Methods: C57BL/6 wild-type mice were used to test the response of brain FoxO to learned helpless 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. FoxO3a-deficient mice had less depression-like behaviors, whereas neuronal FoxO1 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.
Supported by R01MH73723

8. Molecular Imaging of Serotonin Function in Geriatric Depression

Gwenn S. Smith

Johns Hopkins University School of Medicine, Baltimore, MD

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 represents 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 (bilaterally) and right inferior frontal, superior and middle temporal (bilaterally) and left inferior temporal gyri, 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 gyri) and cerebellum (bilaterally).Voxel-wise analyses of the parametric [^{11}C]-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 neuroanatomic changes associated with geriatric depression and the affective and cognitive responses to treatment.
Supported by NIH/NIMH 64823

SYMPOSIUM
The Emerging Neurobiology of Antidepressant Treatment Response

Thursday, May 20, 2010 12:30 PM - 2:30 PM
Location: Grand Chenier - 5th Floor
Chair: Katharina Domschke
Co-Chair: Yvette Sheline*

*Supported by NIMH:2k24MH79510 and 2RO1MH64821

9. Connectivity of the Subgenual Cortex and HPA Axis in Depression

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Background: Our group has reported, using a resting-state fMRI approach, that subgenual cingulate connectivity, within a posterior cingulate-hippocampal-medial prefrontal network, is increased in a mixed group of delusional and nondelusional depressives compared to healthy controls. The subgenual region has been thought to participate in a circuit that involves anterior and posterior cingulate and prefrontal cortex as well as the hypothalamus.
Methods: Herein, we report on the relationship of resting-state functional connectivity in the subgenual region to activity of the hypothalamic-pituitary-adrenal (HPA) axis in 60 patients with major depression (30 delusional and 30 nondelusional) as well as 30 healthy controls. Patients were assessed for serum cortisol and ACTH activity on an hourly basis beginning at 6 p.m. and ending at 9 a.m. in a G-CRC setting. MRI's were obtained after completing blood collections.
Results: Data are presented on the relationship of mean cortisol levels from 6 p.m. to 1 a.m. and from 1 a.m. to 9 a.m. with connectivity profiles of the subgenual region. We also present data on the relationship between hippocampal connectivity and the HPA axis. Implications of these data for understanding a key circuit involved in the pathogenesis of depression are discussed.
Conclusions: Resting-state *f*MRI can identify abnormalities in brain connectivity in depression and relationships with elevated HPA axis activity.
Supported by RO1 MH50604

10. Prediction of Antidepressant Treatment Response - A Pharmaco- and Imaging Genetic Contribution

Katharina Domschke[1], Udo Dannlowski[2], Patricia Ohrmann[2], Christa Hohoff[2], Jürgen Deckert[3], Volker Arolt[2], Thomas Suslow[2], Bernhard T. Baune[4]

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Background: In major depression, an increasing number of pharmacogenetic studies have examined association of antidepressant treatment response with variation in candidate genes. Given only few consistently reproducible findings, we attempted to further refine investigation of the clinical phenotype of depression in pharmacogenetic studies with particular attention to gender,

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 serotonergic, 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 MAO-A VNTR and the COMT val158met variants were found to influence antidepressant treatment response specifically in female patients. The 5-HT1A -1019 C/G polymorphism was associated with treatment response in patients with melancholic, but not atypical depression. 5-HTTLPR, CNR1 rs1049353 and NPY rs16147 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-HTT, 5-HT1A, MAO-A, COMT, CNR1 and NPY gene variants on antidepressant treatment response with differential effects regarding gender and clinical subtypes 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

Yvette Sheline[1], Marcus E. Raichle[2], Mark A. Mintun[2], Abraham Z. Snyder[2], Deanna Barch[3]

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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 down-regulate activity broadly within the DMN. These findings provide a brain network framework within which to consider the pathophysiology of depression.
Supported by NIMH: 2K24MH79510 and 2R01MH64821

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-anhedonic 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.
Supported by limited funding of Medtronic Inc. for IIT

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

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

Konrad Talbot

University of Pennsylvania, Philadelphia, PA

Background: Dysbindin-1 is encoded by DTNBP1, a top candidate gene in schizophrenia (Sz). Its reference sequence transcripts encode the protein's major isoforms: dysbindin-1A, -1B, and -1C. Sz 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 DTNBP1 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.