the medication may improve emotion regulation and reduce the extraneous influence of emotion on response functions in individuals with noradrenergic dysfunction. Suboptimal postsynaptic α_{2A} adrenoceptor regulation of DLPFC function has been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD) (Brennan and Arnsten 2008) and is a promising target for pharmacological treatments for the disorder (Arnsten et al. 2007). Our results support further investigation of the use of guanfacine to treat affect-related regulatory problems in individuals with ADHD.

Conclusions

The present results demonstrate that the α_2 adrenoceptor agonist guanfacine moderates left DLPFC activation associated with the emotional biasing of response execution in healthy adults. Guanfacine inverted the trial- and valence-dependent pattern of DLPFC activation, and thereby increased left DLPFC activation for responses to sad faces relative to happy and neutral faces. These guanfacine actions were associated with improvements in the poor accuracy of responses to sad faces relative to happy and neutral faces in the placebo condition, but had no effect on behavioral measures of response inhibition. The selective action of guanfacine on control networks centered in DLPFC may offer a possible mechanism to address the emotional reactivity and regulation deficits commonly seen in patients with ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Effects of face emotion and drug on go/no-go task performance. **a** Mean percentage of correct responses on go trials cued by happy, sad, and neutral faces following 1 mg guanfacine and placebo. **b** Mean percentage of correct inhibitions on no-go trials cued by happy, sad, and neutral faces following guanfacine and placebo. Error bars indicate standard error of the mean. * $p < 0.01$

Fig. 2.

Brain regions that showed effects of trial type (go vs. no-go), face emotion (happy vs. sad vs. neutral), and drug (guanfacine vs. placebo) on task-related activation. Axial images depict significant main effects of trial type and face emotion in right frontal operculum, trial type $\times$ face emotion interaction in right inferior frontal gyrus pars orbitalis, and trial type $\times$ face emotion $\times$ drug interaction in left dorsolateral prefrontal cortex. Figures thresholded at $p < 0.005$ (cluster corrected for multiple voxel comparisons > 100 contiguous voxels). *Montreal Neurological Institute z-coordinates* indicate the distance (in mm) from the intercommissural line. *Right side of image* corresponds to the right side of the brain.

Fig. 3.

Effects of trial type (go vs. no-go), face emotion (happy vs. sad vs. neutral), and drug (guanfacine vs. placebo) on task-related activation illustrated for regions of interest in prefrontal cortex. Mean parameter estimates of task-related activation were plotted for the significant: **a** main effects of Trial Type and Face Emotion in right frontal operculum; **b** Trial type $\times$ face emotion interaction in right inferior frontal gyrus pars orbitalis; and **c** Trial type $\times$ face emotion $\times$ drug interaction in left dorsolateral prefrontal cortex. *Error bars* indicate standard error of the mean

Table 1

Dependent measures of emotional go/no-go task performance

Variable	Placebo			Guanfacine		
	Happy	Sad	Neutral	Happy	Sad	Neutral
No-go trials						
Correct inhibitions (%)	90.9 (2.4)	90.6 (1.5)	90.2 (1.8)	89.9 (1.1)	89.9 (1.4)	90.5 (2.2)
Go trials						
Correct responses (%) ^a	96.7 (1.1)	88.9 (2.6)	94.9 (1.6)	95.7 (1.9)	96.0 (1.5)	95.0 (1.86)
RT (ms) ^b	485 (27)	501 (26)	512 (39)	478 (20)	499 (22)	521 (23)
Signal detection						
D-prime (<i>d'</i>) ^a	3.7 (0.3)	2.8 (0.1)	3.5 (0.2)	3.6 (0.2)	3.6 (0.2)	3.5 (0.2)
Criterion (<i>c</i>) ^a	-0.3 (0.1)	-0.1 (0.1)	-0.3 (0.1)	-0.4 (0.1)	-0.3 (0.1)	-0.3 (0.1)

Values are presented as mean (standard error of the mean). *RT* reaction time

^a sad < happy = neutral for placebo *but* happy = sad = neutral for guanfacine, *p* < 0.05

^b happy < sad < neutral, *p* < 0.05

Table 2

Regional activation during the emotional go/no-go task that showed significant main effects for Trial (go vs. no-go), Face Emotion (happy vs. sad vs. neutral), and Drug (guanfacine vs. placebo)

Brain region	BA	MNI coordinates			No. of voxels	F value
		x	y	z		
Trial: go > no-go						
Left primary motor cortex	4	-32	-26	60	2,016	55.16
Right cerebellum	---	20	-50	-22	1,358	50.51
Right cerebellum	---	14	-58	-50	229	22.13
Left pulvinar	---	-18	-22	12	2,895	33.91
Right caudate nucleus	---	18	26	2	103	15.34
Left caudate nucleus	---	-10	22	2	242	13.72
Trial: no-go > go						
Right frontal operculum / DLPFC	44/46	44	8	32	2,489	48.87
Left dorsolateral prefrontal cortex	46	-50	26	28	643	28.49
Right dorsal anterior cingulate cortex	32	8	8	48	374	17.31
Right superior parietal lobule	7	20	-72	38	475	16.59
Right fusiform gyrus	37	40	-44	-18	6,669	45.86
Left fusiform gyrus	37	-40	-52	-12	2,689	45.51
Face Emotion: sad > neutral > happy						
Right frontal operculum	44	46	12	28	405	9.07
Drug: guan > placebo						
Bilateral perigenual cingulate cortex	32	2	50	4	1,133	23.92
Right temporoparietal cortical junction	40	44	-26	24	397	20.39
Right cuneus	18	4	-86	24	397	14.47
Left inferior occipital gyrus	18	14	-96	-14	150	12.35
Right posterior insula cortex	---	42	-12	14	602	15.97
Left posterior insula cortex	---	-38	-20	14	187	10.90
Trial × Face Emotion ^a						
Right inferior frontal gyrus	47	48	42	-8	130	10.65
Left primary motor cortex	4	-48	-8	28	158	9.21
Right posterior cingulate cortex	31	6	-36	44	519	11.98

Brain region	BA	MNI coordinates			No. of voxels	F value
		x	y	z		
Left inferior parietal lobule	40	-42	-42	44	524	9.32
Right superior parietal lobule	7	40	-52	48	1,792	14.81
Trial × Drug ^b						
Right posterior cingulate cortex	31	8	-60	8	415	17.42
Left thalamus	---	-8	-14	0	221	14.41
Trial × Face Emotion × Drug ^c						
Left dorsolateral prefrontal cortex	9	-50	22	34	216	8.96

F-values and x, y, and z coordinates refer to the peak voxel of activation within each cluster. All regions were significant at $p < 0.005$, extent threshold corrected for multiple voxel comparisons at $p < 0.01$. There were no significant Emotion × Drug interaction effects.

BA Brodmann area, DLPFC dorsolateral prefrontal cortex, MN/Montreal Neurological Institute

^a nogo > go for sad *but* go > no-go for happy and neutral
^b nogo > go for placebo *but* go > no-go for guanfacine
^c (nogo > go for sad *but* go > no-go for happy and neutral) for placebo *but* (go > no-go for sad *but* no-go > go for happy and neutral) for guanfacine