Aberrant Brain Activation and Behavior During Self-Evaluation in Depression

Introduction

The Problem of Depression

Depression in its various forms is of significant global concern and critical importance. Characterized by depressed mood and/or anhedonia (i.e., lack of pleasure) in combination with other symptoms, depression severely impacts the everyday lives of millions of people. The World Health Organization (WHO) estimates that depression affects at least 4% of the population worldwide (*GBD Results Tool | GHDx*, n.d.; Malhi & Mann, 2018), and is the leading cause of disability worldwide. Within the United States, the National Institute of Mental Health (NIMH) estimated that 17.3 million adults were affected by depression in 2017 alone (~7.1% of the U.S. adult population), with 11 million suffering sever impacts to daily functioning (*NIMH » Mental Illness*, n.d.). The estimated economic burden of depression likewise paints a sobering picture, costing at least $92.7 billion yearly in the U.S. for major depressive disorder (Zhdanava et al., 2021). Furthermore, the impact and prevalence of depression skyrocketed during the COVID-19 pandemic, with some sources estimating nearly 30% of the population suffering from depression (Cénat et al., 2021; Salari et al., 2020; Wu et al., 2021).

Negative Self-Evaluation in Depression

One of the hallmark symptoms of depression is altered self-evaluation. In healthy (i.e., non-depressed) adults, self-evaluation is typically biased in favor of the self, such that individuals have an overly optimistic and generous view of themselves and their traits relative to others (Chipperfield et al., 2019; Haaga & Beck, 1995). This overly positive self-evaluation is thought to be a protective mechanism, allowing the individual to function well in the world and to adjust to adversity (Chipperfield et al., 2019; Haaga & Beck, 1995). In depression, however, this protective form of mild narcissism appears to be lost; depressed individuals are more likely to judge themselves "realistically," (Chang & Overall, 2022; Haaga & Beck, 1995) but this grounded view of the self is accompanied by increased negative thoughts about the self (Chang & Overall, 2022). These negative thoughts appear to be critical, as they tend to persist despite otherwise promising treatment, and their persistence constitutes a risk factor for depression relapse (Butter et al., 2019; Hards et al., 2020; Orchard & Reynolds, 2018).

Self-evaluation in healthy individuals holds other advantages as well. In healthy individuals, self-evaluation is quick and effortless. That is, when judging traits statements about the self compared to a well-known other, individuals are faster (in reaction time) at evaluating themselves , and this process is done without much cognitive effort (Klein & Lax, 2010). In other words, when I think about me, I know who I am and don't have to spend much time contemplating who "I" am. However, when evaluating someone else, I would have to consider what I know about them and why by consulting my memories and previous experiences, a process that takes time and (somewhat) intentional thought. This inherent knowledge about the traits of the self are preserved such that they are resistant even to memory insults such as amnesia (Klein & Lax, 2010). However, we believe this automatic, effortless self-evaluation may be lost or impaired in depression, forcing depressed individuals to evaluate themselves as though they were another.

Self-Evaluation in Depression: Preliminary Work

Preliminary work in our lab suggests that this automatic self-processing may indeed be disrupted in depression. We had small samples of healthy controls (HC, n=7) and depressed (DP, n=12) individuals complete a trait-judgment task wherein they were given a statement either in reference to themselves or a well-known but not relationally close other (e.g., Barack Obama) and were asked to rate how much they believed those statements on a scale of 1-5 (1=Not at all, 5=Completely). We then evaluated the mean reaction times (RT) for HC and DP groups responding to self and other targets, hypothesizing that the self-reference speed effect would be present in HC but not DP groups. Furthermore, we looked at the trial-by-trial RT patterns to see if the level of conviction—the extremity to which a person believes the statement—made a difference.

The behavioral results from this study (Fig. 1) suggest that, indeed, the self-reference effect that is preserved in healthy controls is lost in depression; furthermore, the level of conviction seemed to make a difference, in that depressed individuals exhibited a flattened RT curve for self-referent statements, suggesting that they are slower (less automatic) at responding to trait statements about themselves with high conviction. The first of these findings—that automatic self-processing is disrupted overall in depression—we aimed to replicate in this current study behaviorally. Furthermore, and more critically, the aim of this study was to evaluate if self-related brain activation is disrupted in depression compared to healthy controls.

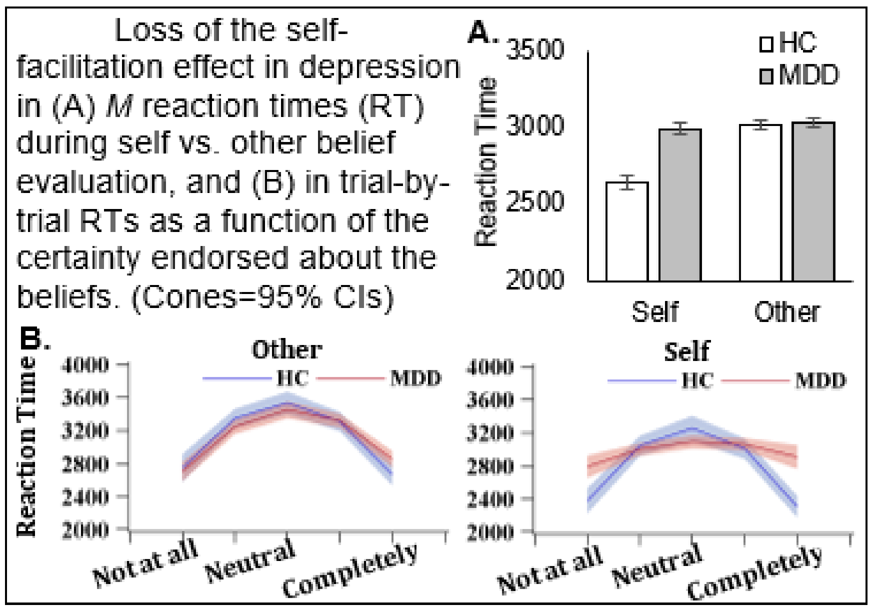

Figure 1 Preliminary behavioral data looking at the reaction times (RT) to self- and other-related statements in healthy controls (HC) and depressed patients (DP). Depressed patients show a loss of the efficient self-reference effect

Behavioral and Neural Self-Evaluation in Depression: Current Study

Overview and Hypotheses

The purpose of this study is to collect behavioral and functional magnetic resonance imaging (fMRI) data regarding self/other evaluation within the MRI scanner. Specifically, we hypothesize that depressed patients will lose the behavioral self-reference speed (RT) advantage seen in healthy controls. Self-processing will be disrupted neurally in depressed patients (DP), such that, compared to healthy controls (HC) they will 1) exhibit less deactivation in the posterior default mode network (DMN), a network involved in social cognitive processing, such that DP activation in this network will look more similar to other-evaluation, and 2) DP will activate a broader array of regions during self-processing than HC, also indicative of other-like processing during self-evaluation in depression.

Methods: Participants

This study consisted of healthy controls (HC, n=35) and depressed patients (DP, n=23), ages 18-40 years. Patients had to meet the MRI inclusion criteria, including: right-handed, no history of head injury, systemic illness or developmental or neurological disorder, average NAART IQ >85, visual acuity >20/40, no current substance or alcohol use disorder or active illicit substance use (except cannabis) over the last 3 months, ability to understand English, no current or past history of psychosis or bipolar disorder. DP also must meet the diagnostic criteria for depression (Spitzer et al., 1992), with elevated symptoms of depression (Rush et al., 2003). For feasibility reasons, DP were allowed to be receiving current treatment at the time of the scan. HC groups needed to have symptom levels below the cutoffs to be included. Both groups were matched on age, race, sex, SES, and IQ.

Methods: Behavioral Trait-Judgment Task

As in the preliminary study, participants completed a behavioral trait-judgment task while in the scanner (Figure 2). The trait statements were taken from the Automatic Thoughts Questionnaire and its positive equivalent (Hollon & Kendall, 1980; Ingram et al., 1996). We specifically chose 20 positive and 20 negative statements that reflected similar traits (but of different valence) and were of importance for our lab. Within the scanner, each statement was shown two times: one with reference to the self, and once with reference to a well-known famous other. The famous others were pulled from a list provided by the participant prior to the scan. For each statement shown, the participant was asked to rate how much they believed the statement about the target indicated (i.e., self or other) on a scale from 1-5 (1=Not at all, 5=Completely). Responses and reaction times for each trial were recorded. A mixed-effects repeated measures model was then conducted on the RTs.

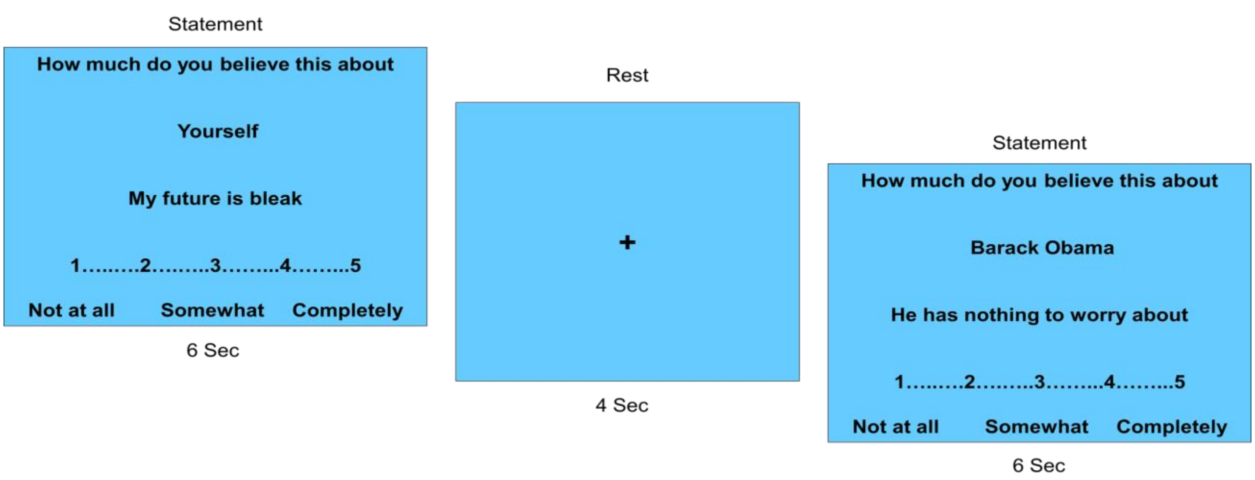

Figure 2 Example of the trait-judgment task given to participants in the scanner.

Methods: fMRI Acquisition & Regions-of-interest (ROI)

We obtained two scans of interest for this study, a structural T1 MPRAGE scan (voxel size=1.5x1.5x8mm, FoV=280mm, slice thickness=8mm, TR=20ms, TE=5ms), and a functional T2 EPI scan (voxel size=3x3x3mm, FoV=204mm, slice thickness =3mm, TR=6000ms, TE=30ms, Multiband accel. factor=1). During the structural scan, participants were instructed to lie quietly. During the functional scan participants completed the behavioral task; responses were collected using a button box in the participant's right hand. The blood-oxygen level dependent (BOLD) signal—the primary measure of neural activity in fMRI—was collected throughout the scan and used to estimate brain activation during self- and other-related positive and negative statements. BOLD signal uses the unique magnetic response of oxygen in the blood to infer activation in brain regions responding to a stimulus.

Specifically, we were interested in the activation of brain regions within three different networks: the Default Mode network (DMN, involved in social processing), the Salience network (involved in directing attention to stimuli), and the Cognitive Control network (important for emotional regulation and planning). These networks have all previously been implicated in depression (Disner et al., 2011; Fournier & Price, 2014; Ironside et al., 2021; Kube et al., 2020; Weingarten & Strauman, 2015). These broad networks were made up of many smaller ROIs, within which we pulled the BOLD responses, namely: bilateral dorsal anterior insula, mPFC, precuneus/posterior cingulate cortex (PCC), dorso- and ventrolateral prefrontal cortex (dlPFC, vlPFC), dorsal anterior cingulate cortex (dACC), and the temporo-parietal junction (TPJ).

fMRI data was preprocessed and first-level models were constructed for each ROI within each individual, after which second-level group effects and interactions were estimated for each

ROI using a mixed-effects repeated measures model. False Discovery Rate (FDR) correction was applied to correct for multiple comparisons.

Results: Behavioral Trait-Judgment Task

Just as in the preliminary study, behavioral reaction times were disrupted during self-processing within depression (Figure 3). Specifically, we observed a group-by-target (self/other) interaction for reaction times (F(1,56)=9.63, p=0.003). Healthy controls, as expected, showed the self-reference speed advantage and were faster at evaluating self- vs other-related statements (t(56)=3.27, p=0.002), but the depressed group was not (t(56)=-0.89 p=0.38), in line with our hypothesis. Other-related response times did not differ between the HC and DP groups, further emphasizing that self-related processing is specifically disrupted in depression.

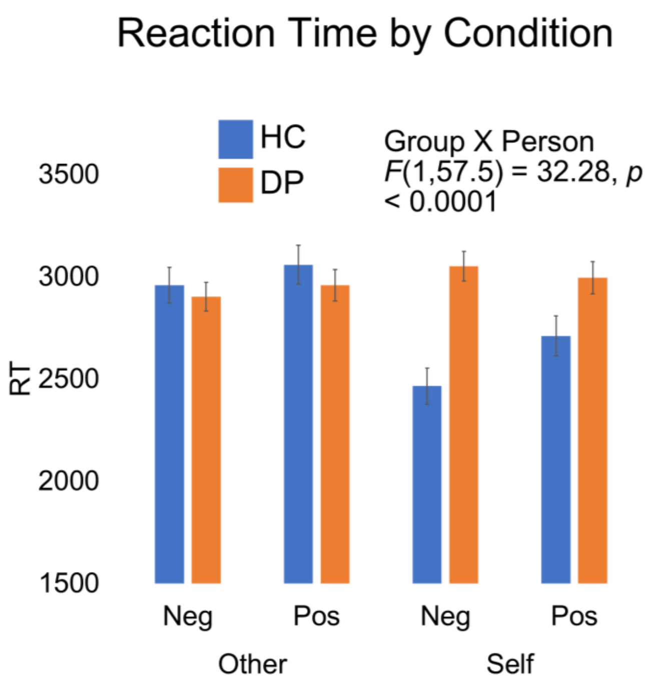

Figure 3 Behavioral trait-judgment reaction time results. As in the preliminary data, HC show an expected self-reference speed advantage which appears to be lost in DP

Results: fMRI Brain Activation

Overall, the depressed group showed increased activation in multiple brain regions during self-evaluation compared to the non-depressed group (Figure 4). Depressed and non-depressed individuals showed differences in neural activation within the mPFC (F(1,85.9)=5.93, *FDR* q=0.02) Precuneus/PCC(F(1,85.9)=5.93, *FDR* q=0.01), left dorsal anterior insula (F(1,94.2)=7.11 *FDR*

q=0.009), dACC (F(1,94.9)=11.13, *FDR* q=0.004), and left vlPFC (F(1,90.8)=5.31, *FDR* q=0.02). In the mPFC (t(56)=3.10, d=0.83, p=0.003), left dorsal anterior insula (insula: t(56) =2.29 , d=0.62, p=0.03), dACC (t(56) =3.86, d=1.04, p=<0.001), and left vlPFC (t(56)=2.22, d=0.60, p=0.03), group differences were due to increased activation in depressed individuals in response to negative statements about the self. In the precuneus/PCC, depressed individuals showed increased neural activation to self- vs other-related statements (F(1,56)=5.30, d=0.63, p=0.03).

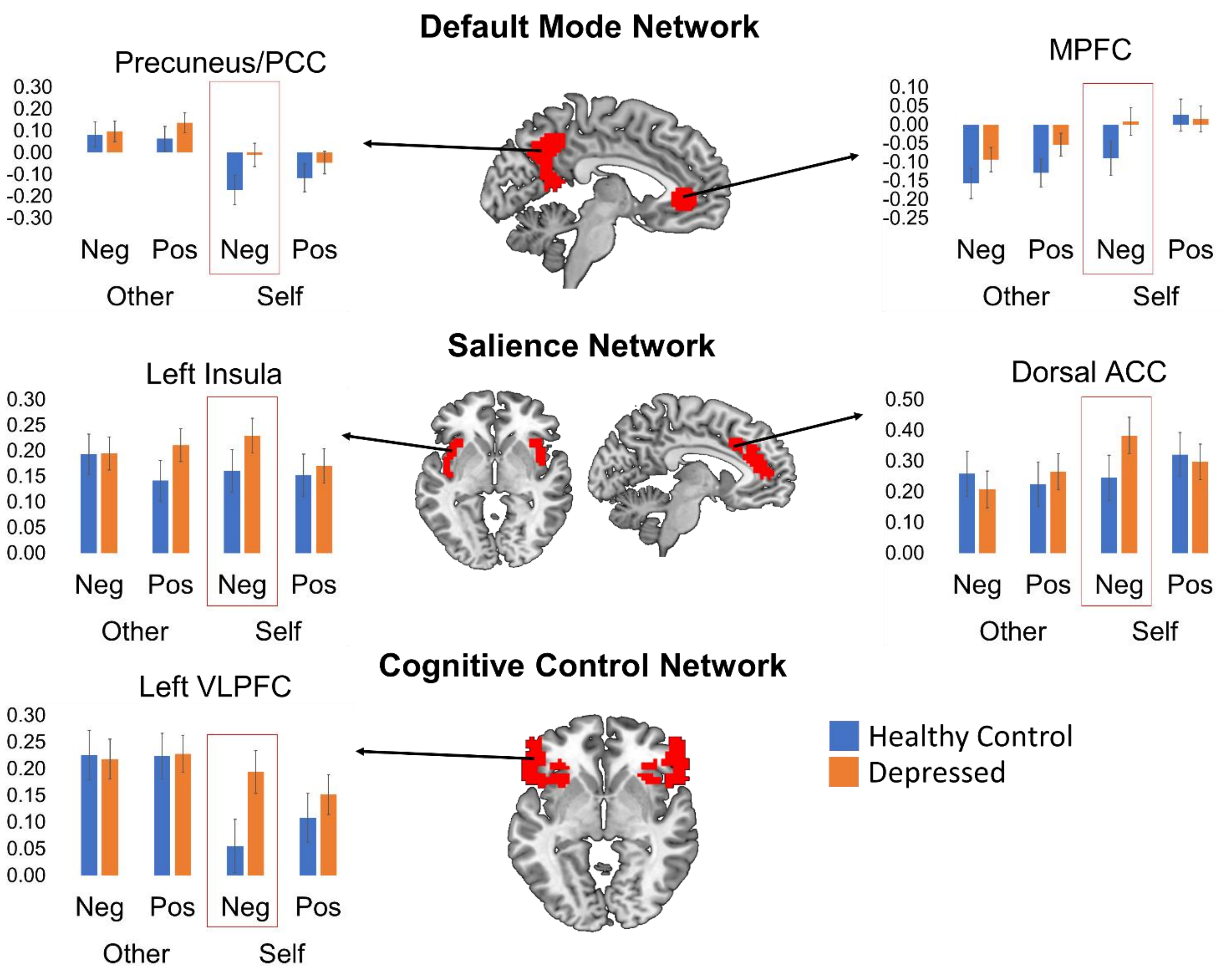

Figure 4 fMRI brain activation ROI results. Displayed results are those with significant interactions (FDR corrected, q<0.05). Red boxes indicate significant pairwise comparisons between HC and DP groups.

Conclusions & Implications

Both our behavioral and neural findings suggest dysfunctional self-related processing in depression. A wider network of brain regions is activated in depressed individuals compared to healthy controls during self-evaluation, a finding that was particularly strong in response to negative statements about the self. These findings were backed by behavioral evidence that the automatic, efficient self-reference effect seen in HC individuals is lost DP, such that depressed individuals respond to statements about themselves and others with similar speed. Addressing this disrupted self-evaluation in depression through treatments targeting these neural areas—and what's activating them—may lead to more efficacious and long-lasting treatment in depressed individuals.

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