09-04

Plasma apolipoprotein E: roles and targets in schizophrenia and bipolar disorder

S Sundram[1,2,3]

[1]Northern Psychiatry Research Centre; [2]Molecular Psychopharmacology, Mental Health Research Institute of Victoria; and [3]Department of Psychiatry, The University of Melbourne, Melbourne, Victoria, Australia

Apolipoprotein E (apoE) belongs to a large heterogeneous family of lipid-binding proteins and is produced by a variety of tissues including the brain and liver where it subserves a diversity of functions. The primary metabolic role of apoE is as a key regulator of cholesterol and triglyceride transport between cells. It has three isoforms, E2, E3 and E4, and genetic variation in the distribution of these isoforms are associated with plasma lipid levels and atherosclerosis; the E4 isoform is also associated with increased risk for Alzheimer's disease, impaired cognition and decreased neurite outgrowth. As both lipid metabolism and synaptic connectivity are disturbed in schizophrenia and bipolar disorder, the role of apoE has been investigated in these disorders. The majority of studies have focused on the association between the genetic polymorphisms of apoE and schizophrenia with inconsistent results; however, measurement of protein apoE levels in the brain report changes in both disorders. We report here the first study to our knowledge of measurement of plasma apoE levels in subjects with schizophrenia and bipolar disorder in a medication-free state and following 6 weeks of treatment. In both medication-free schizophrenia and bipolar disorder subjects, plasma apoE levels were significantly decreased compared with control subjects and although there were increases in both groups following treatment, levels were still significantly less than for the control group. These results will be discussed in reference to their implications for altered lipid metabolism in these two disorders and the potential for the development of therapeutics to rectify these deficits leading to improved health outcomes for people with schizophrenia and bipolar disorder.

Identifying Gene-brain Markers of Cognition and Emotion: Implications for Psychiatric Disorders

L Williams

The Brain Dynamics Centre, Westmead Millennium Institute, Westmead Hospital and Discipline of Psychological Medicine, University of Sydney, Australia

Overview

This symposium reviews the biological underpinnings of particular genes and will examine biological markers of emotional and cognitive dysfunction in healthy samples. The data presented will be drawing from a standardized integrative database that includes measures of neural and autonomic activity, and behaviour. In particular, the interacting effects of environmental influences (stress) will be examined, as well as moderating effects of gender. This work was supported by an ARC-linkage grant (LP0455104).

10-01

Understanding genotype-phenotype relationships using the Brain Resource International Database: Implications for psychiatric conditions

C Dobson-Stone[1], JM Gatt[2], S Kuan[2], RH Paul[3], E Gordon[4], LM Williams[2], PR Schofield[5]

[1]Prince of Wales Medical Research and Garvan Institutes, Australia; [2]The Brain Dynamics Centre, Westmead Millennium Institute, Westmead Hospital and Western Clinical School, University of Sydney, Australia; [3]Brown Medical School, USA; [4]The Brain Resource International Database (The Brain Resource Company), Australia; and [5]Prince of Wales Medical Research and Garvan Institutes, Australia

Background: Psychiatric disorders are characterized by breakdowns in higher brain functions (eg, memory, attention, emotion), which have a substantial genetic component. Elucidating the relationship between genetic variation and brain function variation is an important step in understanding the dispositions to psychiatric disorder. Some functional polymorphisms that have consequences for aspects of brain function will be described. These include the Val66Met substitution in brain-derived neurotrophic factor, the Val108/158Met substitution in catechol-o-methyl transferase, the ε2/3/4 polymorphism in apolipoprotein E, the serotonin transporter promoter deletion polymorphism and a variable number tandem repeat (VNTR) polymorphism that alters expression of monoamine oxidase A (MAOA).
Methods: We are investigating these variants using the Brain Resource International Database (BRID), a standardized and integrated database of brain function from healthy volunteers and targeted clinical groups. Data collected include neuropsychological and DASS-NEO test scores, cognition and emotion event-related potentials, autonomic measures, and structural and functional magnetic resonance imaging.
Results: This approach is illustrated by our investigation of the MAOA VNTR polymorphism in 312 BRID

https://doi.org/10.1017/S0924270800032403 Published online by Cambridge University Press

participants. We detected subtle deficits in information processing and vigilance in people bearing the low-expressing genotype. Men with the 'low' genotype exhibited additional deficits in executive function.
Conclusions: Study of the genetic contributors to variation in normal brain function will provide insight into normal neurological processes and have direct relevance to our understanding of such disorders as depression, anxiety and Alzheimer's disease. Because the consequences of individual polymorphisms are generally subtle, an integrative approach that allows for large cohorts is essential to assess their effects.

10-02

The neurodevelopmental effects of apolipoprotein E alleles on brain function

DM Alexander[1], JM Gatt[2], S Kuan[2], C Dobson-Stone[3], EG Todd[4], PR Schofield[3], E Gordon[1], LM Williams[2]

[1]The Brain Resource International Database (The Brain Resource Company), Australia; [2]The Brain Dynamics Centre, Westmead Millennium Institute, Westmead Hospital and Western Clinical School, University of Sydney, Australia; [3]Prince of Wales Medical Research and Garvan Institutes, Australia; and [4]Garvan Institute of Medical Research, Australia

Background: Neuroimaging evidence shows the ε4 allele of the apolipoprotein E (*APOE*) gene is related to brain-functional differences during memory tasks in young, middle-aged and elderly adults. Developmental studies, however, indicate that the ε4 allele confers a cognition-enhancing/protective effect in children and young adults. This study uses a new measure of spatiotemporal wave activity that has shown greater sensitivity and larger effect sizes than EEG power measures.
Methods: About 415 normal subjects were genotyped and divided into three *APOE* status groups: ε2 (ε2/ε2 or ε2/ε3), ε3 (ε3/ε3) and ε4 (ε3/ε4 or ε4/ε4) and four age bands: 6–15, 16–30, 31–50 and 51–65 years old. The ε3 'controls' were age and gender matched to the ε2 and ε4 subjects. Subjects were tested on the Brain Resource International Databa cognitive battery. EEG was measured during a visual working-memory task and analyzed using measures of event-related power and spatiotemporal wave activity.
Results: Analysis of covariance (controlling for age) showed no differences for *APOE* status on most cognitive tests. However, the ε4 group had *improved* performance on two tests of verbal fluency, compared with ε3, across all age bands. ε4 subjects showed less spatiotemporal wave activity in the theta band at ~200 ms poststimulus, but no power differences.
Conclusions: This study confirms previous findings of brain-functional differences between ε3 and ε4 subjects across a broad range of ages. However, the verbal fluency results, supported by previous studies showing developmental benefits of ε4, suggest that brain-functional *differences* do not necessarily imply *deficits* prior to the risk period for dementia.

10-03

Identifying pathways to depressed mood and cognitive dysfunction: the BDNF Val66Met polymorphism and early life stress

JM Gatt[1], S Kuan[1], C Dobson-Stone[2], RH Paul[3], PR Schofield[2], E Gordon[4], LM Williams[1]

[1]The Brain Dynamics Centre, Westmead Millennium Institute, Westmead Hospital and Western Clinical School, University of Sydney, Australia; [2]Prince of Wales Medical Research and Garvan Institutes, Australia; [3]Brown Medical School, USA; and [4]The Brain Resource International Database (The Brain Resource Company), Australia

Background: The BDNF Val66Met polymorphism involves a valine (Val) to methionine (Met) substitution, with the Met allele implicated in phenotypes (poor memory, depressed mood) and endophenotypes (abnormal hippocampal-prefrontal function) of depression. Given a well-established link between stress and depression, we examined whether early life stress moderates the depressogenic and related cognitive effects of BDNF Val66Met in humans and whether hippocampal loss and autonomic dysregulation mediate these effects.
Methods: About 374 healthy subjects from the Brain Resource International Database provided data from cheek swabs (for genotyping), cognitive tests, psychometric questionnaires of mood and personality, tonic and phasic measures of autonomic function (average heart rate and variability during resting conditions and during cognitive- and emotion-related tasks) and magnetic resonance imaging.
Results: Path analysis showed that with increasing stress, BDNF Met status predicts direct effects on hippocampal loss and indirect effects on depressed mood and poor cognition (working memory, executive function/processing speed, verbal memory). These effects were mediated by gray matter atrophy, autonomic dysregulation (raised average heart rate, reduced heart rate variability) and neuroticism.
Conclusions: The findings suggest that the BDNF Met allele carriers may show an increased risk for structural brain deficits and autonomic dysregulation if exposed

https://doi.org/10.1017/S0924270800032403 Published online by Cambridge University Press