

DISCOVERING NEW GENETIC AND PSYCHOSOCIAL PATHWAYS IN MAJOR DEPRESSIVE DISORDER: THE NEWMOOD PROJECT

Annabel Freeborough & Jessica Kimpton

The Neuroscience and Psychiatry Unit. The University of Manchester, UK

SUMMARY

The World Health Organisation predicts that Major Depressive Disorder (MDD) will be the second greatest contributor to the global burden of disease by 2020, however, the neurobiological mechanisms behind the disease and the risk factors for it are yet unknown. NewMood (New Molecules for Mood Disorders) was a research project funded by the EU, collaborating work from 10 European countries with the aim of finding new molecular mechanisms behind MDD to develop more effective treatment options.

This review explains the aims and objectives of NewMood and how it intends to achieve them with regards to the current literature. It also outlines two of its most recent projects: genome wide association replication study for single nucleotide polymorphisms (SNPs) increasing susceptibility to MDD and stress related pathways in depression using the cortisol awakening response (CAR). Both of these studies had significant results and could further contribute to our current understanding of MDD.

Key words: depression - anti-depressants - molecular mechanisms – stress - single nucleotide polymorphisms

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THE NEWMOOD PROJECT

The NewMood (New Molecules for Mood Disorders) Study was an EU funded project collaborating work from 13 clinical and basic science groups from 10 European countries. The groups researched new molecular mechanisms contributing to the pathophysiology of Major Depressive Disorder (MDD) in the hope of identifying new biomarkers for the disorder (Deakin et al. 2011).

MDD is becoming increasingly prevalent worldwide and is now the fourth greatest cause of disability. The recurrent nature of MDD and its significant impact on the sufferer's quality of life supports the need to study the aetiology behind the condition. Furthermore, the mechanism of action of MDD treatments remain incompletely understood, despite similar pathways being targeted for over thirty years.

These studies aimed to identify novel treatments and interventions for MDD through animal and human research in order to benefit our understanding of MDD aetiology, treatment and prevention.

REACHING THE AIMS OF NEWMOOD

Molecular pathways for depression initially investigated micorarrays in animal models manifesting three aspects of depression: anhedonia, sensitivity to stress and negative assessment of circumstances. These traits are endophenotypes for depression. The animal studies used endophenotypic measures to explore MDD as these traits can be cross validated in human studies. It was hypothesised that the personality aspects of depression would be closer to the genetic susceptibility mechanisms that the depressed phenotype as a whole.

In the study by Hoyle et al, four animal models were compared to identify molecular processes implicated in MDD pathogenesis.(Hoyle et al. 2011) These models were knockouts of the cannabinoid receptor (CB1), serotonin transporter, glutamate transporter 1 gene and a knockdown model inducing glucocorticoid impairment. The upregulation and downregulation of genes within these models were investigated for correlations. Results in each of the four molecular pathways demonstrated the shared role of cellular stress and synaptic remodelling in depression, suggesting these mechanisms as final common pathways (Hoyle et al. 2011).

A further knockout study performed in mice by Martin et al, focused on emotional behaviour traits mediated through the CB1. (Martin, Ledent, Parmentier, Maldonado, & Valverde, 2002) This demonstrated the importance of the receptor for learning and memory processes as well as emotional responses (Martin et al., 2002).

NewMood animal studies have therefore identified genes that were consistently associated with MDD models of endophenotypic traits. These interesting genes have been replicated and utilised in formulating hypotheses for pathways leading to MDD pathogenesis in humans (Juhász et al. 2009). In further studies expression changes have been reversed by standard and novel therapeutic agents to explore the impact on the MDD phenotype and attempt to understand the mechanism of action of well known antidepressant medications.

The main limitation of the animal studies has been the subjective nature of life experiences, which is difficult to replicate in an animal model. It is thought that depression may not be a categorical disease state but on a spectrum of normal variation. Therefore human

studies are vital for demonstrating the multiple mechanisms in the brain which may have a synergistic or antagonistic effect depending on the environment. Thus, in parallel with the animal studies, molecular pathways of interest were translated to humans using the experiments of nature afforded by natural variation in genes. One such study focused on the CB1 receptor gene (CNR1) and other genetic polymorphisms that may moderate the risk of depressive side effects of the withdrawn anti-obesity drug rimonabant, which is an antagonist of the CB1. (Lazary, Juhasz, Hunyady, & Bagdy 2011) Therefore investigating the different impact of interrupting molecular pathways depending upon the individuals genetic profile.

Other human studies depended upon subjective, self reported questionnaires to determine subgroups that represent endophenotypic processes in MDD. This reflects intermediate phenotypes that may predispose an individual to depression such as anxiety and impulsivity (Benko et al. 2010, Lazary et al. 2009). One personality score was determined from items within the 'Big-5 inventory' exploring traits including; neuroticism or the tendency to experience negative emotions. Polymorphisms within the CNR1 gene have been associated with such traits, rather than the overall MDD phenotype (Juhasz et al. 2009). A further personality score reported on the tendency to repetitive thought or rumination. This trait has been associated with polymorphisms within the CREB-BDNF-NTRK2 pathway. These genetic variants have been demonstrated to impact on memory processes (Egan et al. 2003, Lazary et al. 2011).

Brain imaging has further advanced the ability to understand specific phenotypes in human subjects. The completion of tasks, during functional brain imaging, has been vital for determining the areas of the brain involved in cognitive processes. Particular experiments using face recognition tasks have been useful for understanding regions involved in emotional processing and for understanding the areas of the brain affected by selective serotonin reuptake inhibitors during these cognitive tasks (Anderson et al. 2011).

Therefore the use of animal studies with the combination of paper-based and imaging human studies has enabled cross validation of findings and provides support for the genetic processes suggested by the NewMood research.

CONTRIBUTING FACTORS IN THE SUSCEPTIBILITY TO MDD

Studies have hypothesised that a proportion of the risk of MDD is due to polymorphisms within susceptibility genes. This genetic basis is supported by twin studies that estimate the heritability to be between 30-40% (Sullivan et al. 2000). The relative risk for an individual who has a 1st degree family member with MDD is 2-3 times more than the general population. This has prompted the use of genome-wide association

studies (GWAS) to identify important susceptibility genes in the aetiology of depression. This method is advantageous as it has the hypothesis-free potential to detect all susceptibility loci in patients with a known phenotype in a sufficiently large sample (Wray et al. 2010). The principle is that with 500,000 DNA sequence variations, single nucleotide polymorphisms (SNPs), throughout the genome, disease association with a particular SNP allele will identify risk loci.

However, GWAS have been inconsistent in their findings and individual SNPs have a small impact. An important reason for this may be the neglect of gene by environment interactions in which, for example, genotype influences risk only if a particular environmental factor is present. Furthermore, the modest heritability of MDD indicates that environmental factors are very important (Wray et al. 2010).

This theory has been substantiated through the addition of environmental interactions into genetic susceptibility processes (Juhasz et al. 2009). Work into the serotonin transporter supports the role of environment by gene interactions as variants within the promoter region of the serotonin transporter gene, SLC6A4, effect stress sensitivity (Caspi et al. 2010, Lazary et al. 2008) Therefore this gene strongly influences the impact of negative environmental risk factors on a particular individual. Further studies have identified other regions within the serotonergic system that are dependent upon interactions with recent stressful life events to increase depression and anxiety symptom scores (Mekli et al. 2011).

Indeed it is beyond doubt that early childhood adversity sets up vulnerability to later depression and that current life stresses trigger episodes. These are likely to contribute along a pathway, resulting in the expression of MDD. Such theories are strongly supported by the key role of the stress response in both animal and human studies. It is widely assumed that stress-induced increases in cortisol secretion might, through its effects on the brain, mediate the effects of stress on the risk of depression or on inducing symptoms themselves. However, cortisol is thought to mediate adaptive, protective responses to the stressor. If the stressor and hence hypercortisolaemia is chronically sustained it may cause neurotoxic effects on the brain regions involved in hypothalamic-pituitary-axis (HPA) control, altering its function. The HPA-axis then escapes from normal feedback inhibition leading to chronically increased cortisol concentrations, which could lead to further neuroplastic changes and depression.

Thus depression may be the result of an endophenotype vulnerability that pre-disposes the individual to the disorder particularly if exposed to stressful life events. The identification of specific pathways leading to MDD pathogenesis has led to a more holistic view of the overall mechanisms involved (Juhasz et al. 2011). This enables the synergistic impact of multiple genetic polymorphism and environmental

risk factors on the eventual MDD phenotype. The two current NewMood studies evaluate the role of genetics and psychosocial factors in the pathway to stress related neuronal changes and ultimately MDD.

RECENT PROJECTS

GWAS replication study for SNPs increasing susceptibility to MDD

The inconsistencies in GWAS data have led to replication studies into the most significant SNPs to identify genetic pathways implicated in MDD. The study used data from previous GWAS and replication studies to investigate how SNPs associated with psychiatric disorders in previous studies influenced the susceptibility to MDD. We explored whether genetic polymorphisms could account for phenotypes by amplifying or tuning down brain responsiveness to adverse experiences or interactions with personality traits and explained the role of SNPs in the accumulation of neuronal damage on a pathway to MDD.

Hypothalamic-adrenal axis (HPA) related genes and psycho-social stress vulnerability to depression

Dysregulation of the cortisol stress response has long been implicated in the pathophysiology of depression. The cortisol awakening response (CAR) has received particular attention as it has high intra-individual stability and is more sensitive to mild and remitted depression. The study investigated whether the CAR was influenced by current or previous depression compared to those without a personal or family history of depression and whether personality traits, life events or SNPs in different genes associated with HPA-axis control had individual or cumulative effects.

CONCLUSIONS

The studies suggest that MDD is the result of a complex interplay between genetic polymorphisms and environmental factors. Single susceptibility genes containing the risk of MDD are unlikely but multigenic mechanisms alongside environmental risk factors seem to contribute to pathways which result in a depressive phenotype.

To date, the significant genes arising from the NewMood studies are particularly involved in mediating the stress pathway. These polymorphisms could sensitize the stress pathways, predisposing these individuals to depression if exposed to adverse life events. Future studies would need to consider the interactions between polymorphisms in the stress pathways and how these are implicated in the specific mechanisms known to increase the MDD risk.

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Correspondence:

Annabel Freeborough

The Neuroscience and Psychiatry Unit

G.907 Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

E-mail: Annabel.Freeborough@student.manchester.ac.uk