How Does ECT Work?

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Conflict of Interest

- In the last three years I have been a member of an advisory board for Lundbeck
“I was totally negative and thought about suicide most of the time. I could not think properly, let alone work. I had panic attacks if left alone. Sleep was impossible and when I awoke I felt worse. The future was hopeless. I was convinced I would never recover.”

Lewis Wolpert
Causes of Depression

- Familial Risk
- Childhood experience
- Life Events (particularly losses)
- Life Difficulties (social disadvantage)
- Neurotic temperament
- Dysfunctional attitudes (low self-esteem, perfectionism etc)
- Physical illness
- Substance misuse
- Previous history of depression
Neurobiology of Depression

- Genetic - few current clues from molecular studies
- Cortisol hypersecretion
- Neurochemical - monoamines, glutamate and GABA
- *Loss of synaptic plasticity and decreased neurogenesis* - *Volume loss of brain tissue*
- *Abnormalities in connectivity of neural circuitry involved in experience and regulation of mood*
Occipital cortex γ-aminobutyric acid (GABA) concentrations for all subjects in the combined data set broken down by DSM-IV subtypes of major depressive disorder. Boxed symbols represent subjects who also met the criteria for psychotic features.
Effects of ECT and CBT on Brain GABA in Depressed Patients Measured by MRS

Sanacora et al 2003
GABA and Depression

- Decreased GABA in brain measured by MRS
- Reduced levels of GABA interneurones in post-mortem studies of depressed patients
- Increased cortical excitability (TMS)
- ECT probably increases brain GABA

Sanacora 2010
Brain Structural Pathology in Depression

Atrophy of the Hippocampus in Depression

MRI Studies in Depression

Meta-analysis by Arnone et al (2011) 101 studies-4000 patients

‘This comprehensive meta-analysis of morphometric studies suggests that individuals with unipolar depression are characterised by volume reductions in the frontal cortex, orbitofrontal cortex, hippocampus, cingulate cortex and striatum, and an excess of white matter lesion in comparison with healthy controls.’

Volume reductions were positively associated with length and severity of illness and age of onset
Cellular Pathology and Loss of Brain Volume

Current theories associate loss of brain volume with cellular pathology including:

- Loss of neurones and glia (increased apoptosis)
- Decreased neuronal plasticity and synaptic density.
- Decreased synthesis of neurotropins such as BDNF
- Decreased neurogenesis
Role of neural plasticity in depression pathophysiology (clinical imaging and post-mortem studies)

- Decreased OFC volume in depression
- Decreased markers of plasticity (Arc, BDNF)
- Reduced neuron and glial cell density
- Decreased synaptic numbers

**Neural plasticity marker in PFC**

<table>
<thead>
<tr>
<th>Control</th>
<th>Unmedicated</th>
<th>Medicated</th>
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<tr>
<td>Arc mRNA (fold change)</td>
<td>1.0</td>
<td>0.5</td>
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* *p<0.05
MDD, major depressive disorder

**Synapse density in PFC**

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<th>Control</th>
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<tr>
<td>Spine synapses per µm³</td>
<td>0.5</td>
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ECT and Neural Plasticity

- In experimental animals ECT increases markers of neuronal plasticity (Arc) and increases BDNF and neurogenesis in hippocampus.
- ECT increases serum BDNF in depressed patients

Drivig et al, 2012; Taliaz et al, 2013; Brunoni et al 2014
Neural Circuitry in Depression-Functional Imaging

- Overactivity of limbic system (emotional perception and automatic appraisal)
- Underactivity of cortical regulatory regions (dorsolateral prefrontal cortex)

Usually measured as patients carry out a task that requires ‘emotional processing’
Figure 1   Neural systems of relevance to major depressive disorder. Key neural regions implicated in emotion and reward processing, and voluntary and automatic regulation of emotion are shown superimposed on a greyscale depiction of the human brain. DLPFC=d...
Neural Circuitry in Depression - Functional Imaging

- Overactivity of limbic system (emotional perception and automatic appraisal)
- Underactivity of cortical regulatory regions (dorsolateral prefrontal cortex)
- Increased resting state activity of default mode network (medial temporal, medial cortical, posterior cingulate, parietal cortex).
Connectivity map from the dorsal nexus to all of the voxels in the brain.
Functional connectivity in severely depressed patients before ECT (displayed in orange) and persisting connectivity after ECT (displayed in cyan), showing a substantial reduction in cortical connectivity after ECT treatment.

Conclusions

- Much is known about the social and personal antecedents of depression but the neurobiology is only just starting to be elucidated.

- Biological approaches to the neurobiology of depression have moved from the focus on a single neurotransmitter to notions of system level disruption associated with deficient neuroplasticity accompanied by brain volume loss in regions critical to emotional regulation.

- This provides new ways of thinking about the action of ECT based on changes in neuroplasticity as well as effects mediated through changes in the connections of neural networks.