**Thursday Abstracts**

**Methods:** C57BL/6 wild-type mice were used to test the response of brain FoxO to learned helplessness stress-induced depression. FoxO knockout mice were used to examine the role of FoxO in several depression- and anxiety-related behavioral tests. D-fenfluramine was administered to mice to test the effect of serotonin on phosphorylation and nuclear/cytosolic distribution of brain FoxO. The response of FoxO to pharmacological treatments was tested *in vitro* and in mice.

**Results:** When wild-type mice were subjected to the learned helplessness paradigm, the nuclear FoxO was significantly increased, indicating increased activity. FoxO KO knockout mice exhibited lower anxiety-like behavior. The serotonin enhancer d-fenfluramine increased the inhibitory phosphorylation and reduced the nuclear contents of FoxO in mouse brain, and the effect was mediated by the PI3K/Akt signal pathway. Importantly, FoxO activity was reduced by both chronic imipramine and lithium treatment.

**Conclusions:** The serotonin- and neurotrophin-regulated FoxO is a stress-responsive transcription factor. Pharmacological control of brain FoxO activity or modulation of its signal pathways may have therapeutic implication in depression.

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**8. Molecular Imaging of Serotonin Function in Geriatric Depression**

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**Background:** The evidence implicating the role of the serotonin system in mood disorders, as well as neurogenesis, provides a compelling rationale for the study of the serotonin system in geriatric depression. Positron emission tomography (PET) molecular imaging methods represent a unique opportunity to test hypotheses generated from animal models to geriatric mood disorders.

**Methods:** PET studies of the cerebral metabolic response to citalopram, as well as occupancy of the serotonin transporter (SERT; [11C]-DASB), have been performed in unmedicated, geriatric depressed patients.

**Results:** Cerebral glucose metabolism was decreased during citalopram treatment in the right anterior cingulate (BA 24), superior and middle frontal (bilateral) and right inferior frontal, superior and middle temporal (bilaterally) and left inferior temporal gyrus, precuneus and posterior cingulate (bilaterally), midbrain (bilaterally), right pons, parahippocampal gyrus and amygdala (bilaterally). Increased metabolism was observed in the putamen (bilaterally), right thalamus (pulvinar and medial dorsal nuclei), inferior parietal lobule (bilaterally) occipital (right cuneus and left middle and inferior occipital gyrus) and cerebellum (bilaterally). Voxel-wise analyses of the parametric [11C]-DASB images showed significant SERT occupancy (70% or greater), as well as correlations between SERT occupancy and mood symptom improvement. The regions of significant correlation are similar to the regions of metabolic decrease (anterior cingulate, middle frontal, superior and middle temporal gyri, precuneus, parahippocampal gyrus) and increase (inferior parietal lobule, cuneus) by citalopram.

**Conclusions:** A serotonergic mechanism may underlie the functional neuroanatomical changes associated with geriatric depression and the affective and cognitive responses to treatment.

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melancholic and anxious depression as well as the intermediate phenotype of emotional processing.

Methods: In a sample of 256 Caucasian patients with Major Depression, candidate gene variants of the serotoninergic, noradrenergic, NPY and endocannabinoid systems were investigated for their impact on antidepressant treatment response. A subsample of 35 patients was additionally scanned by means of fMRI at 3 T under visual presentation of emotional faces using an imaging genetics approach.

Results: The MAOA VNTR and the COMT val158met variants were found to influence antidepressant treatment response specifically in female patients. The 5-HTTLPR/S/C polymorphism was associated with treatment response in patients with melancholic, but not atypical depression. 5-HTTLPR, CNR1 rs1049533 and NPY rs16427 were observed to significantly impair treatment response particularly in anxious depression via altered brain activity in amygdala, prefrontal and striatal regions during processing of depression-related emotional stimuli.

Conclusions: The present results suggest a significant impact of 5-HTTLPR, 5-HTTLPR, MAOA-C, COMT, CNR1 and NPY gene variants on antidepressant treatment response with differential effects regarding gender and clinical subtype of melancholic and anxious depression, potentially mediated via distorted emotional processing in the limbic-frontal circuit. These findings point towards a network model of cellular (genetic) and circuit (brain network) factors contributing to antidepressant treatment success.

11. The Role of the Default Mode Network (DMN) in Understanding Emotional Circuitry in MDD Pre- and Post- Antidepressant Treatment

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Background: The recently discovered default mode network (DMN) is a group of areas in the human brain characterized, collectively, by functions of a self-referential nature. In normal individuals activity in the DMN is reduced during non-self-referential goal directed tasks, in keeping with the folk-psychological notion of losing one’s self in one’s work. Imaging and anatomical studies in major depression have found alterations in both the structure and function in some regions that belong to the DMN suggesting a basis for the disordered self-referential thought of depression.

Methods: Here we sought to examine DMN functionality as a network in patients with major depression, asking whether the ability to regulate its activity and, hence, its role in self-referential processing was impaired. To do so we asked patients and controls to examine passively negative pictures as well as actively re-appraise them.

Results: In widely distributed elements of the DMN—ventromedial prefrontal cortex (BA 10), anterior cingulate (BA 24/32), lateral parietal cortex (BA 39) and lateral temporal cortex (BA 21)—depressed, but not control subjects, exhibited a failure to reduce activity while both looking at negative pictures and reappraising them. Further, looking at negative pictures elicited a significantly greater increase in activity in other DMN regions (amygdala, parahippocampus and hippocampus) in depressed than in control subjects.

Conclusions: These data suggest depression is characterized by both stimulus-induced heightened activity as well as a failure to normally dampen-regulate activity broadly within the DMN. These findings provide a brain network framework within which to consider the pathophysiology of depression.

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Thursday Abstracts

12. From Resetting Chemical Dysbalance to Modulating Networks - Lessons on the Neurobiology of Treatment Resistant Depression from Deep Brain Stimulation

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Background: Deep brain stimulation (DBS) is a procedure that referring to stereotactic placement of electrodes in a given brain region with electrodes connected to a neurostimulator implanted under the skin of the chest. It is a FDA approved method for control of severe forms of tremor in Parkinson’s disease, essential tremor and primary dystonia. Recently, it has been proposed as a treatment in treatment resistant major depression. It might be, that more focused, targeted treatment approaches modulating well defined targets within affective networks will prove a more effective approach to help treatment-resistant patients.

Methods: We assessed antidepressant effects of bilateral DBS to the nucleus accumbens in fourteen patients suffering from treatment resistant depression not responding to pharmacotherapy, psychotherapy, and ECT. The mean (+/−SD) length of the current episode was 10.5 (+/−7.4) years, the number of past treatment courses was 20.8 (+/−8.4), the mean Hamilton Depression Rating Scale (HDRS) was 32.9 (+/−5.1).

Results: Twelve months after initiation of DBS treatment 7 patients reached the response criterion (Responders, HDRS = 15.4 (+/−2.8). The number of hedonic activities increased significantly in the responders only. Interestingly, ratings of anxiety measured with the Hamilton Anxiety Scale were reduced in both responders and non-responders, but more pronounced in the responders.

Conclusions: We demonstrate antidepressant and anti-anxiety effects of DBS to NA in patients suffering from extremely TRD. In contrast to other DBS depression studies, there was a specific anti-anxiety effect. The presentation will discuss relevance of these results and others from DBS studies for the understanding of TRD.

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Symposium

Gene Expression Across Human Brain Development and Schizophrenia

Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Bayside BC - 4th Floor
Chair: Joel E. Kleinman

13. Dysbindin-1 Transcripts and Isoforms are Differentially Affected in Schizophrenia

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Background: Dysbindin-1 is encoded by DTNBPI, a top candidate gene in schizophrenia (S2). Its reference sequence transcripts encode the protein’s major isoforms: dysbindin-1A, -1B, and -1C. S2 cases often display lower dysbindin-1 levels in the hippocampal formation (HF), but the causes and affected isoforms remain unknown.

Methods: We studied cultured lymphoblastoid cells from controls and postmortem brain tissue from schizophrenia cases and matched controls. We quantified DTNBPI gene expression using qRT-PCR with primer pairs for the major transcripts. We quantified dysbindin-1 isoforms and TRIM32 using Western blotting with validated antibodies.

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