Archival Report

Biological Psychiatry: CNNI

Distinct Neural-Functional Effects of Treatments With Selective Serotonin Reuptake Inhibitors, Electroconvulsive Therapy, and Transcranial Magnetic Stimulation and Their Relations to Regional Brain Function in Major Depression: A Meta-analysis

David T. Chau, Phoebe Fogelman, Pia Nordanskog, Wayne C. Drevets, and J. Paul Hamilton

ABSTRACT

BACKGROUND: Functional neuroimaging studies have examined the neural substrates of treatments for major depressive disorder (MDD). Low sample size and methodological heterogeneity, however, undermine the generalizability of findings from individual studies. We conducted a meta-analysis to identify reliable neural changes resulting from different modes of treatment for MDD and compared them with each other and with reliable neural functional abnormalities observed in depressed versus control samples.

METHODS: We conducted a meta-analysis of studies reporting changes in brain activity (e.g., as indexed by positron emission tomography) following treatments with selective serotonin reuptake inhibitors (SSRIs), electroconvulsive therapy (ECT), or transcranial magnetic stimulation. Additionally, we examined the statistical reliability of overlap among thresholded meta-analytic SSRI, ECT, and transcranial magnetic stimulation maps as well as a map of abnormal neural function in MDD.

RESULTS: Our meta-analysis revealed that 1) SSRIs decrease activity in the anterior insula, 2) ECT decreases activity in central nodes of the default mode network, 3) transcranial magnetic stimulation does not result in reliable neural changes, and 4) regional effects of these modes of treatment do not significantly overlap with each other or with regions showing reliable functional abnormality in MDD.

CONCLUSIONS: SSRIs and ECT produce neurally distinct effects relative to each other and to the functional abnormalities implicated in depression. These treatments therefore may exert antidepressant effects by diminishing neural functions not implicated in depression but that nonetheless impact mood. We discuss how the distinct neural changes resulting from SSRIs and ECT can account for both treatment effects and side effects from these therapies as well as how to individualize these treatments.

Keywords: Electroconvulsive therapy, Major depressive disorder, Meta-analysis, Positron emission tomography, Selective serotonin reuptake inhibitors, Transcranial magnetic stimulation

http://dx.doi.org/10.1016/j.bpsc.2017.01.003

The debilitating consequences of major depressive disorder (MDD) (1) have motivated concerted scientific efforts to develop treatments for this disease. Given that some of the most pursued treatment options for depression arose serendipitously (2,3), scientists have turned to functional neuroimaging to gain a clearer understanding of the neural effects of these treatments. In the context of assessing mood states such as MDD, which occur on a coarser temporal scale than emotions, the most directly applicable of these approaches are those that assess changes in baseline levels of brain activity—as aliased by regional glucose or oxygen utilization—resulting from a course of therapeutic intervention (4). Using these methods, we have been able to investigate at a neural-functional level how treatments for depression exert therapeutic effects as well as how the side effects associated with these treatments arise.

Given that methods used most frequently to measure resting brain activity—positron emission tomography (PET) and single photon emission computed tomography (SPECT)—are cumbersome and involve administering radioisotopes to participants, sample sizes for studies of the functional effects of antidepressant therapies are typically small and have correspondingly low signal strength. Moreover, particular aspects of individual studies, such as gender composition or

SEE COMMENTARY ON PAGE 305

the ongoing medication status of the sample tested, can both affect results obtained and undermine the generalizability of findings (5). Further, individual studies can overrepresent neural foci of interest to scientists at a given time, potentially ignoring more robust and ultimately meaningful findings. Given these concerns, meta-analytic synthesis of extant data regarding changes in brain function resulting from antidepressant therapy can be used to identify the robust and generalizable findings in the literature. Additionally, functional neuroimaging meta-analysis allows for comparison of results across different independent variables. Therefore, in the present study, we were able to compare the functional effects on the brain of different therapeutic options for treating MDD to identify both the neural commonalities and the differences of these approaches.

In the present investigation, we synthesized and compared data reflecting changes in brain function resulting from three antidepressant interventions: pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs), electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS). Additionally, we investigated the degree of neural overlap between reliable changes associated with these treatments and neural-functional abnormalities in MDD—as determined from meta-analytic synthesis of PET and SPECT studies comparing resting brain activity in depressed relative to healthy control samples. Given that SSRI pharmacotherapy, ECT, and rTMS are distinct in terms of their modes of administration and their time course of therapeutic response and relapse (6–8), we hypothesized that these therapies would have correspondingly distinct functional effects on the brain. Moreover, given the modest long-term therapeutic efficacy of SSRIs, ECT, and rTMS (7,9,10) and, in SSRI pharmacotherapy and ECT, the prevalence of reliable side effects (11–13), we predicted that these treatment options affect neural systems distinct from those shown reliably to be functionally abnormal in depressed relative to healthy samples.

METHODS AND MATERIALS

Overview

To identify reliable changes in brain activity in MDD resulting from the selected treatment modalities, we used multilevel kernel density analysis, a widely implemented meta-analytic technique for functional neuroimaging that yields results comparable to those of other coordinate-based meta-analytic methods (14,15). We first conducted a literature search to identify studies that investigated changes in resting regional cerebral blood flow or glucose or oxygen utilization as measured with PET, SPECT, or arterial spin labeling functional magnetic resonance imaging (fMRI) in patients with MDD before and after a course of treatment with SSRIs, ECT, or rTMS. Next, we generated binary indicator maps for each study; these maps represented reported coordinates of changes in neural activity in MDD resulting from treatment. Following this step, we summed the indicator maps, voxel-wise, for each of the three treatment modalities and determined levels of statistical significance for these summary maps via Monte Carlo simulation. Finally, we conducted intersection analyses on statistically thresholded maps to determine the reliability of spatial overlap of treatment modalities both with respect to one another and with respect to meta-analytically reliable functional abnormalities in MDD as determined by PET-based or SPECT-based comparisons of samples with MDD and healthy control samples (16).

Study Selection

For our literature search, we used an iterative procedure incorporating multiple databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (17) guidelines. Two investigators (DTC and PF) independently conducted electronic searches of potentially relevant studies published between January 1, 1990, and June 1, 2016, using PubMed, Web of Science, and Google Scholar. We employed a reductive screening process involving the following steps: 1) searching for studies related to depression; 2) screening studies found in step 1 for studies that used PET, SPECT, or arterial spin labeling fMRI to measure regional cerebral blood flow, glucose utilization, or oxygen utilization; and 3) screening the studies found in step 2 for studies administering SSRI pharmacotherapy, ECT, or rTMS. A more detailed description of our initial search procedure, exclusion criteria applied to studies identified by the initial search, and decisions regarding studies with partially overlapping samples can be found in the Supplement. Table 1 presents the studies included in our meta-analysis (18–37).

Calculating the Meta-analytic Statistic

Following the same procedure as other multilevel kernel density–based studies (16,38), we constructed indicator maps in Talairach space from reported coordinates of regional activity increases and decreases resulting from treatment. We converted coordinates reported in Montreal Neurological Institute standard space to Talairach space using mni2tal (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). In constructing indicator maps (I) for each of N contributing studies, we centered 12-mm-radius spheres (constructed at 1 mm^3 spatial resolution) with value = 1 for activation increases from pretreatment to posttreatment and value = −1 for activation decreases resulting from treatment, at the reported coordinates of activity change. Instead of the 10-mm-radius spheres used typically in fMRI meta-analyses (39), we used 12-mm-radius spheres for the current meta-analysis both to compensate for the lower spatial resolution of PET and SPECT and to increase the sensitivity of our spatial-intersection analyses, thereby employing a more stringent test of our hypothesis that the treatment modalities tested affect non-overlapping neural substrates.

Using these indicator maps, we constructed three meta-analytic statistical maps, one for each treatment modality. We summed indicator maps from N studies per category into meta-analytic maps where the meta-analytic statistic ($\hat{P}_v$) at each voxel, v, was calculated as follows:

$$\hat{P}_v = \sum_{n=1}^{N} w_n I_n$$

where w_n is the square root of the sample size of the nth of N studies. By weighting each study in this manner, studies with