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Erin McClure
Georgia State, etone@gsu.edu

Abby Adler
National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services

Christopher Monk
University of Michigan - Ann Arbor

Jennifer Cameron
National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services

Samantha Smith
National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services

See next page for additional authors

RUNNING HEAD: FMRI PREDICTORS

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Erin B. McClure*[1]; Abby Adler[2]; Christopher S. Monk[3]; Jennifer Cameron[4]; Samantha Smith[4]; Eric E. Nelson[2]; Ellen Leibenluft[5]; Monique Ernst[2]; Daniel S. Pine[2]

[1]Department of Psychology, Georgia State University

[2]Emotional Development and Affective Neuroscience Branch, Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services

[3]Department of Psychology and the Center for Human Growth and Development, University of Michigan at Ann Arbor

[4]Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services

[5]Unit on Affective Disorders, Pediatrics and Developmental Neuropsychiatry Branch, Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services

*Correspondence to: Erin B. McClure; Department of Psychology; Georgia State University; P.O. Box 5010, Atlanta, Georgia, 30302-5010; emcclure@gsu.edu.

Abstract

A growing number of studies have found evidence that anxiety and depressive disorders are associated with atypical amygdala hyperactivation, which decreases with effective treatment. Interest has emerged in this phenomenon as a possible biological marker for individuals who are likely to benefit from tailored treatment approaches. The present study was designed to examine relationships between pre-treatment amygdala activity and treatment response in a sample of anxious children and adolescents. Participants, who were diagnosed predominantly with Generalized Anxiety Disorder (GAD), underwent functional magnetic resonance imaging (fMRI) scanning prior to treatment with fluoxetine or cognitive behavioral therapy (CBT). Results indicated significant negative associations between degree of left amygdala activation and measures of post-treatment symptom improvement in the group as a whole. Taken together with research on associations between adult amygdala activation and treatment response, these findings suggest that patients whose pre-treatment amygdala activity is the strongest may be particularly likely to respond well to such widely used treatments as selective serotonin reuptake inhibitor (SSRI) medications and CBT.

Recent years have seen an intense research focus on the amygdala as a potential neural substrate of various mood and anxiety disorders. This attention stems from convergent findings in the neuroscience literature that the amygdala plays a prominent role in processing emotional cues (1). Given the atypical emotional responses of individuals with anxious or depressive disorders, researchers have hypothesized that anomalies in neural structures involved in perceiving, evaluating, and responding to emotional stimuli may characterize these patient groups. Consistent with this hypothesis, accumulating evidence associates aberrant amygdala function, typically enhanced activity, with anxiety disorders and major depressive disorder (MDD) (2-6).

In adults, amplified amygdala responses to salient emotional cues have been demonstrated in patients with social anxiety disorder (3, 7), post-traumatic stress disorder (PTSD) (2, 4), and specific phobias (5), as well as MDD (8-10). A smaller body of research in adolescents with mood and anxiety disorders has generated similar evidence of atypical amygdala responsiveness (6, 11-13), mostly hyperactivity. One study, however, found hypoactivity in a small sample of depressed females (6). Limited research has focused on youth with specific anxiety disorders; however, in a larger study comparing amygdala responses between patients with GAD and healthy peers (14), we found compelling evidence of a distinctive pattern of elevated amygdala activity in youth with GAD when their attention was constrained to their own internal emotional states.

Effective treatments appear to alter these atypical patterns, in that they produce significant decreases in amygdala activity in anxious and MDD adults, as do pharmacological challenges in healthy adults (3, 8, 9, 15-18). Studies of adults have found decreases in amygdala activation to relate to successful treatment of MDD (8, 9) and social phobia (3, 16, 17). Whereas

some studies have found decreased activation to be limited to the left amygdala (8), others have obtained evidence of bilateral decreases in activation in this region (9, 16). Whether comparable treatment-related changes are evident in youth remains unclear due to a dearth of studies examining neural correlates of therapeutic response in children and adolescents.

These findings have spurred interest in pre-treatment amygdala hyperactivation as a potential marker of symptomatology likely to diminish with treatment. Such work is important in that it might ultimately allow measures of amygdala function to be used as predictors of treatment. One recent study of adult MDD, for example, found significant associations between magnitude of treatment response and pre-treatment amygdala activation during the processing of emotional information (10). Specifically, enhanced pre-treatment reactivity in the right amygdala predicted a better response to cognitive behavioral psychotherapy (CBT). It remains unclear whether a similar association is apparent in individuals with anxiety disorders or in individual receiving psychotherapeutic treatments besides CBT.

The overwhelming majority of research on amygdala activity and psychopathology has been performed in adults. In particular, no study in youth has examined associations between amygdala activity and response to treatment. Such work is important in mood and anxiety disorders, given emerging data on amygdala function in these conditions (6, 12), coupled with questions surrounding therapeutics. For instance, it is unclear why youth show a different pattern of responses to antidepressant medications, including a possible increased risk of suicidal ideation, than adults (19). Similar questions have emerged about CBT, as one recent study in adolescent MDD found that CBT alone showed no advantage over pill-placebo, but CBT was helpful when combined with fluoxetine (20).

Heterogeneous treatment response patterns have emerged in pediatric research. Some patients exhibit robust treatment responses, whereas others respond more poorly, perhaps reflecting pathophysiological heterogeneity (21-23). However, it is difficult to distinguish between responders and non-responders prior to treatment; in particular, clinical measures have fared poorly as strong, consistent predictors of treatment response. If pre-treatment measures of amygdala activity could be shown to predict patient outcomes, such measures might provide novel insights into mechanisms underlying heterogeneous treatment responses.

This study examines associations between pre-treatment amygdala activation and treatment response in pediatric anxiety disorders, in a sample predominantly diagnosed with Generalized Anxiety Disorder (GAD). We tested the hypothesis that enhanced pre-treatment amygdala activity predicts a better treatment response. This hypothesis is based on the premise that amygdala activation is one substrate on which CBT and selective serotonin reuptake inhibitor (SSRI) medications act. Thus, treatment response is predicted to relate significantly to degree of pre-treatment amygdala activation; individuals who show less activity are presumed to suffer from anxious symptoms stemming from a different neural basis than those with higher levels of activation. This hypothesis receives support from work in adults, where pre-treatment amygdala hyperactivation predicts response to CBT (10).

Method

Subjects. Fifteen children and adolescents with DSM-IV anxiety disorder diagnoses (7 female; 11.7± 2.0 years) were recruited from the local community to participate in a study at the National Institute of Mental Health (NIMH). Post-treatment clinical data were not available for 3 of these adolescents, who were excluded from analyses. Demographic data for the 12 participants with complete data, as well as for those who were excluded, are presented in Table 1. During a

screening visit, each participant completed the Wechsler Abbreviated Scales of Intelligence (WASI) (24) and a battery of behavioral tasks, all administered by trained research technicians. Additionally, either a psychologist or psychiatrist assessed each participant with the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (25). The majority (n=9) received current diagnoses of GAD; three participants received primary diagnoses of social phobia. For three subjects, while symptoms of GAD were present, they were less severe or impairing than symptoms of social phobia.

Current severity was rated by trained clinicians (psychologists and psychiatrists) using the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) scales (26). The CGI-S generates severity ratings along a seven-point scale, where 1 indicates normal functioning and 7 indicates extreme illness. The CGI-I, which scores participants along an eight-point scale from 1 (completely recovered) to 8 (much worse), was also used to assess participants' improvement during treatment. Ratings were completed at baseline, four weeks, and at the end of treatment. All patients had been free of psychotropic medication for at least one year.

After three weeks of screening and supportive therapy, participants were acclimated to the MRI environment in a mock scanner and then underwent the pre-treatment fMRI scan. They were then enrolled in eight weeks of treatment consisting of either fluoxetine (n=5) or CBT (n=7). Choice of treatments was based on preference of the families. For patients in the fluoxetine condition, medication was started at 5 mg and increased every two weeks as recommended by a clinician to a maximum of 40 mg by week four. Dosage increases were based on both symptoms and side effects, using procedures from the RUPP Anxiety Study. The remaining participants met with a licensed clinical psychologist for weekly CBT. Each session lasted approximately 60-90 minutes and focused on exposure and skills training, using methods

outlined in the Social Effectiveness Therapy for Children (SET-C) manual developed by Beidel and colleagues (27) and other manualized treatments (28). Participants underwent post-treatment MRI scanning in the week after treatment ended. The study was approved by the NIMH Institutional Review Board and all participants/parents provided written informed assent/consent.

fMRI Task. The face-attention paradigm, described in detail in prior publications (29, 30), requires participants to view a randomly ordered series of 32 standardized grayscale evocative faces (eight stimuli representing each of four emotions: afraid, happy, neutral, angry) drawn from three widely used stimulus sets (31-33). Each face is viewed repeatedly, once during each of four epochs that alternate in randomized order. During three epochs, participants adopt different attention states, each of which directs them to make a specified rating ("How afraid are you?", "How hostile is the face?", "How wide is the nose?") of each face stimulus. During the fourth epoch, subjects passively view stimuli. Stimuli are presented through Avotec Silent Vision Glasses (Stuart, FL). Rating and response time for each trial are recorded using a 5-key MRI-compatible glove device (MRI Devices, Waukesha, WI).

The task uses a rapid-event-related-mixed/hybrid design, in which 32 4000 msec "blank" trials or "null-events" are interspersed among stimulus trials. This design ensures that each stimulus appears at a randomly varying point within the hemodynamic response function (HRF).

The task is presented in one 160-trial run (14-minutes, 42-seconds). During this run, the four epochs/rating blocks (each of which comprises 10 randomly-ordered 4000 msec events—eight face and 2 "null event" trials—preceded by a 3000 msec instruction screen) alternate. Participants rate the stimuli during the 4000 ms period when faces are displayed. Each event is followed by an inter-trial interval varying in duration from 750-1250 ms.

Subjects participating in this study had also participated in a larger study comparing amygdala responses between patients with GAD and matched healthy adolescents (14). This larger study showed that patients with GAD exhibited a pattern of amygdala hyperactivity that was most pronounced during the contrast of fearful-face-viewing events with happy-face-viewing events, when both are viewed in the "*How afraid*?" attention state. All subjects in the current study had participated in this previous study. Given that this contrast most robustly and precisely differentiated anxiety patients from healthy youth in the prior study (14), the analyses for the current report focus only on the degree to which amygdala activation within this contrast predicts treatment response.

Procedures. We gathered functional MRI data on a 3-Tesla GE-scanner using echo-planar single shot gradient echo T2* imaging (axial plane, 23 slices) after sagittal localization and manual shimming (64x64 matrix; TR=2000 ms, TE=40 ms, FOV=240 mm; 3.75 x 3.75 x 5 mm voxels). We acquired images in 23 contiguous slices parallel to the AC-PC line. We also acquired high-resolution T1 weighted anatomical images to aid with spatial normalization (180 1-mm axial slices, FOV=256, NEX=1, TR=11.4 ms, TE=4.4 ms, matrix=256x256, TI=300 ms, bandwidth=130 Hz/pixel, 33 kHz/256 pixels).

fMRI pre-processing. For all participants, movement was < 1 voxel in any plane. We conducted analyses with SPM software (SPM99, Wellcome Department of Neurology) and Matlab 5.3 routines. We corrected functional data for slice timing and motion, co-registered them to the anatomical data, spatially normalized and re-sliced them. After pre-processing, we evaluated the quality of the normalization procedure via visual inspection of fMRI images.

Data Analysis: We estimated event-related response amplitudes at the individual participant level for each event type (angry, fearful, happy, neutral faces) in each attention state

(how afraid, how wide is the nose, how hostile is the face, passive viewing) using the General Linear Model (GLM). The waveform for each event-related response was a rectangular pulse (4s duration) convolved with the HRF specified by SPM99. For analysis of amygdala activation, we calculated separate mean contrast values for the entire volume of each participant's left amygdala and right amygdala using unsmoothed data for the fear vs. happy comparison within the "How afraid are you?" attention state. This approach circumvented potential problems with partial volume effects that can arise when smoothed data are used, as is required for the standard small volume correction approach. Such problems are particularly likely to affect small neural structures such as the amygdala, which are vulnerable to susceptibility artifacts. The amygdala ROIs were drawn from the MNI template and individual subject brains were normalized to the MNI brain (34).

Statistical Tests: We used Bonferroni corrected Spearman correlations to examine associations between pre-treatment relative amygdala activation in the afraid-fear vs. afraid-happy contrast and both post-treatment CGI-I scores and CGI-S change scores between pre- and post-treatment assessments. Additionally, we conducted linear regression analyses, with CGI-S post-treatment score as the outcome variable, amygdala activation as the predictor variable, and CGI-S pre-treatment score as a covariate to control for differences in pre-treatment symptom severity.

Results

Neither amygdala activation nor CGI-S or CGI-I scores were significantly associated with age or sex (all p's > .025); therefore, demographic variables were not included as covariates in further analyses.

Overall, participants showed significant improvement with treatment; paired samples t-tests showed significant differences between pre-treatment and post-treatment CGI-S scores,

t(11)=5.348, p < .001 (see Figure 1), with a mean CGI-I score of 2.33 (SD=1.23). Pre-treatment CGI-S score was not significantly associated with activation during the afraid-fear vs. afraid-happy contrast in either the left amygdala, r=.17, p=.59, or the right amygdala, r=.04, p=.90. Spearman correlations, however, yielded evidence of significant associations between pre-treatment amygdala activation and measures of both post-treatment symptom severity and clinical improvement. Specifically, we found a significant negative association between activation in the left amygdala in the afraid-fear vs. afraid-happy contrast and post-treatment CGI-I score, $\rho = -.65$, $p<.02$. A non-significant trend for association was evident between left amygdala activation in this contrast and CGI-S score, $\rho = -.61$, $p<.04$ (see Figures 2a and 2b). Associations were not statistically significant between activation in the right amygdala in the afraid-fear vs. afraid-happy contrast and either post-treatment CGI-S score, Spearman r=-.27, p=.41, or CGI-I score, $\rho = -.10$, p=.75.

Regression analyses with pre-treatment CGI-S score included as a covariate yielded comparable findings. Left amygdala activation in the afraid-fear vs. afraid-happy contrast significantly predicted post-treatment CGI-S scores, Beta = -,61, R^2 Change = .36, F Change (1,9)= 5.09, p=.05. Right amygdala activation in the same contrast, however, did not significantly predict CGI-S score at post-treatment, Beta = -,04, R^2 Change = .001, F Change (1,9)= .01, p=.91.

Discussion

Results of the present study indicate that better responses to medication or CBT treatment were associated with greater pre-treatment activation in the left amygdala during pediatric anxiety disorder patients' attention to their own internal, emotional responses to fearful faces compared to happy faces. Associations were strongest when improvement between screening and

Week 8 of treatment served as the measure of treatment response; however, analyses focused on post-treatment symptom severity also approached significance. In contrast, pre-treatment symptom severity was not significantly associated with activation in either the right or left amygdala. These findings suggest that fluoxetine or CBT treatment may be most effective for youth who show a pattern of amplified amygdala reactivity while attending to their internal responses to emotionally salient cues.

The absence of significant associations between pre-treatment symptom severity and amygdala activation is consistent with some prior research; however, findings in this area are highly inconsistent. The few adult studies that have examined correlations between amygdala activity and anxiety severity have yielded mixed findings, with some showing evidence of significant positive relationships (35) and others demonstrating non-significant associations between the two (36). Two recent studies found amygdala activation to relate to one, but not a second, measure of anxious symptoms Similar inconsistency is evident in studies of youth; whereas some recent research in a clinical adolescent sample yielded no evidence of a relationship between symptom severity and amygdala activation (37), findings in another study focused on a healthy sample point to a linear association (11). Patterns of correlation appear to vary depending on a number of factors, including the sample under study and the task used to elicit amygdala activation; clearly further study that carefully controls such factors is needed to elucidate the relationship between pre-treatment symptomatology and amygdala activation.

The present findings are necessarily preliminary, given the limitations of the current study. In particular, our sample was small and heterogeneous with regard to both age (8-16 years) and diagnosis, which increases the risk of Type II error by reducing statistical power. However, in the present study we obtained positive findings, which suggests that power was

adequate, despite the small sample size. Replication in a larger, homogeneous group of pediatric patients is clearly warranted; the present data could serve as a useful basis for hypothesis generation in such research.

It is of note that post hoc analyses revealed no significant associations between age and either amygdala activation or treatment response, which suggests that effects may be similar across developmental periods during youth. Power to detect such diffs is limited in small sample Additionally, the number of participants in each treatment condition was too small to permit comparison of patterns of association across the two. Future studies should include an adequate sample size to permit separate examination of effects for different treatment modalities or placebo control; this will be critical to determine whether amygdala reactivity is more strongly associated with response to any particular therapeutic approach or if it relates instead to a natural course of remission, regardless of treatment. Furthermore, we did not include post-treatment MRI scan data, which would be necessary to show that amygdala activation decreased in treatment responders. Such data would address a related but conceptually different question than the one addressed here, concerning the relationship between pre-treatment fMRI response and treatment prediction. The current study is designed to consider the possible utility of fMRI measures as predictors of treatment success. Finally, because we did not include a placebo-control group, it is unclear whether amygdala activation is associated with treatment response per se or with symptom improvement, which could occur in the absence of treatment.

Despite the preliminary nature of the present findings, they are broadly consistent with the results of comparable research in adults. In particular, one very recent study provided compelling evidence that pre-treatment amygdala reactivity may effectively predict adult response to CBT for MDD (10). In this study, Siegle and colleagues found that right amygdala

reactivity to negative verbal stimuli prior to treatment was significantly associated with strength of response to treatment with CBT in MDD patients. The present study obtained similar findings in a sample of anxious youth diagnosed predominantly with GAD, such that pre-treatment left amygdala activation to negative visual cues, particularly during attention to one's own emotional response to those cues, related significantly to magnitude of improvement across the treatment period.

These two studies differ in several notable ways. First, the patients in the present study were undergoing either medication or cognitive behavioral treatment for anxiety disorders, predominantly GAD; those in the Siegle et al. study were exclusively undergoing CBT for MDD. Second, whereas the adult study required participants to attend to negative verbal stimuli during fMRI scans, the present study directed participants' attention to their internal responses to emotional faces. These key differences may contribute to the disparity between studies in laterality of amygdala responses that predicted treatment outcome. In particular, a growing number of studies indicates that attentional factors exert considerable influence over patterns of amygdala activation add katie (14, 30, 38, 39). Future research using comparable paradigms in both adult and child patient samples will be useful for clarifying whether the differences in laterality of activation associated with outcome reflect methodological inconsistencies between studies, differences in diagnostic status of participating patients, or developmental differences in the neural substrates of varied psychopathologies.

Despite their differences, if the present study and Siegle and colleagues' groundbreaking work are taken together, they suggest that amygdala hyperactivity may be a pathological feature associated with an array of mood and anxiety disorders. Further, they raise the possibility that such hyperactivity could serve as one means by which to identify subgroups of patients who are

likely to respond well to standard treatments. Identification of such a biological marker of treatment response among pediatric patients would advance the field dramatically. As recent reviews have concluded, randomized controlled trials indicate that current treatments are effective for only a subset of youth with anxiety and mood disorders (40, 41). Although symptom severity and the presence of comorbid disorders sometimes predict poorer outcomes (23), this is not always the case. Biological characteristics offer a possible alternative means of identifying likely responders; research indicates, for instance, that tendencies to preferentially process dichotic auditory stimuli using the left hemisphere may relate to better treatment response among adults (42-44). The present findings, along with those of Siegle and colleagues (10), suggest that amygdala hyperactivation could serve a similar function.

It is important to note, however, that even if further research confirms that amygdala hyperactivation effectively indexes probability of a positive response to some treatments for anxiety and mood disorders, it will likely relate less clearly to responses to others. This likelihood is particularly strong, given that pediatric internalizing disorders are likely heterogeneous, with different substrates underlying different types of dysfunction (41). Thus, amygdala dysfunction may only characterize one subset of youth with disorders that can respond to medication or CBT. For other youth, it will be necessary to identify both alternative treatments and markers associated with efficacy and effectiveness of those treatments. Nonetheless, although research on biological markers of potential treatment response is in its early stages, it holds promise for dramatically improving the precision and power of both well-tested and novel therapeutic approaches to pediatric anxiety and mood disorders.

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Figures

Figure 1. Participants showed a significant change in Clinical Global Impressions (CGI) scale scores between pre- and post-treatment assessments.

Figure 2. Pre-treatment left amygdala activation was significantly and negatively associated with both post-treatment Clinical Global Impressions (CGI) symptom severity scores and CGI-Improvement scores.

Table 1.

	Participants with Complete Data N = 12	Participants missing Post-Treatment Data N = 3
Gender, n (%)		
Female	6 (50)	1 (33.3)
Male	6 (50)	2 (66.6)
Age, mean (SD)	11.8 (1.8)	11.3 (3.1)
Age Range	10.0-16.0	8.0-14.0
IQ, mean (SD)	113.9 (14.9)	107.3 (15.1)
Treatment, n (%)		
Cognitive Behavioral Therapy	7 (58.3)	2 (66.6)
Medication	5 (41.7)	1 (33.3)
CGI severity, mean (SD)		
Baseline	4.3 (0.87)	4.0 (0.82)
Week 8	2.1 (1.0)	2.0 (0.82)
Pre-Treatment Diagnoses (Current Ongoing)		
Generalized Anxiety Disorder	9 (75%)	3 (100%)
Separation Anxiety Disorder	5 (42%)	--
Social Phobia	6 (50%)	--
Specific Phobia	3 (25%)	--

Oppositional Defiant Disorder	2 (17%)	1 (33%)
Dysthymia	1 (8%)	--

Figure 1

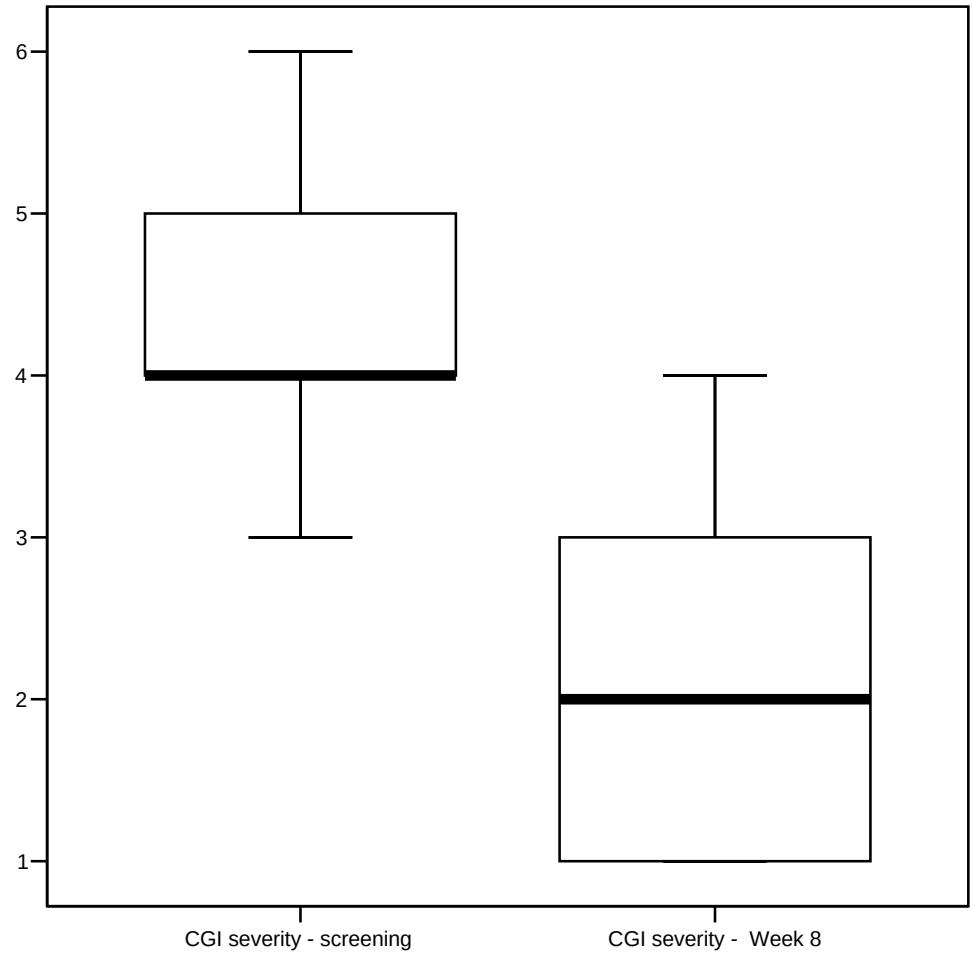
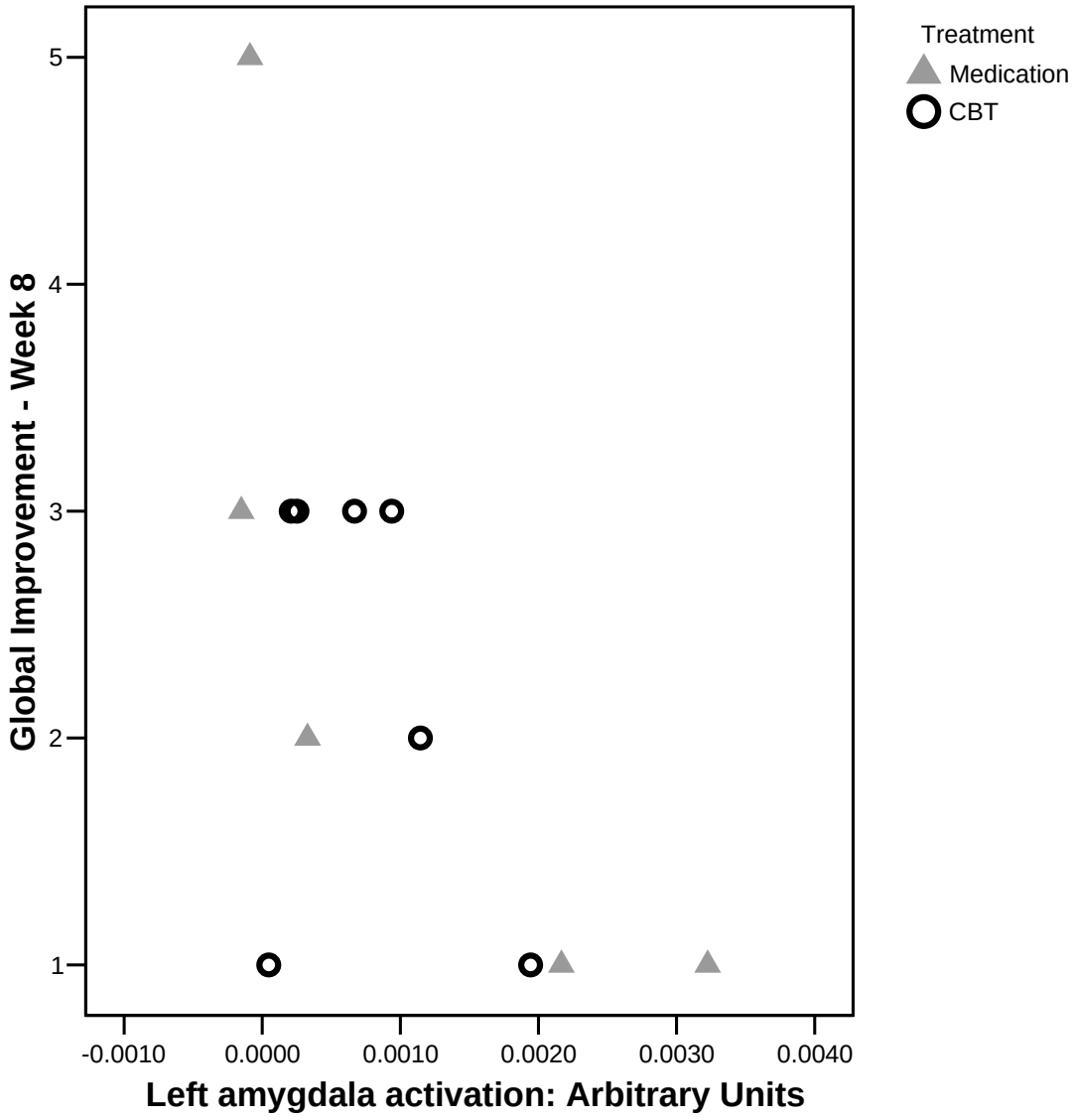
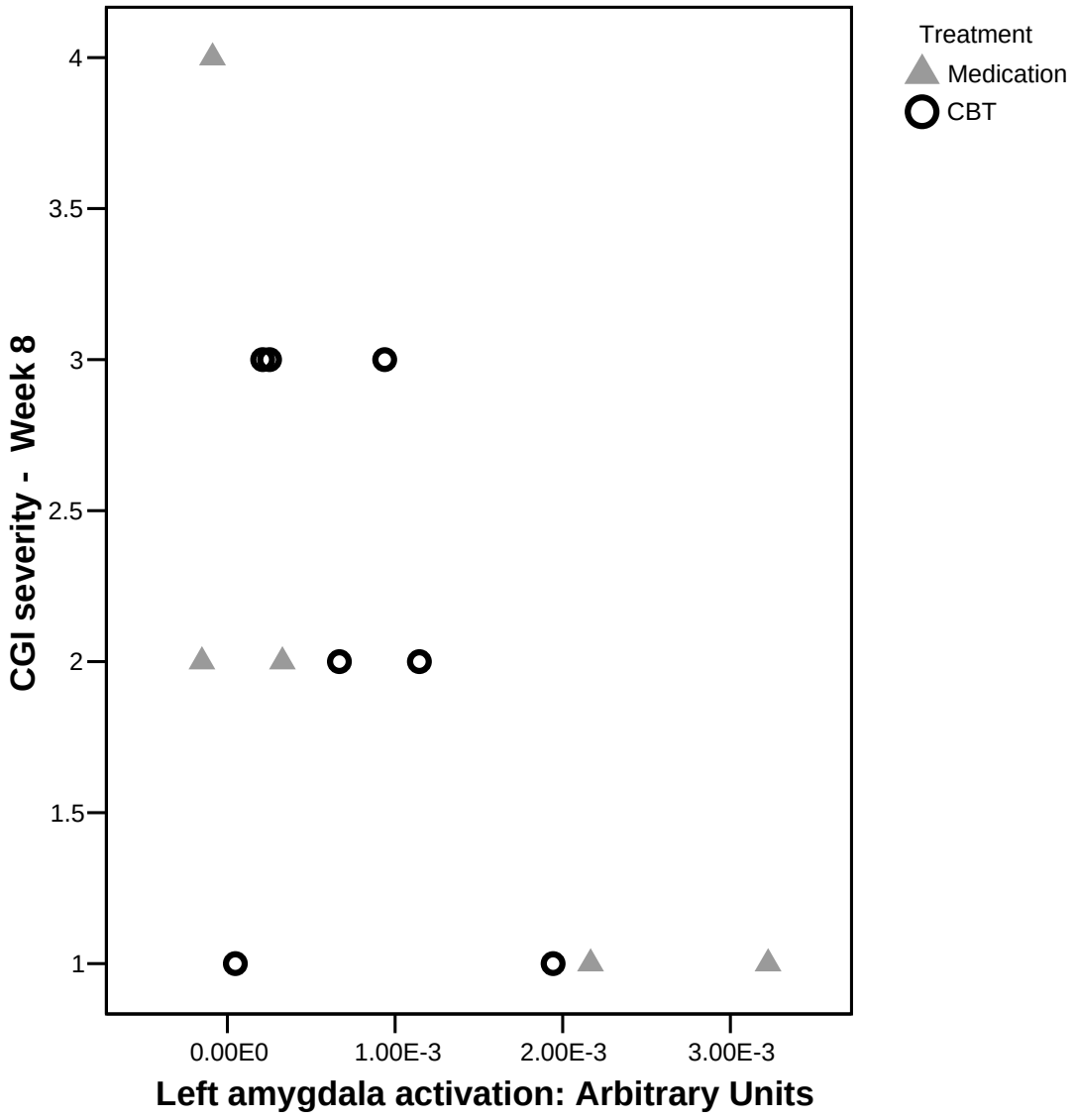


Figure 2


Treatment
Medication
CBT
Global Improvement - Week 8
5
4
3
2
1
-0.0010
0.0000
0.0010
0.0020
0.0030
0.0040
Left amygdala activation: Arbitrary Units


Treatment
Medication
CBT
CGI severity - Week 8
4
3.5
3
2.5
2
1.5
1
0.00E0
1.00E-3
2.00E-3
3.00E-3
Left amygdala activation: Arbitrary Units