

Multimodal imaging of electroconvulsive therapy at the human system level

Wednesday, Jun 20: 8:00 AM - 9:15 AM

1140

Symposium

Wednesday - Symposia AM

Unipolar and bipolar Major Depressive Disorder (MDD) is a leading cause of disability worldwide. Despite fifty years of intensive research on its underlying pathophysiology, treatment options are still unsatisfactory, leading to severe disability and chronicity with large socio-economic consequences. Currently, one third of all MDD patients suffer from a treatment-resistant form of depression. Notably, this group of patients consumes almost 50% of the total budget that arises for treatment costs (Murray and Lopez, 1997). Hence, it is of particular importance to investigate the neurobiological mechanisms of actions of those treatments that do have the best effect in these cases. While knowledge on symptoms and treatment guidelines of MDD forms part of academic teaching programmes in medical schools and postgraduate courses (e.g. in molecular epidemiology, neurosciences, and concepts of personalized medicine), comparatively limited attention has been paid to the underlying mechanisms of the most potent treatment, i.e. electroconvulsive therapy in research and teaching programs. However mechanistic effects of ECT as well as the biomarkers that predict the response have to be understood to develop new treatments and treatment guidelines.

Objective

- Definition and treatment options for chronic depression
- Neurobiological mechanisms of the most powerful biological treatment form of depression
- Application options for multimodal imaging techniques as well as analyses in this clinical context

Target Audience

Given the broadness of the topic at hand, we expect researches from the field of affective neuroscience, but also researchers from the field of clinical neuroimaging and analyses methods.

Organizer

Indira Tendolkar, Donders Institute for Brain, Cognition and Behavior

Presentations

Longitudinal Structural Covariance Associated with Antidepressant Electroconvulsive Therapy Response ([index.cfm?do=ev.viewEv&ev=1606](#))

Introduction Major depressive disorder (MDD) is a highly prevalent and symptomatically heterogeneous disorder [1] with substantial variability in treatment response. The Hamilton Depression Rating Scale (HDRS) [3] is commonly used to evaluate clinical improvement, though different neural systems may account for changes in particular symptom profiles. Electroconvulsive therapy (ECT) shows rapid and robust clinical effects in patients with treatment resistant MDD [2]. Here, we address how symptom dimensions segregate, change, and relate to structural neuroplasticity over ECT index in a large multisite cohort of ECT patients with MDD. We further introduce a novel representation of relative treatment-related volumetric changes based on graph theory. **Methods** Participants. 157 patients (age=49.5±4.3 years; 96 females) from 4 independent sites participating in the Global ECT-MRI Research Collaboration (GEMRIC) all experiencing a DSM-IV defined major depressive episode and eligible to receive ECT were recruited as participants in ongoing studies of treatment responsive biomarkers for antidepressant response in MDD. All patients were evaluated prior to (T1) and following (T2) ECT. Patients received structural MRI imaging at both time points and the HDRS (17-item) assessed therapeutic response. **Feature representation.** Bayesian estimation was used to identify HDRS items which were reliably reduced by more than 0.5 points with ECT (Figure 1a). Items meeting this criterion were combined into a single factor using an oblimin rotation (Figure 1b); the

resultant factor was treated as the outcome of interest throughout and instantiates a weighted average of change in ECT-responsive HDRS items. Imaging features consisted of cortical thickness and subcortical volumetric measures extracted for each subject according to the FreeSurfer's Desikan atlas [4]. The percent change of each region over ECT index was calculated. Next, the pairwise ratios of regional percentage changes were computed for each subject, yielding N p-by-p matrices of regional ratios. Each matrix was transformed to an adjacency matrix by applying thresholds between 2:8 resulting in 7 adjacency matrices per subject. We then calculated the undirected node degree for each adjacency matrix where said node degree for region j under threshold t in subject i indicates the number of regions in subject i that region j changed by more than t-fold (Figure 1c). Patient age, sex, site, and baseline HDRS factor score were also included as predictors in the model. Statistical modeling. Random forest (RF) [5] regression was used to associate node degree distributions (NDD) with the symptom factor. Rigorous 10-repeated 10-fold cross-validation with nested recursive feature selection (RFE) was used to evaluate the model's performance. RF and RFE parameters were tuned over an extensive grid search in which average root mean squared error of the predictions was minimized. Results Mean ($p < 0.001$) and variance ($p < 0.01$) of NDD were significantly less confounded with site than raw measures of regional change. Permutation tests (100 shuffles) revealed the RF predicted symptom reduction significantly above chance ($p < 0.01$; RMSE=0.67; Figure 2a-b). NDD of the right entorhinal cortex, temporal pole, and right anterior hippocampus were prominently associated with symptom improvement. Directionality of associations between these NDDs and symptom improvement were recovered using simulations (Figure 2c). Conclusions We identified a subset of ECT-responsive MDD symptoms captured by the HDRS and identified a single factor to describe their covariance. A novel measure of longitudinal structural connectivity capturing the rich spectrum of structural covariance and that was less sensitive to scanner hardware or population differences was introduced and used to predict symptom change over ECT. Symptom improvement was accurately predicted largely by connectivity information about right anterior and medial temporal lobe. References [1] Kessler, R. C. and Bromet, E. J. (2013), "The epidemiology of depression across cultures," *Annu Rev Public Health*, vol. 34, pp. 119-38. [2] Husain, M. M., Rush, A. J., Fink, M., Knapp, R., Petrides, G., Rummans, T., et al. (2004), "Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report," *J Clin Psychiatry*, vol.65, pp. 485-91. [3] Hamilton, M. (1960), "A rating scale for depression". *J Neurol Neurosurg Psychiatry*, vol. 23: pp. 56-62. [4] Dale, A. M., Fischl, B., and Sereno, M. I. (1999), "Cortical surface-based analysis. I. Segmentation and surface reconstruction," *NeuroImage*, vol. 9, pp. 179-94. [5] Breiman, L. (2001), "Random Forests," *Machine Learning*, vol. 45, pp. 5-32.

Presenter

Benjamin Wade, UCLA

Volume of the human hippocampus and clinical response following electroconvulsive therapy ([index.cfm?do=ev.viewEv&ev=1607](#))

Understanding the biological effects of electroconvulsive therapy (ECT) may have profound implications for development of new treatment alternatives for depressive disorders. One hypothesis advanced by translational models is that a decrease of adult neurogenesis in the hippocampus is causally linked to depression and can be reversed by ECT. Over the past decade, neuroimaging studies have repeatedly shown that ECT causes a significant increase in the size of the human hippocampus, and an emerging understanding has been that ECT may normalize aberrant structure/function relationships occurring in depressed individuals. However, dose effects of the number of ECT sessions on hippocampal volume and how ECT-induced growth of the hippocampus relates to clinical outcome, remain uncertain. In this talk the results of a large multisite neuroimaging study of patients with major depression followed prospectively during ECT treatment (N=281) and untreated non-depressed controls (N=91) will be

presented. The results of the links between hippocampal volume, number of ECT treatments and therapeutic response will be discussed.

Presenter

Philip van Eindhoven, Donders Institute for Brain, Cognition and Behavior

Electroconvulsive therapy affects key regions implicated in depression: A review of longitudinal neuroimaging studies ([index.cfm?do=ev.viewEv&ev=1608](#))

In this lecture, we will present the assessment of studies that report longitudinal neurobiological changes in depressed patients before and after ECT, observed with structural and functional magnetic resonance imaging modalities. Structural and functional changes in the brain occur after ECT at a large scale, and these changes may indicate a partly reversal recovery from the pathophysiological changes found in MDD. We find sufficient largely converging evidence for increased volume in the medial temporal lobe and anterior cingulate cortex, which also show changes in function and connectivity after ECT. However, there is limited evidence that medial temporal lobe changes relate to clinical improvement, while most studies do indicate that ECT normalizes changes present in the depressed brain. There are several explanations for the lack of convergence between neurobiological changes and the strong clinical effects in depression. Primarily, the sample sizes in ECT-studies are usually small and, while possibly sufficient to report longitudinal differences in a paired fashion, even with response rates as high as 60-70% studies might simply be underpowered to detect relationships between treatment and neurobiology in a robust fashion. Furthermore, this relation may be affected by differences between potential responders and non-responders at baseline. Another explanation is that attempting to correlate clinical improvement to longitudinal changes in single structures or connections is a too simplistic approach, as depression is similarly not limited to single brain regions but instead is linked to widespread changes in structure and function. Finally, some studies opt to include both unipolar and bipolar depression, which have been shown to exhibit different underlying neurobiology. Based on these findings we will make suggestions for future avenues of research

Presenter

Peter Mulders, Donders Institute for Brain, Cognition and Behavior
