antipsychotics as an adjunctive therapy to mood stabilizers (Yatham Bipolar Disord 2003, 5 7–19), reawakening interest in neurotransmitter dysfunction as a potential basis of the disorder. Morphological studies indicate that there is an apparent disruption in cortical neuronal/glial balance in subjects with bipolar disorder (Rajkowska et al. Biol Psychiatry 2001, 49 741–752; Cotter et al. Cereb Cortex 2002, 12 386–394). Furthermore, impaired executive function suggests that functionality of the dorsolateral prefrontal cortex may be compromised (Martinez-Aran et al. Psychother and Psychosom 2002, 71 39–46). Studies in our laboratory have shown that in the dorsolateral prefrontal cortex, Brodmann's area 9, there is little sign of alterations in neurotransmission as defined by receptor number. However, there are quite profound changes in some of the molecules involved in mediating normal synaptic function. Together, these data suggest that the functionality of this brain region may be disrupted in bipolar disorder.

03-04

Genetic and genomic approaches to better understanding bipolar disorder

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Background: Bipolar affective disorder (BP) is a severe mood disorder characterized by alternating periods of mania and depression, with estimates of lifetime prevalence up to 4%.
Methods: Studying BP families, genetic linkage analysis has been used to identify susceptibility loci. Positional cloning and association analysis was used to identify the susceptibility gene. Microarray analysis of gene expression profiles of mice treated with antimanic drugs was performed.
Results: The cadherin gene FAT was identified by positional cloning. Association with bipolar disorder was seen in two case-control cohorts with a family history of psychiatric illness, and in two cohorts of parent-proband trios where association was identified among bipolar cases who had exhibited psychosis. Pooled analysis further supported association ($P = 0.0002$, odds ratio = 2.31, 95% confidence interval: 1.49–3.59). Expression of FAT, and putative interacting proteins beta-catenin and the Ena/VASP proteins were investigated in mice following administration of the mood-stabilizing drugs, lithium and valproate. FAT was significantly downregulated ($P = 0.027$), and Catnb and Enah were significantly upregulated ($P = 0.0003$ and 0.005), in response to lithium. Expression of genes encoding murine homologs of the FAT-interacting proteins was investigated by microarray analysis, with eight genes showing significantly altered expression in response to lithium (binomial $P = 0.004$).
Conclusions: Together, these data provide convergent evidence that FAT and its protein partners may be components of a molecular pathway involved in susceptibility to bipolar disorder. Genetic and genomics approaches may provide a means to better understanding the genes involved in BP onset and progression.

03-05

Treatments and outcomes in bipolar disorder

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The treatment of bipolar disorder remains a major challenge. A wide variety of psychopharmacological treatments are available, which are usually considered under the groupings of antimanic drugs, antidepressant drugs and mood stabilizers. In real-life clinical practice, monotherapy is the exception, and the challenge is to obtain rational polypharmacy. Even, with a wide range of available drugs, and a high likelihood of being able to achieve remission from any particular mood episode, the probability of recurrence and/or chronic residual symptoms is high. The greatest therapeutic challenges are in the areas of depressive and mixed symptom states.

PTSD and Neuroimaging: Neural Correlates of Affective, Cognitive and Clinical Response

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Overview

Multidisciplinary research is increasingly focused on identifying potential biological markers of post-traumatic stress disorder (PTSD). Convergent evidence leads to theoretical models of a dysregulation in medial prefrontal inhibitory and limbic arousal networks in PTSD. This symposium provides insight into medial prefrontal and limbic function by examining cognitive, affective and clinical processes in PTSD using event-related potential and functional magnetic resonance imaging methodologies. Working memory and inhibitory processing will be explored in cognitive paradigms, fear processing will be examined in an affective paradigm and neural correlates of treatment response and clinical subtypes of PTSD (dissociation) will showcase clinical applications of this research.

04-01

Abnormal recruitment of brain networks during trauma-neutral verbal working memory processing in PTSD

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Post-traumatic stress disorder (PTSD) is characterized by disturbances in concentration and memory, symptoms that are a source of further distress for patients. Abnormalities in working memory (WM) updating have been identified in PTSD (Clark et al. 2003), indicating dysfunction in left hemisphere brain regions critically involved in WM updating. However, it remains unclear whether this finding is because of underlying abnormalities in WM systems in PTSD. Functional magnetic resonance imaging was done for 13 patients with severe PTSD and matched nontraumatized controls, during WM performance where participants either maintained or continually updated verbal stimulus material in separate conditions. The PTSD group failed to show differential activation during WM updating, instead showing abnormal recruitment of WM updating network regions during WM maintenance. These regions included bilateral dorsolateral prefrontal cortex and inferior parietal lobe. Several other regions were abnormally decreased during WM updating in PTSD including the hippocampus, anterior cingulate and brainstem pons. These results suggest compensatory recruitment of WM networks normally only deployed during updating, which may be linked to the abnormally decreased activity in PTSD during WM updating in other key regions, regions that have been consistently implicated in the neurobiology of PTSD. These abnormalities reflect the difficulty patients with PTSD have engaging with their day-to-day environment.

04-02

Topography of event-related potentials to visuoverbal working memory updating and target detection in PTSD

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This study examined the topography of event-related potentials (ERPs) during working memory updating in medicated ($n = 14$) and unmedicated ($n = 20$) groups of patients with PTSD and age- and gender-matched controls. ERPs were recorded from 26 scalp sites during a working memory paradigm that involved identifying when a letter appeared twice in a row in a series of letters. A large positive component at around 400 ms (P3wm) following presentation of nontarget stimuli was considered an index of working memory updating. Group differences were found in the amplitude of this component and also in P3 amplitude and latency following target stimuli. Contrary to expectations, these effects were most apparent in the medicated subgroup. Both groups of patients with PTSD exhibited delayed reaction time, but only the medicated participants were impaired in target detection accuracy. Neither ERP nor behavioural abnormalities were related to CAPS symptom scores. These results are consistent with research that suggests SSRI medication may alter working memory performance, but the results may be due to some other characteristic of the medicated participants such as differing symptom profiles.

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