Model abstract examples

The following four abstracts have been selected as model abstracts because they meet important criteria of a good scientific abstract:

a. Succinct description of the clinical/scientific background and/or prior work introducing the current study.

b. Short description of the methodology but with appropriate level of detail.

c. Giving details of statistical analyses.

d. Clear presentation of real data; abstract includes the outcome of the statistical analyses.

e. Concise description of the conclusion(s) of the study, which are underscored by the data presented.

EXAMPLE 1

Structural brain alterations in major depression: findings from the ENIGMA Major Depressive Disorder Working Group

L. Schmaal[1] , D.J. Veltman[1], T.G. Van Erp[2], P.G. Sämann[3], T. Frodl[4]

[1]VU University Medical Center, Department of Psychiatry, Amsterdam, The Netherlands
[2]University of California, Department of Psychiatry and Human Behavior, Irvine, USA
[3]Max Planck Institute of Psychiatry, Neuroimaging Research Group, Munich, Germany
[4]University of Dublin, Trinity College, Department of Psychiatry, Dublin, Ireland

Background: Patterns of structural brain alterations in major depressive disorder (MDD) remain unresolved. This is in part due to small sample sizes of neuroimaging studies resulting in limited statistical power, disease heterogeneity and the complex interactions between clinical characteristics and brain morphology. Therefore, we initiated the ENIGMA-MDD Working Group to identify robust imaging markers of MDD using coordinated standardized image processing and statistical analysis protocols. Here, we investigated subcortical volume alterations in MDD in the largest sample to date using an individual participant data (IPD) based meta-analysis approach.

Methods: Structural T1-weighted MRI scans from 1,728 MDD patients and 7,199 controls from 15 research samples worldwide were analyzed locally using FreeSurfer. Segmentations of subcortical regions, lateral ventricles and total intracranial volume were visually inspected for accuracy and compared between patients and controls using regression models controlling for age, sex, and intracranial volume locally following standardized protocols designed to facilitate harmonized image analysis across multiple sites. Separate stratified analyses comparing age of onset, stage of illness (first versus recurrent episode patients), and symptom severity were performed. Results were combined in random-effect meta-analysis models. Meta-regression analyses were used to test whether mean age of each sample, field strength of MR images, FreeSurfer version, percentage of patients acutely depressed, percentage of patients taking antidepressants, and percentage of patients taking antipsychotics explained a significant proportion of the variance in effect sizes across sites in the meta-analysis. Results were considered significant if they exceeded a Bonferroni corrected P-value threshold ($P=0.05/9$ regions$=5.6\times10^{-3}$).

Results: Relative to controls, patients had significantly lower hippocampal volumes (Cohen's $d=-0.14$) – an effect driven by recurrent MDD patients ($d=-0.17$). Age of onset ≤ 21 was associated with a smaller hippocampus ($d=-0.20$) and a trend towards smaller amygdala ($d=-0.12$) and larger lateral ventricles ($d=0.14$). Symptom severity was not associated with regional brain volumes. Sample characteristics including mean age, proportion of antidepressant users and proportion of remitted patients did not moderate brain

volume alterations. Samples with a higher proportion of antipsychotic medication users showed larger caudate volumes in MDD patients compared to controls.

Conclusions: Results of this first initiative of the ENIGMA-MDD working group clearly indicate a key role of the hippocampus in the pathophysiology of MDD, showing robust hippocampal volume reductions particularly in recurrent patients and patients with an age of onset of MDD ≤ 21. Brain changes in other subcortical regions in MDD were less evident. Our findings suggest that the hippocampus is a prime target region for future research aimed at further unravelling the pathophysiology of MDD and improving treatment. The important next step within our consortium will be examining cortical brain alterations associated with MDD and we are in the process of applying similar methods to cortical surface thickness and surface area measures.

EXAMPLE 2

COMT × DRD2 epistasis modulates a putative emotional connectomic intermediate phenotype for schizophrenia

H. Cao[1], A. Schäfer[1], O. Grimm[1], L. Haddad[1], H. Walter[2], A. Heinz[2], S. Witt[1], M. Rietschel[1], S. Cichon[3], H. Tost[1], A. Meyer-Lindenberg[1]

[1]Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany
[2]Charité Universitaetsmedizin Berlin, Department of Psychiatry and Psychotherapy, Berlin, Germany
[3]University of Bonn, Department of Genomics, Bonn, Germany

Our prior work using graph theory based method, presented at the 43rd Annual Meeting of Society for Neuroscience, has identified a disrupted visual-limbic subnetwork in unaffected first-degree relatives of schizophrenia during emotion processing, and validated this connectomic finding as a robust and task-specific intermediate phenotype (presented at the 20th Annual Meeting of Organization for Human Brain Mapping) . Here, to further investigate the utility of this potential phenotype in imaging genetics, we examined the main effects and interaction of two dopaminergic risk variants on this identified subnetwork: a candidate variant for emotion dysregulation (COMT val158met) [1] and a genome-wide supported schizophrenia risk variant in DRD2 (rs2514218) [2].
Our sample consisted of 289 healthy individuals of European ancestry without a first-degree relative with mental illness (mean age 33.73±9.78 years, 155 females). The subjects were recruited from the communities in Mannheim, Bonn and Berlin. For each individual, the COMT val158met polymorphism was directly genotyped by the DNA arrays while DRD2 rs2514218 genotype was imputed with Impute2 using reference haplotypes derived from the 1000 Genomes Project [3]. Following the procedures of the previous studies, the carriers of the presumed protective alleles were combined into one group (COMT: val/val + val/met; DRD2: risk C allele number <1.5). The observed genotype distributions did not deviate from Hardy-Weinberg equilibrium (COMT: 207 Val-carriers, 82 Met/Met, P=0.79; DRD2: 174 T-carriers, 115 CC, P=0.36). The four genotype groups for both variants did not show significant differences in demographic, psychological and fMRI performance data (all P values >0.10).

All the subjects underwent a well-established emotional face-matching task. The image preprocessing followed the standard procedures implemented in SPM8. The mean time series were extracted from each of the 90 anatomical regions defined by AAL template and corrected for noises. Whole-brain connectivity matrices were subsequently computed by the pairwise correlations between the corrected time series of each of the 90 nodes. Here, the averaged connectivity measures of the same subnetwork reported in our previous studies were extracted and entered as the dependent variable into an ANCOVA model with genotypes (COMT and DRD2) as variables of interest and age, sex and site as covariates of non-interest. Significance was measured at P<0.05.

No significant main effects for both COMT and DRD2 genes on this phenotype measures were found (COMT: P=0.95, DRD2: P=0.15). However, the epistatic study demonstrated a strong COMT × DRD2 interaction (p=0.01). Specifically, in the group of COMT met/met homozygotes, there was a significant decrease of the phenotype in DRD2 CC homozygotes compared to T carriers (p=0.01). In contrast, no significant difference was found between DRD2 genotypes in the group of COMT val carriers (p=0.36), indicating that COMT val158met is epistatic to DRD2 rs2514218 on the identified phenotype.

This study showed that genetic epistasis between COMT val158met and DRD2 rs2514218 could modulate the identified emotional connectomic phenotype for schizophrenia and highlighted the utility of this potential phenotype in imaging genetics.

References

[1] Mier, D., Kirsch, P., Meyer-Lindenberg, A., 2010. Neural substrates of pleiotropic action of genetic variation in COMT: a meta-analysis. Molecular Psychiatry 15(9), 918-927.

[2] Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511(7510), 421-427.

[3] Howie, B., Marchini, J., Stephens, M., 2011. Genotype imputation with thousands of genomes. G3 1(6), 457-470.

EXAMPLE 3

Determining the CNS effects of ebselen: a potential lithium-mimetic

N. Singh[1], A. Sharpley[1], U. Emir[2], C. Masaki[1], T. Sharp[3], C. Harmer[1], S. Vasudevan[3], P. Cowen[1], G. Churchill[3]

[1]University of Oxford, Department of Psychiatry, Oxford, United Kingdom
[2]University of Oxford, Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom
[3]University of Oxford, Department of Pharmacology, Oxford, United Kingdom

Background: Bipolar disorder has a lifetime prevalence of 3.9% [1] and is a life-long, debilitating mental health illness. Lithium is the gold standard for the treatment of bipolar disorder and although efficacious, it has problematic side effects, and a narrow therapeutic index. Therefore, it remains crucial to develop new lithium-like drugs. One of lithium's possible therapeutic targets is inositol monophosphatase (IMPase), and recently, it was reported that ebselen, a drug originally developed for its antioxidant and anti-inflammatory properties, was a potent IMPase inhibitor [2]. In animal models, ebselen has some lithium-like effects, and since it has a known clinical safety, it can be studied in man.

Objective: To demonstrate that ebselen, a potential lithium-mimetic, (a) shows target engagement in the brain by virtue of lowering myo-inositol, which is a product of IMPase; and (b) to characterise the central nervous system (CNS) effects of ebselen in an experimental medicine study with healthy volunteers.

Methods: In a randomised, double-blind, placebo controlled, cross-over healthy volunteer (n=16) study, we assessed the effects of ebselen on brain myo-inositol levels using proton magnetic resonance spectroscopy following 3×600mg doses of ebselen, and in the same cohort, the effect the on sleep architecture after 4×600mg doses. In a separate double-blind, placebo controlled, randomised, parallel group healthy volunteer (n=40) study, we administered 3×600mg ebselen and tested the effects on tasks of emotional processing. Questionnaires were also used to determine baseline characteristics of the groups, quality of sleep and side-effects, if any. Statistical significance was ascertained by t-tests, curve fitting, or repeated measures ANOVA, as appropriate.

Results

myo-Inositol: Ebselen decreased myo-inositol in the anterior cingulate cortex compared to placebo ($p=0.026$), but not in the occipital cortex.
Sleep: In the sleep polysomnogram, ebselen decreased slow-wave sleep significantly ($p=0.035$). It had no effect on any other sleep parameters, for example, Rapid Eye Movement (REM). Additionally, ebselen did not affect the quality of sleep as measured by the Leeds Sleep Evaluation Questionnaire.

Emotional processing: In the facial expression recognition task, participants on ebselen showed an increase in recognition of ‘disgust’ and ‘happiness’ ($p<0.0001$ and $p=0.003$, respectively). In a reward-punishment task,

ebselen showed a decrease in the learning of reward reinforcement stimuli, and a trend in increased learning of punishment (p=0.01). Finally, ebselen showed a decreased latency to response in an acoustic startle task (p=0.01). Ebselen had no effect on positive or negative emotional memory tasks, the attentional vigilance task, and the auditory verbal learning task (AVLT). There were no statistically significant differences between the ebselen and placebo groups, with regard to demographics and baseline questionnaire measures.

Conclusion: Ebselen lowered myo-inositol and hence showed that it inhibits IMPase in vivo. Additionally, ebselen showed CNS effects in various tasks designed to demonstrate effects of psychoactive drugs. Ebselen was found to be safe and well tolerated at the doses administered. Hence, a clinical trial for testing the efficacy of ebselen in bipolar disorder is warranted.

References

[1] Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 62, 593-602.

[2] Singh, N., Halliday, A.C., Thomas, J.M., Kuznetsova, O.V., Baldwin, R., Woon, E.C.Y., et al., 2013. A safe lithium mimetic for bipolar disorder. Nat. Comms. 4, 1332.

EXAMPLE 4

Effect of fluoxetine and MIML4-11, a novel tropomyosin-related kinase receptor agonist, in a lipopolysaccharide-induced model of depression

M.J.F. Levy[1], F. Boulle[1,2], V.S. Martin[1], C. Poilbout[1], D. Rognan[3], L. Lanfumey[1]

[1]INSERM U. 894, Centre de Psychiatrie et Neurosciences, Paris, France
[2]Maastricht University - European Graduate School for Neuroscience EURON, Department of Psychiatry and Neuropsychology, Maastricht, The Netherlands
[3]UMR7200 CNRS, Laboratoire d'Innovation Thérapeutique, Strasbourg, France

Purpose: Brain-derived neurotrophic factor (BDNF) and its tropomyosin-related kinase receptor (TrkB) have been proposed to play a key role in the pathophysiology of mood disorders, including depression. In rodents, direct infusion of BDNF protein in the hippocampus showed antidepressant-like effects [1]. In addition, antidepressant treatments are reported to exert their effects, at least in part, via the modulation of neurotrophin and growth factors. In particular, the selective serotonin reuptake inhibitor fluoxetine has been abundantly reported to increase both BDNF mRNA and protein expressions after chronic in vivo administration [2]. However, growth factors and neurotrophins have shown to display considerable limitations, including a poor blood-brain barrier penetration and a short half-life in plasma, making these small proteins difficult to use as a therapeutic tool. Identification of neurotrophin mimetics remains a current challenge, and may represent an interesting target for the development of a new class of therapeutic agents for mood-related disorders. We recently identified MIML4**-**11 as a potential TrkB agonist, which we characterized here in vitro on TrkB phosphorylation and in vivo, in a model of depression-like behaviour induced by the acute administration of lipopolysaccharide (LPS) [3].

Methods: In vitro experiments were conducted on primary cortical cultures. Cortices of E16 embryo from CD1 mice were isolated and incubated for 5 days at 37 °C and 5% CO_2. Cells were then stimulated with MIML4–11 (10µM) and TrkB phosphorylation was assessed using immunofluorescence assay.
In vivo studies were performed using 8-weeks CD1 mice injected with LPS through two different protocols [4]: (1) Mice were injected with either fluoxetine (20mg/kg), MIML4–11 (2mg/kg, i.p.) or vehicle 30 minutes before a LPS i.p. injection (0.33mg/kg or vehicle). 24 hours later, a series of behavioural tests were performed to evaluate the effects of MIM-L4–11 and fluoxetine, including tail suspension test (TST), saccharine preference test and coat state. (2) Mice were injected with LPS and received fluoxetine or MIML4–11 (same doses as in protocol 1) 24h later. After another 30 minutes, the similar series of behavioural investigations were performed on drug- versus vehicle-injected mice.

Results: In vitro data showed that MIML4–11 significantly increased TrkB phosphorylation (+ 22.6±4.8%, $p<0.05$, Student t test) on cortical cells. In in vivo treatment, as expected, LPS induced a depressive like behaviour in CD1 mice, demonstrated by an increase in both the immobility time in TST ($F(1,40)=6.815$; $p=0.0127$, two way ANOVA) and coat state score ($F(1,41)=33.42$; $p<0.0001$, two way ANOVA), and a decrease in saccharine preference ($F(1,64)=10.92$; $p=0.0016$, two way ANOVA). Fluoxetine could prevent LPS-induced immobility time increase in TST in both protocols. Interestingly, MIML4–11 reversed LPS-induced increase in immobility time and coat state score only in protocol 2.

Conclusion: Altogether our results showed that in vitro, MIML4 displayed TrkB receptor agonist properties. In vivo, this compound could reverse the effect of LPS, suggesting that a TrkB agonist could display therapeutic effect on mood disorders. Whether these effects are direct or are linked to neuroinflammation pathways are currently addressed.

References

[1] Deltheil, T., Guiard, B.P., Cerdan, J., David, D.J., Tanaka, K.F., Reperant, C., Guilloux, J.P., Coudore, F., Hen, R., Gardier, A.M., 2008. Behavioral and serotonergic consequences of decreasing or increasing hippocampus brain-derived neurotrophic factor protein levels in mice. Neuropharmacology 55, 1006-1014.

[2] Nibuya, M., Nestler, E.J., Duman, R.S., 1996. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. J. Neurosci. 16(7), 2365-2372.

[3] Ohgi, Y., Futamura, T., Kikuchi, T., Hashimoto, K., 2013. Effects of antidepressants on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. Pharmacol. Biochem. Behav. 103, 853-859.

[4] Walker, A.K., Budac, D.P., Bisulco, S., Lee, A.W., Smith, R.A., Beenders, B., Kelley, K.W., Dantzer, R., 2013. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. Neuropsychopharmacology 38, 1609-1616.