NeuroImage: Clinical 28 (2020) 102388

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Response to SSRI intervention and amygdala activity during self-referential processing in major depressive disorder

Kymberly D. Young[a,*], Edward S. Friedman[a], Amanda Collier[b], Susan R. Berman[c], Joshua Feldmiller[b], Agnes E. Haggerty[d], Michael E. Thase[e], Greg J. Siegle[a]

[a] University of Pittsburgh School of Medicine, Pittsburgh, 15213 PA, USA
[b] University of Pittsburgh Medical Center, Pittsburgh, 15213 PA, USA
[c] Carnegie Learning, Inc., Pittsburgh, 15219 PA, USA
[d] University of Miami Miller School of Medicine, Miami, 33136 FL, USA
[e] University of Pennsylvania School of Medicine, Philadelphia, 19104 PA, USA

ARTICLE INFO

Keywords:
SSRIs
Major depressive disorder
Recovery
Amygdala

ABSTRACT

There are conflicting reports on the impact of antidepressants on neural reactions for positive information. We thus hypothesized that there would be clinically important individual differences in neural reactivity to positive information during SSRI therapy. We further predicted that only those who responded to SSRIs would show increased amygdala reactivity to positive information following treatment to a level similar to that seen in healthy participants. Depressed individuals (n = 17) underwent fMRI during performance of a task involving rating the self-relevance of emotionally positive and negative cue words before and after receiving 12 weeks of SSRI therapy. At post-treatment, SSRI responders (n = 11) had increased amygdala activity in response to positive stimuli, and decreased activity in response to negative stimuli, compared to non-responders (n = 6). Results suggest that normalizing amygdala responses to salient information is a correlate of SSRI efficacy. Second line interventions that modulate amygdala activity, such as fMRI neurofeedback, may be beneficial in those who do not respond to SSRI medications.

1. Introduction

Clinically, some patients report that antidepressant medications blunt their reactions to positive information (Opbroek et al., 2002), and others say their ability to engage with positive information is increased, though not to the level that all antidepressants, particularly, escitalopram, can generally be said to treat anhedonia (Cao et al., 2019; Yee et al., 2015). As reduced amygdala hemodynamic activity to positive stimuli, particularly positive autobiographical memories (AMs) appears to be a causal mechanism interfering with recovery from major depressive disorder (MDD) (Victor et al., 2010; Young et al., 2016), we hypothesized that there would be individual differences in changes to neural reactivity to positive information associated with SSRIs and that only those whose reactivity to positive information in the amygdala increased following treatment would recover. Indeed, recent work by our lab suggests that real-time fMRI neurofeedback (rtfMIR-nf) training appears to enhance the amygdala's response to positive AMs and also significantly reduces depressive symptoms in patients diagnosed with MDD (Young et al., 2017). As antidepressant pharmacotherapy, particularly treatment with selective serotonin reuptake inhibitors (SSRIs), is one of the first interventions recommended for patients with MDD, yet up to two-thirds of patients fail to respond to their first intervention (Cain, 2007), understanding individual differences in response, and how to best treat residual mechanisms of depression in those who fail to respond, is a clinically important goal. The current study thus aimed to examine the how the amygdala response to positive self-referential stimuli changes with treatment and is related to response to SSRI medications, and to qualify these changes with understanding of 1) whether pre-treatment differences in amygdala reactivity were predictive of response, 2) whether changes in amygdala reactivity following treatment were associated with response and 3) whether a broader network of brain regions contributed to predictive power.

There have been numerous studies examining regional changes that occur following SSRI interventions (Cheng et al., 2017; Fitzgerald et al., 2008; Fu et al., 2004; Ruhe et al., 2012; Wang et al., 2015). These studies have generally reported that SSRIs result in reduced amygdala reactivity to emotional stimuli (e.g., (Fitzgerald et al., 2008; Ruhe et al., 2012), raising the concern that SSRIs may increase anhedonic

* Corresponding author at: Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, USA.
E-mail address: youngk@pitt.edu (K.D. Young).

https://doi.org/10.1016/j.nicl.2020.102388
Received 17 April 2020; Received in revised form 14 August 2020; Accepted 17 August 2020
Available online 20 August 2020

symptoms (Sansone and Sansone, 2010). However, the majority of reactivity studies found significant changes to negative stimuli only and either did not assess (Anand et al., 2007; Anderson et al., 2007; Del-Ben et al., 2005; Fu et al., 2004; Phillips et al., 2015) or did not find changes (Arce et al., 2008; Harmer et al., 2006; Murphy et al., 2009) in amygdala responses to positive stimuli (Delaveau et al., 2011).

Yet, in some studies, decreased amygdala activity to negative stimuli and increased activity to positive stimuli has been found following SSRI administration. For example, within the amygdala, MDD-associated abnormalities are "doubly dissociated" from healthy individuals by virtue of their greater response to negative stimuli and attenuated/negative response to positive stimuli (Suslow et al., 2010; Victor et al., 2010), including positive autobiographical memories (AMs) (Young et al., 2016). This pattern of amygdala activity is observed at baseline in both those who go on to be considered treatment responsive and treatment non-responders, suggesting a shared neurobiological mechanism for the experience of MDD (Godlewska et al., 2016). However, SSRI responders showed increased amygdala BOLD activity to happy faces following treatment that was not seen in treatment non-responders (Godlewska et al., 2016). These studies have largely utilized tasks measuring implicit processing or cognitive appraisals of emotional faces (is this a man or a woman).

Effects of SSRIs on more ecological positive information processing (sustained reactions to self-referential positive stimuli) have not been examined, though compared to non-personally relevant stimuli such stimuli may be more related to functional deficits patients with depression experience, as self-referential autobiographical processing is critical for problem solving (Raes et al., 2005), emotion regulation (Raes et al., 2006), and social bonding (Alea and Bluck, 2003). Therefore, the goal of the current study was to determine whether there were individual differences in whether SSRI intervention dampens amygdala reactivity during positive, as well as negative, emotional self-referential processing, or normalizes activity by decreasing responses to negative stimuli and increasing responses to positive stimuli in a clinically depressed population.

The current study employed an autobiographical/self-referential processing task in which participants are asked to evaluate the personal relevance of emotional words (Siegle et al., 2006, 2012). We have used neural reactivity on this task *during processing of negative stimuli* to predict responses to SSRIs (Miller et al., 2013) and cognitive therapy (CT) as well as evaluate change in CT (Siegle et al., 2006, 2012). A secondary goal of the current study was therefore to determine whether an analysis using the same task with a focus on activity to positive as well as negative stimuli would replicate the results of our previous SSRI study.

We predicted that the amygdala will be hyperactive to negative stimuli and hypoactive to positive stimuli at baseline in participants with depression, compared to controls, and will revert with successful antidepressant intervention (decreased activity to negative, increased to positive). Should non-responders to SSRI interventions show a decreased amygdala response to positive self-referential stimuli that does not resolve with pharmacotherapy, this would support secondary line interventions targeting amygdala reactivity (e.g., neurofeedback) when SSRI treatment fails.

2. Materials and methods

2.1. Participants

Participants in this study are part of a larger study that also included CT. Participants were able to self-select their treatment (CT or SSRI). 229 subjects were screened and 96 subjects were recruited over 33 months, of whom 32 self-selected into the SSRI group. Participants completed a baseline assessment and fMRI scan, then began treatment within an average of five days of completing the scan (range 1–14 days). Participants received 12 weeks of treatment and then completed a follow-up assessment, including fMRI, within an average of 6 days (range 1–12 days) of completing treatment.

Per inclusion criteria, baseline Hamilton Depression Ratings Scale (HDRS; Hamilton, 1961) scores were $\geq$14 and participants met diagnostic criteria for a current major depressive episode according to the SCID-IV. 15 participants did not provide two scans of useable data. Thus, the final analyzed sample included 17 individuals diagnosed with MDD in a current major depressive episode (See CONSORT diagram in the supplement, Figure S1) and a comparison group of 20 healthy controls (HCs) with no current or lifetime axis I disorder who engaged in the same task and whose data have been previously reported on (Siegle et al., 2012). All participants had a North American Adult Reading Test (NAART) equivalent FSIQ $>$ 85, and described no history of psychosis, manic or hypomanic episodes on a structured clinical interview (SCID-IV), or antidepressant use within 2 weeks of testing (6 weeks for fluoxetine) and having no exposure to/no previous experience with at least one of the study drugs (escitalopram, sertraline, or fluoxetine). Participants also reported no health problems, eye problems, or psychoactive drug or alcohol dependence in the preceding 6 months. Data presented are part of a larger clinical trial comparing antidepressant pharmacotherapy to CT (clinicaltrials.gov identifier NCT00787501). After receiving a complete explanation of the study procedures, all participants provided written informed consent to participate, as obtained according to the Declaration of Helsinki and approved by the University of Pittsburgh IRB.

2.2. Clinical protocol

In the context of the ongoing preference trial of SSRI and CT treatment for depression, we made the number of pharmacotherapy sessions equivalent to the CT group (per Beck et al., 1979) – 16–20 sessions over 12 weeks. Pharmacotherapy sessions were 30–45 min in length and were conducted by a psychiatric nurse who inquired about general mood status, did a HDRS assessment, and provided psychoeducation about medication effects and adverse effects. A psychiatrist consulted with the nurse and patient for the final 5–10 min of the session. Symptoms, adverse effects, and treatment progress were reviewed with the psychiatrist using the Frequency and Intensity of Burden of Side Effects Rating scale (FIBSR; Wisniewski et al., 2006) and treatment recommendations were made. Pharmacotherapy was titrated to as close to an escitalopram-equivalent target dose as was tolerated. Subjects were offered either escitalopram (N = 12; target = 20 mg, max dose M = 19.33 mg, SD = 4.58 mg), sertraline (N = 3, target = 125 mg, max dose M = 125.00 mg, SD = 28.87 mg), or fluoxetine (N = 2, target = 30 mg, max dose M = 27.50 mg, SD = 9.57 mg) depending upon their past treatment history. No psychotherapy or supportive counseling was provided. The discussion of subject's thoughts, feelings, and/or behaviors by the pharmacotherapy team was forbidden.

2.3. Clinical response

Our primary outcome measure was the 24-item Hamilton Ratings Scale for Depression (HDRS). Standard definitions of response (50% reduction in the initial HDRS score) and remission (HDRS score $<$ 7) were employed (Nierenberg and DeCecco, 2001). Clinical outcome was operationalized using residual severity, calculated as the residuals of post-treatment scores regressed on pre-treatment scores.

2.4. Personal relevance rating task

As in our previous publications (Siegle et al., 2006, 2007), in 60 slow-event related trials, participants viewed a fixation cue (1 s; row of Xs with prongs around the center X) followed by a positive, a negative, or a neutral word (200 ms; only negative and positive words analyzed herein), followed by a mask (row of Xs; 10.8 s). Participants pushed a

Table 1
Demographic and Clinical Characteristics.

	N	% Female	% Caucasian	% Receiving escitalopram	Age	HDRS-Pre	HDRS-Post
Responders	11	82%	73%	73%	34.8 (9)	15.2 (4.1)*	3.6 (2.1)^
Non-Responders	6	83%	83%	67%	31.5 (9)	18 (2.3)*	13.8 (5.9)
Healthy Controls	20	78%	80%	–	33.7 (10)	1.1 (1.6)	1.4 (2.09)^

Numbers in parentheses indicate one standard deviation of the mean. * indicates a significant difference from the healthy controls at $p < 0.05$. ^ indicates a significant difference from the non-responders at $p < 0.05$.
HDRS = Hamilton Rating Scale for Depression.

button to indicate whether the word was relevant, somewhat relevant, or not relevant to them or their lives (button orders balanced across participants), as quickly and accurately as they could. To maximize chances of affective reactivity, half of the words were normed to be affectively intense for most people, and half were idiosyncratically generated by the participant. For the current analyses, we were interested in personally relevant ecologically valid information processing, thus, analyses in this manuscript focus primarily on the idiosyncratically generated words. To obtain these personally relevant stimuli, participants were asked to generate words between three and 11 letters long prior to testing. Participants were instructed to generate "10 personally relevant negative words that best represent what you think about when you are upset, down, or depressed," as well as "10 personally relevant positive words that best represent what you think about when you are happy or in a good mood," and "10 personally relevant neutral (i.e., not positive or negative) words that best represent what you think about when you are neither very happy nor very upset, down, or depressed" (Siegle et al., 2003).

2.5. fMRI acquisition and processing

fMRI scans were acquired at pretreatment and after 12 weeks of SSRI treatment. Data were collected between 2008 and 2012 on the same scanner with the same protocol, and were preprocessed at that time using the technology proposed in the grant which funded that work (NIMH MH074807; Pittsburgh Foundation, Emmerling Fund M2007-0114). Twenty-nine 3.2 mm slices were acquired parallel to the anterior commissure–posterior commissure line using a posterior to anterior echoplanar imaging pulse sequence to minimize susceptibility artifacts in the amygdala and orbitofrontal regions (3 T Siemens Trio [Siemens Medical Solutions], T2*-weighted images depicting blood oxygenation level–dependent (BOLD) contrast; repetition time, 1500 ms; echo time, 27 ms; field of view, 24 cm; flip angle, 80°), yielding 8 whole-brain images per 12-second trial. Stimuli were displayed in black on a white background via a back-projection screen (0.88° visual angle). Responses were recorded using a data glove (Psychology Software Tools).

Standard preprocessing steps were performed using AFNI, augmented by the NIS suite (NeuroImaging Software; Fissell et al., 2003), and custom Matlab routines, and consisted of slice time correction, motion correction, linear detrending and despiking, voxelwise outlier rescaling, conversion to percent change, temporal smoothing [7-point gaussian filter], 32-parameter nonlinear warping to the Montreal Neurological Institute Colin-27 brain data set, spatial smoothing [6-mm full width half maximum]. To capture sustained activity, the mean fMRI signal 6–10.5 s after presentation of negative and positive words (separately) was computed minus the pre-stimulus baseline for each trial for each participant at pre-intervention and post-intervention. Left and right amygdala regions-of-interest were anatomically defined using the AFNI provided masks, and the percent signal change values extracted for each participant at each time point and valence and entered into a repeated measures ANOVA in SPSS.

Additionally, change scores were calculated for each participant by subtracting the post-intervention values from pre-intervention values. Mean voxelwise condition related responses results were entered into 3dLME (linear mixed-effects modeling analysis; Chen et al., 2013) to conduct an auxiliary analysis examining the group (responder vs. non-responders) × valence (positive vs. negative) interaction on change in whole brain activity. Significance criteria was set $p_{corrected} < 0.05$ (calculated using AFNI's 3dClustSim using the 2016 "acf" autocorrelation function at voxel $p < 0.005$, yielding an empirically detected cluster size > 15 voxels). Percent signal change values for each participant within each significant cluster were extracted and entered into SPSS to determine which group/valence was driving the effect. Percent signal change values within the regions significant in the 3dLME analysis were also extracted for healthy controls and compared to the two patient groups via *t*-test in order to determine what an average healthy person's response was so as to determine whether being similar to the healthy control group was associated with treatment response.

To further examine associations between clinical change and brain activity, the significant percent signal change values associated with the t-tests were entered into a linear regression with residual depression scores as the dependent variable.

3. Results

3.1. Clinical characteristics

Demographic and clinical characteristics for each group are presented in Table 1. For those who completed the study, response, as determined by change in the HDRS was variable but generally decreased (pre-intervention: mean = 16.2, SD = 3.77; post-intervention: mean = 7.22, SD = 6.20; change mean = -8.98, SD = 6.74 [$t(16) = 6.13$, $p < 0.001$, $d = 1.58$]). Initial severity accounted for 29.7% of variance in final severity. Eleven of the 17 participants were designated as responders to the medication and 6 were designated as non-responders. The responders and non-responders did not differ on their pre-intervention HDRS scores ($t(15) = 0.69$, $p = 0.50$, $d = 0.35$) but did differ from each other on the post-intervention scores ($t(15) = 5.26$, $p < 0.01$, $d = 2.30$; Table 1). Of those who responded to the intervention, 10 of the 11 met criteria for remission (defined as HDRS score < 7), and 1 had a final score of 7. Of those who did not respond to the intervention, no participant met criteria for remission. The healthy controls differed from both groups at baseline (ts > 8.5, ps < 0.001, ds > 3.7) and from the non-responders at follow-up ($t(20) = 8.2$, $p < 0.001$, $d = 2.80$) but were not significantly different from the responders at follow-up ($t(25) = 1.7$, $p = 0.12$, $d = 1.05$).

3.2. Amygdala ROI results

Because we did not have a hypothesis regarding laterality of amygdala activation, values were combined to create a single amygdala value for each for each participant at each time-point and valence. A repeated measures ANOVA with the within subject variables of time (pre vs post-intervention) and valence (positive, negative), and the between subjects variable group (responders, non-responders, HCs) showed a significant Time × Valence × Group interaction ($F(2,35) = 5.45$, $p = 0.009$, partial $\eta^2 = 0.24$; Fig. 1; Table 2). Prior to

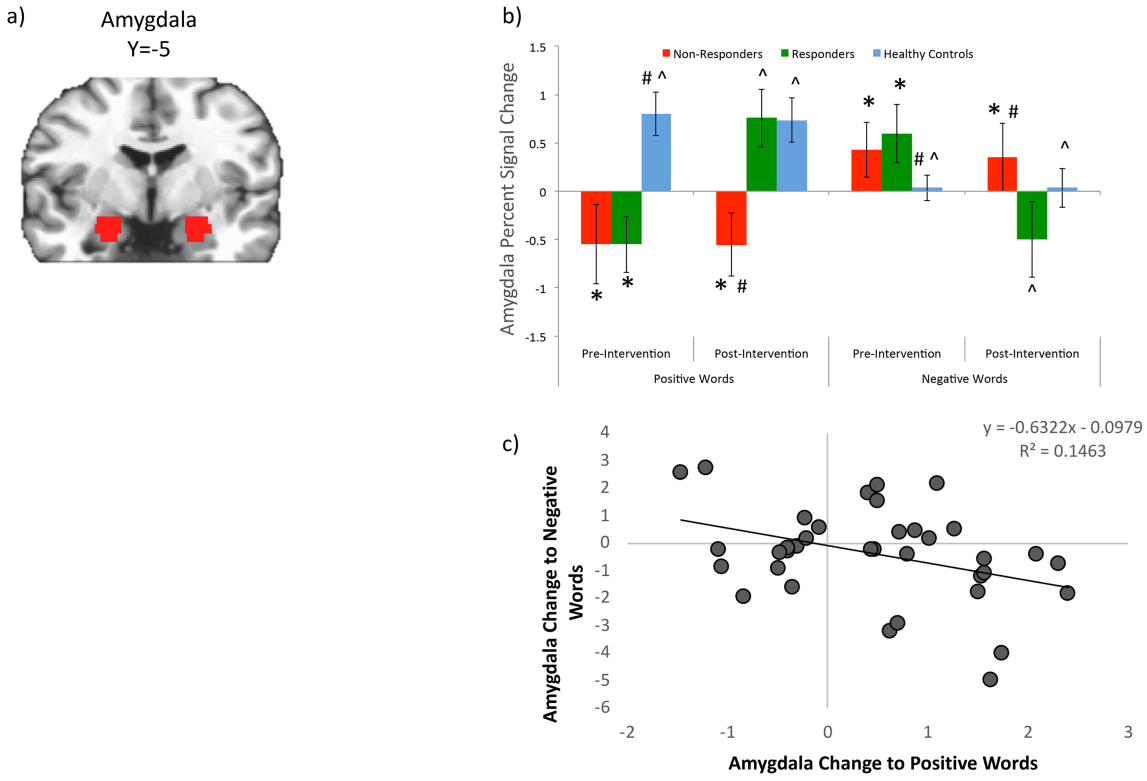

Fig. 1. Group Differences in Pre- and Post-Intervention Amygdala Hemodynamic Activity During Processing of Positive and Negative Self-Referential Cue Words. a) The amygdala mask in AFNI used for the ROI analysis b) amygdala hemodynamic activity to positive and negative words at pre and post intervention for each group c) within the MDD group, correlation between increased amygdala activity to positive words and decreased activity to negative. Error bars indicate ± 1 standard error of the mean.* indicates a significant difference from the healthy controls at $p < 0.05$. ^ indicates a significant difference from the treatment non-responders at $p < 0.05$. # indicates a significant difference from the treatment responders at $p < 0.05$.

the SSRI intervention, responders and non-responders did not differ from each other in amygdala activity to positive or negative words (ts (16) < 0.313, ps > 0.76, ds < 0.16), but differed significantly from the HCs (ts > 2.83, ps < 0.009, ds > 0.91). Patients had increased amygdala activity to negative words and decreased activity to positive words relative to HCs. Supplement S1 suggests that these results were unique to idiosyncratic stimuli and did not replicate for the normed words. Supplement S2 suggests these effects were driven by responses in the left, rather than the right amygdala.

At post-intervention, non-responders had significantly different amygdala activation to both positive and negative words from both the responders and HCs (ts > 6.21, ps < 0.001, ds > 3.1), who no longer differed significantly from each other (ts(30) < 1,03, ps > 0.32, ds < 0.39). Responders and HCs has increased amygdala activity to positive words and decreased activity to negative words relative to non-responders. Paired samples t-tests revealed that while neither the HC nor the non-responders had a significant change in amygdala activity to words of either valence following SSRI intervention (ts < 0.38, ps > 0.71, ds < 0.34), responders had a significant increase in amygdala activity to positive words ($t(10) = 5.15$, $p < 0.001$, $d = 3.2$) and a marginally significant decrease to negative words ($t(10) = 2.19$, $p = 0.051$, $d = 0.93$).

Finally, change in amygdala activity to positive and negative words were correlated ($r = -0.38$, $n = 37$, $p = 0.02$; Fig. 1c), indicating that in those individuals whose amygdala activity increased to positive words, activity also decreased to negative words. Note that the correlation was the same magnitude when just considering the MDD participants, but due to the small sample, this correlation did not reach significance ($r = -0.37$, $n = 17$, $p = 0.14$).

Table 2
Regions that showed a significant Group × Valence interaction in activity change during the processing of personally relevant emotional stimuli.

				Change from Pre to Post Intervention					
				Positive Words			Negative Words		
Area	x,y,z	Cluster Size	F Value	Non-responders	Responders	HC	Non-responders	Responders	HC
Amygdala ROI				−0.004 (0.53)	1.31 (0.25)*	−0.06 (0.16)	−0.08 (0.57)	−1.10 (0.50)*	0 (0.37)
R Parahippocampus	19, −42, −5	27	4.56	0.29 (0.95)	0.99 (0.51)*	0.30 (0.33)	0.08 (0.31)	−1.54 (0.29)*	−0.08 (0.36)
L Thalamus	−10, −14, 7	22	20.1	0.59 (0.42)	−2.06 (0.39)*	0.14 (0.30)	−0.95 (0.77)	−0.09 (0.35)	0.01 (0.36)
L sgACC / BA 25	−1, 18, −19	17	8.82	−0.11 (0.55)	0.93 (0.24)*	0.01 (0.03)	−0.01 (0.08)	0.15 (0.16)	0.07 (0.18)

Abbreviations: BA = Brodmann Area; L = left; R = right; sgACC = subgenual anterior cingulate cortex.
Coordinates correspond to the stereotaxic array of Talairach and Tournoux (1988). Cluster size refers to the number of contiguous voxels for which the voxel t value corresponds to $p_{corrected} < 0.05$. Numbers in parentheses indicate one standard deviation of the mean.
* indicates a significant difference from 0 (indicating no change following the intervention).

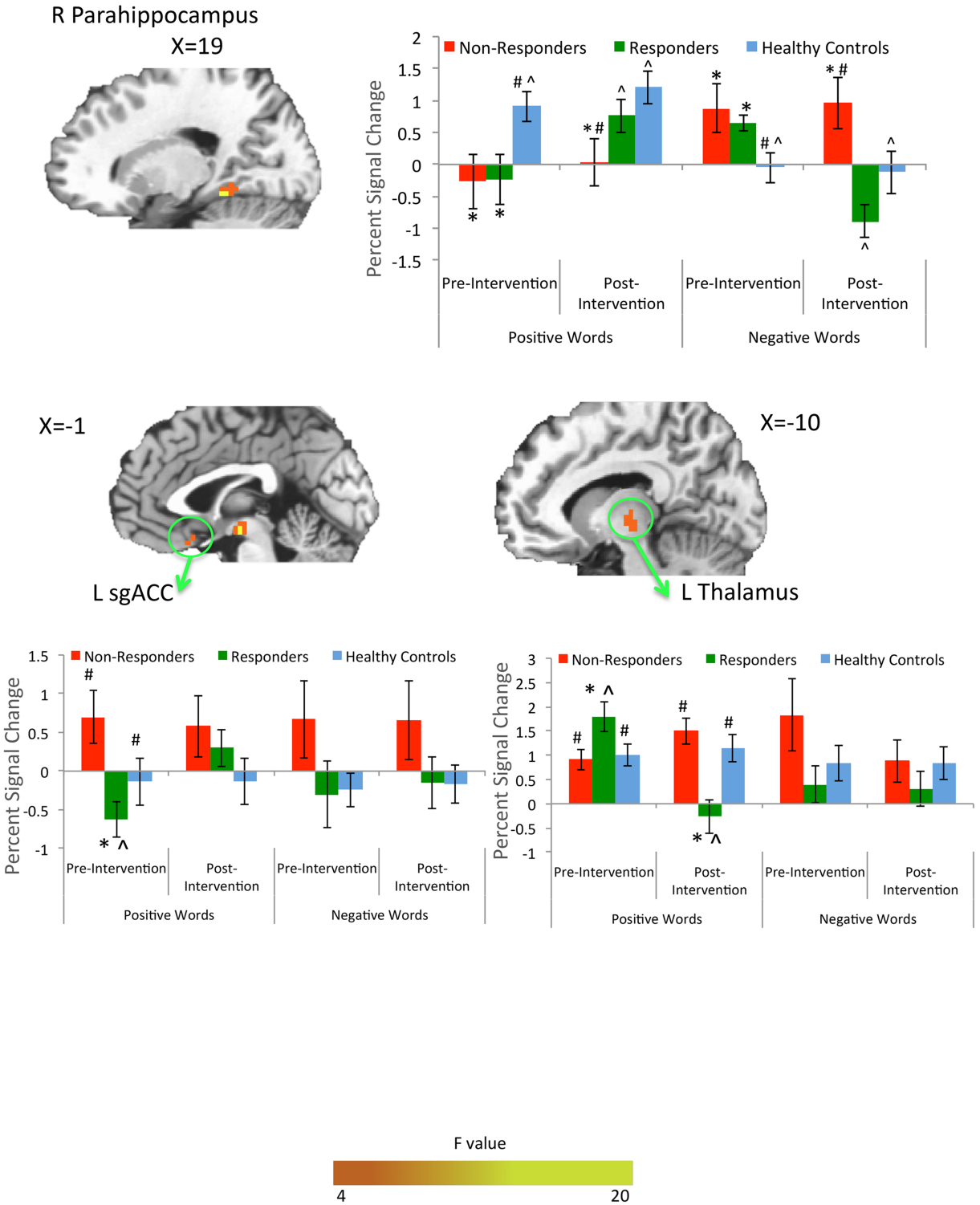

Fig. 2. Group × Valence Interaction in Regional Hemodynamic Activity during Processing of Positive and Negative Self-Referential Cue Words. Regions where the change in hemodynamic activity from pre- to post-intervention distinguished SSRI responders and non-responders during processing self-referential cue words versus baseline ($p_{corrected} < 0.05$). Using the significant clusters in Table 2 as ROIs, percent signal change values were extracted for pre-intervention and post-intervention activity for responders, non-responders, and controls. Error bars indicate ± 1 standard error of the mean. * indicates a significant difference from the healthy controls at $p < 0.05$. ^ indicates a significant difference from the treatment non-responders at $p < 0.05$. # indicates a significant difference from the treatment responders at $p < 0.05$.

3.3. Whole brain analysis

When a broader range of brain regions was analyzed, significant differences associated with treatment response were also revealed, highlighting additional regions of interest that could potentially be used for stratifying patient response to SSRIs. The results of the Group × Valence interaction for change in whole brain activity pre to post-intervention are presented in Table 2 and Fig. 2. In the right parahippocampal gyrus during processing of positive idiosyncratic words, responders had a significant increase in activity following the

intervention relative to both the non-responders and HCs (ts > 2.22, ps < 0.03, ds > 0.80). Both responders and non-responders had decreased activity at baseline relative to HCs (ts > 2.03, ps < 0.05, ds > 0.70), while after the intervention responders' activity was not different from HCs (t(30) = 0.50, p = 0.62, d = 0.20), and both were greater than that seen in the non-responders (ts > 4.11, ps < 0.001, ds > 2.01). The opposite pattern was observed during processing of negative idiosyncratic cue words, with responders showing a significant decrease in activity following the intervention relative to both non-responders and HCs (ts > 3.03, ps < 0.01, ds > 1.56). At baseline, both responders and non-responders had increased activity relative to HCs (ts > 2.13, ps < 0.05, ds > 0.80), while after the intervention responders' activity was not different from HCs (t(30) = 1.63, p = 0.11, d = 0.64), and both were lower than that seen in the non-responders (ts > 3.33, ps < 0.01, ds > 1.60). The change in activity to both positive and negative words was significant for the responders (ts(11) > 5.31, ps < 0.001, ds > 2.23), but not for the HCs or non-responders ts < 0.90, ps > 0.38, ds < 0.26).

Change in activity with treatment in the thalamus also showed a group × valence interaction. During processing of positive idiosyncratic words, responders had a significant decrease in thalamic activity following the intervention (t(11) = 5.35, p < 0.001, d = 1.55) that was greater than that seen in either the non-responders or HCs (ts > 4.26, ps < 0.004, ds > 2.24). Neither the non-responders (t(5) = 1.42, p = 0.22, d = 0.14) nor the HCs (t(19) = 0.45, p = 0.66, d = 0.09) had a significant change in thalamic activity to positive words. At baseline, responders had higher thalamic activity to positive words than both the non-responders and the HCs (ts > 2.18, ps < 0.04, ds > 0.74), while the non-responders and HCs did not differ from each other (t(24) = 0.22, p = 0.83, d = 0.39). At post-treatment HCs and non-responders still did not differ from each other in thalamic activity (t(24) = 0.66, p = 0.51, d = 0.35), while the responders had significantly less activity than both groups (ts > 3.07, ps < 0.005, ds > 1.13). During processing of negative idiosyncratic words, no group showed a significant change in activity (ts < 1.23, ps > 0.27, ds < 0.50), nor were there any significant group differences in thalamic activity at baseline or follow-up (ts < 1.66, ps > 0.11, ds < 0.63).

Finally, activity in the left subgenual anterior cingulate cortex (sgACC) during processing of positive words increased significantly in the responders (t(11) = 3.86, p = 0.003, d = 1.12) but did not significantly change in the non-responders(t(5) = 0.66, p = 0.52, d = 0.32) or HCs (t(19) = 0.04, p = 0.97, d = 0.01). The change in responders' sgACC activity during positive processing was significantly greater than that observed in the non-responders or HCs (ts > 2.19, ps < 0.03, ds > 0.75). At baseline, responders had decreased activity relative to both the non-responders and HCs (ts > 2.01, ps < 0.05, ds > 1.48), who did not differ significantly from each other (t(24) = 0.96, p = 0.35, d = 0.50). At follow-up, groups did not differ from each other (ts < 1.82, ps > 0.09, ds < 0.64). During processing of negative idiosyncratic words, no group showed a significant change in activity (ts < 0.33, ps > 0.75, ds < 0.10), nor were there any significant group differences in sgACC activity at baseline or follow-up (ts < 1.38, ps > 0.19, ds < 0.61).

3.4. Association with clinical change

A linear regression was performed using residual HDRS scores as the dependent variable and regional hemodynamic change for positive and negative cues from the amygdala and Table 2 as the predictor variables. The change in the amygdala to positive stimuli was significant in the model (Fig. 3a; Table 3), as was the change in the parahippocampal gyrus to negative stimuli (Fig. 3b; Table 3). No other regional changes significantly explained variance in residual HDRS scores (Table 3). The adjusted R^2 for this model = 0.71 and the model was significant (F(8,17) = 6.30, p = 0.006).

4. Discussion

The results of the current study are consistent with the emerging literature that in those who respond to them, SSRI medications normalize amygdala reactivity by increasing responses to personally relevant positive emotional stimuli (Godlewska et al., 2016; Victor et al., 2010) and decreasing responses to negative stimuli (Godlewska et al., 2012), rather than dampening reactions more generally. Previously, we have also found that, directly targeting the amygdala hemodynamic response via real-time fMRI neurofeedback training to increase activity during positive autobiographical memory resulted in significant clinical improvements in patients with MDD (Young et al., 2017). The finding that SSRI non-responders did not have a detectable change in amygdala activity, though the responders did, supports a role for the amygdala response to emotional stimuli in recovery from MDD as did our finding that the change in amygdala activity to positive words explained significant variance in the treatment response. To the extent that these results replicate, targeting amygdala responses to positive information directly, e.g., via amygdala real-time neurofeedback, could share similar mechanisms to SSRIs, while offering a lower side effect profile for neurofeedback relative to pharmacotherapy (Hawkinson et al., 2012) and may be useful to consider as a second-line intervention or to augment SSRI treatment in those who only partially respond. Whether the same or different people would respond to each of these types of intervention would be useful to consider in future studies in helping to plan for mechanistically targeted moderator-informed precision treatment prescription.

The observed normalization of amygdala activity following SSRI intervention, rather than a non-specific dampening is in contrast with the traditionally accepted mechanism of action for SSRI antidepressants which focuses on 5-HT_{1A} receptors that hyperpolarize the membrane and decrease neuronal excitability (Gross et al., 2000). The fact that there was a significant correlation between increased amygdala activity to positive stimuli and decreased activity to negative supports the assertion that individuals are regulating their amygdala activity in an adaptive manner following SSRI treatment. Explanations for this change would likely be more nuanced, e.g., due to SSRI-associated changes in BDNF. SSRI medications have the downstream effect of stimulating the cAMP cascade, leading to an increase in CREB and BDNF and ultimately neurogenesis and synaptic plasticity (Duman et al., 2001). As neuroplasticity is associated with the ability of neuronal systems to incorporate and adapt to environmental stimuli and make adaptive responses (Harmer et al., 2017), it may explain how amygdala activity is normalized in SSRI treatment responders. The observation that amygdala activity is not generally dampened by SSRI treatment may be particularly important as our data (Fig. 1b) observe relative deactivations of the amygdala to positive information at baseline. This observation is consistent with our previous studies, which have reported decreased BOLD activity in the amygdala, compared to rest, in depressed participants as they recall positive autobiographical memories (Young et al., 2016, 2017), and others have reported relatively decreased amygdala BOLD responses to negative faces following administration of escitalopram (Godlewska et al., 2012).

An auxiliary whole brain analysis revealed several other regions that changed significantly with treatment response. Consistent with a role of the peri-amygdaloid complex in recovery from MDD (Schaefer et al., 2006), activity in the parahippocampus increased to positive and decreased to negative idiosyncratic words, and did not change in the non-responders or HCs. Activity in the thalamus significantly decreased in response to positive idiosyncratic cues in the responders. Given the role of the thalamus as a relay station directing sensory information to cortical regions (Gazzaniga et al., 2014), the reduced activity in the responders following intervention may reflect decreased effort needed to relay positive information. Finally, we found increased sgACC activity while processing personally relevant positive words following the intervention only in the responders group. This region is commonly

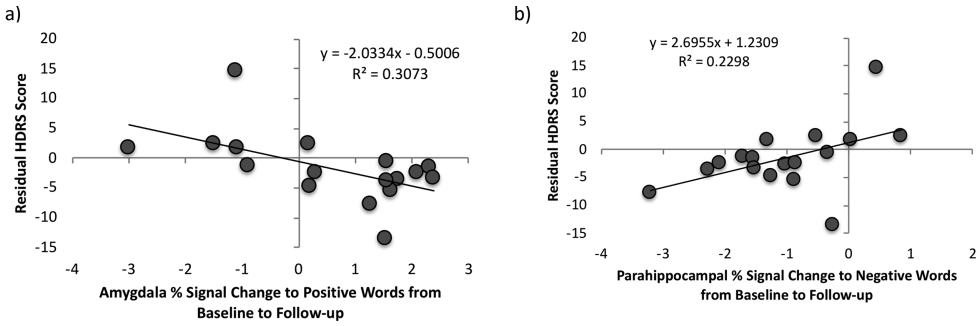

Fig. 3. Correlation between Hemodynamic Activity Change and Residual Symptoms. Correlation between residual HDRS scores at post-intervention and the change in hemodynamic activity in the a) amygdala response to positive stimuli and b) parahippocampal gyrus response to negative stimuli.

Table 3
Results of the Regression Analysis Predicting Residual HDRS Scores from Regional Brain Changes Following Treatment.

Region	β	t	p value
Positive Self-Referential Words			
Amygdala	−3.36	3.99	0.003*
Parahippocampus	−1.61	1.68	0.13
Thalamus	0.78	0.85	0.42
Subgenual Anterior Cingulate	−1.91	1.7	0.12
Negative Self-Referential Words			
Amygdala	0.21	0.28	0.79
Parahippocampus	2.57	3.05	0.01*
Thalamus	1.99	1.69	0.13
Subgenual Anterior Cingulate	−0.84	1.02	0.33

* indicates a significant relationship between the change in hemodynamic activity and residual depression scores.

activated in neuroimaging studies focused on self-referential processing (Northoff et al., 2006), and has been implicated in reward and pleasure, as reduced sgACC activity is associated with decreased stimulation of dopamine release resulting in anhedonia, apathy, and absence of behavioral incentive (Drevets et al., 1998, 1997, 2008). The increased activity in the responders following intervention suggests that SSRIs work by increasing the affective value of self-relevance of positive stimuli. Overall, these nonamygdala regions changed primarily to positive stimuli, and may be considered important for recovery from MDD upon replication.

Several limitations of the present study merit comment. Our sample size was small, especially with respect to treatment non-responders. However, large effect sizes were observed in a single a priori region, suggesting some level of interest, particularly if they are replicated in a larger sample. The strong response rate could reflect that the design was atypical for psychopharmacology; participants were seen biweekly at first and then weekly. This visit schedule is consistent with psychotherapy studies and was instituted as the trial was done in a clinic that was running concurrent psychotherapy research so all participants were seen on the same schedule. This visit frequency could have affected the types of observed change and associated predictors. The strong response rate could also be accounted for by nonspecific effects which have shown an average of HDRS point improvement per follow-up visit (Posternak and Zimmerman, 2007). Despite accounting for all of the medication and non-specific effects, amygdala reactivity differentiated individuals who did and did not respond, suggesting the robustness of our finding. Our follow-up period was also relatively short. Future studies would benefit from including longer-term outcome data to determine if there is a sustained benefit in the responder group associated with a particular pattern of amygdala activation.

In conclusion, data are consistent with the hypothesis that for those who respond, SSRIs normalize amygdala reactivity during emotional processing of self-referential stimuli. Activity in the amygdala significantly changed in responders but did not change in non-responders suggesting SSRIs work via normalization of the amygdala response to emotional stimuli. For those who do not respond to SSRIs it may be that the drugs blunt, or at least, do not increase amygdala reactivity. Interventions that directly target these regions but are free from the side-effects typically observed with SSRIs, such as real-time neurofeedback, may therefore be effective treatments for MDD.

Author contributions

KY was involved in data analysis and manuscript preparation; EF was involved in the study design, data collection, and interpretation of results; AC and SB were involved in study design and data collection; JF was involved in data management and analysis; AH was involved with study design, data collection, and data analysis; MT was involved in the study design and manuscript preparation; GS was involved with study design, data collection and analysis, interpretation and manuscript preparation.

Funding

This work was supported by the National Institutes of Health/ National Institute of Mental Health under award number NIMH MH074807 and through the Pittsburgh Foundation, Emmerling Fund under award number M2007-0114. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Conflict of interest

Michael Thase has no conflicts of interest to disclose pertaining to this research. Dating back to 1984, he has had a number of relationships with companies that develop and/or market medications for treatment of mental disorders; these relationships include consulting, advising and - prior to 2010 - being a member of speaker's bureaus. Since 1987 he has been the principal investigator of research grants awarded to his universities from the companies manufacturing essentially every novel medication being developed for treatment of depressions, anxiety disorders or bipolar disorder. The other authors have no financial conflicts of interest or disclosures to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102388.

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