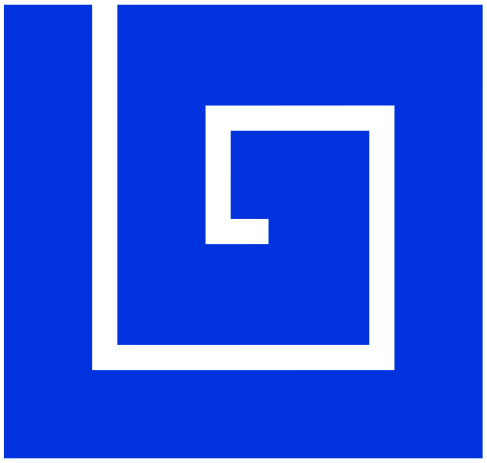
2019

PSYCHIATRIA FENNICA



SUPPLEMENTUM 1

THE 4TH FINNISH SYMPOSIUM ON
BIOLOGICAL PSYCHIATRY

Helsinki 2019

PSYCHIATRIA FENNICA
Foundation for Psychiatric Research
Publication Series

ABSTRACT BOOKLET

THE 4TH FINNISH SYMPOSIUM ON BIOLOGICAL PSYCHIATRY

Psychiatria Fennica 2019, vol. 50, suppl. 1

ISSN: 2489-6152

PSYCHIATRIA FENNICA

2019, vol. 50, suppl. 1

Publisher

Foundation for Psychiatric Research

Fredrikinkatu 71 A, 4
FI-00100 Helsinki
Finland

(+358) 50 512 52 92)

December 17, 2018

Biomedicum, lecture hall 2

University of Helsinki

Organizers:
Tiina Paunio
Iiris Hovatta
Mikaela Laine
Alexandra Lahtinen

In collaboration with

B&M
Doctoral Program
Brain & Mind

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Do neurocognitive inferences based on diffusion MRI depend on magnetic field strength and artifact correction?

Arias, J.C.[1], Marino, J.[1], Leemans, A.[2], Caballero Bello, A.[3] & Björnholm, L.J.[4]

1 CCLINEC, Chubut, Argentina
2 Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands
3 Universidad de Córdoba, Córdoba, Spain
4 University of Oulu, Oulu, Finland

Introduction: Diffusion-weighted magnetic resonance imaging (DW-MRI) provides a way to locally quantify brain connectivity. Diffusion tensor imaging (DTI) was the first model applied for obtaining microstructural information from DW-MRI. Frequently used DTI indices include fractional anisotropy (FA) and mean diffusivity (MD), which are sometimes reported in relation with scores in cognitive tests. The effects of scanner and artifact correction processing steps in connectivity indices have been separately assessed by previous studies. The purpose of this work was to assess both effects in connectivity indices of the uncinate fasciculus and in their relations with cognitive performance.

Methods: Fifteen healthy volunteers were scanned on a 1.5 T Philips and a 3.0 T Siemens scanners with a DW-MRI scan protocol of 32 directions, b-value of 1000 s/mm2, isotropic voxel size of 2 mm, one b0 image. The processing pipeline incrementally included Gibbs ringing, subject motion, eddy currents and EPI distortions correction. The uncinate fasciculus was segmented by one expert judge. FA and MD were compared between the scanners through the processing pipeline by paired t-tests. Correlations between the connectivity indices and cognitive performance were also assessed throughout processing by calculating correlation coefficients.

Results: Significant inter-scanner differences were observed, with higher FA and lower MD for the Philips scanner. Inter-scanner differences decreased for FA and increased for MD after processing. Most processing steps produced a decrease in FA (~0.02). In MD, only the first and second correction steps produced significant changes (increase and decrease, respectively). Connectivity values derived from the Siemens scanner correlated more strongly with the cognitive tests.

Discussion: We have shown connectivity index-specific scanner and processing effects in tract-averaged measures. Data obtained with different processing pipelines should be compared with caution. Correlations with scores in cognitive tests varied significantly, thus extending this caution to the comparison of results across cognitive microstructure studies.

Caudalized brain organoids for modelling human brain development and disease

Molchanova, S.[1,2,#,*], Cherepkova, M.[1,*], Abdurakhmanova, S.[3], Pörsti, E.[1], Saarimäki-Vire, J.[1], Balboa, D.[1], Domanskyi, A.[4], Gainetdinov, R.[5], Kuivanen, S.[6], Vapalahti, O.[6], Piepponen, P.[7], Taira, T.[2], Otonkoski, T.[1] & Bespalov, M.M.[1]

1 Faculty of Medicine, RPU, Molecular Neurology, Biomedicum Stem Cell Center, University of Helsinki, Finland
2 Department of Veterinary Biosciences and Neuroscience Center, University of Helsinki, Finland
3 Institute of Biomedicine, Faculty of Medicine, University of Helsinki, Finland
4 Institute of Biotechnology, University of Helsinki, Finland
5 Institute of Translational Biomedicine, St. Petersburg State University, Russia
6 Department of Virology, Faculty of Medicine, University of Helsinki, Finland
7 Department of Pharmacy, University of Helsinki, Finland

Current address: Medical Neurogenetics Group, Molecular Neurology, Faculty of Medicine, University of Helsinki, Finland
* Equal contribution

Defects in the development of synaptic connectivity and neuronal networks very likely underlie pathological changes, seen in neurodevelopmental disorders, such as autism spectrum disorder and schizophrenia. Here, we describe the in vitro model of developing human functional neuronal network. We generate expandable human neuroepithelial stem cells (hNESC) from pluripotent stem cells (PSC) that have caudal identity (HoxA2-expressing), and differentiate into neurons and glia. In suspension, NESC form brain organoids, containing self-organized structures resembling developing brain. They secrete serotonin and, upon rostralization with FGF8, dopamine and its metabolites. By studying organoids of different ages, we were able to demonstrate the development of basic excitable properties of the neurons and formation of the synaptic network. Also, during maturation, neurons shift from long-lasting plateau-like activity to the adult-type irregular action potential firing. By the age of 4 months, most of the neurons show repetitive action potential firing and spontaneous synaptic excitatory and inhibitory currents, meaning that the cells are differentiated enough to generate and conduct electrical impulses. Overall, our data suggest that developing neurons with human genetic background, cultured in 3D system, may be used as in vitro model for studying human synaptic development in healthy and pathological conditions. Organoids can also be regionalized to mimic various brain regions such as forebrain, midbrain and hippocampus. In addition, brain organoids can be created from induced PSC harvested from patients and/or from genetically engineered PSC to model neurodevelopmental diseases.

Prenatal exposure to maternal cigarette smoking and structural properties of the human corpus callosum

Björnholm, L.[1], Nikkinen, J.[2], Veijola, J.[1] & Paus, T.[3,4]

1 Department of Psychiatry, Research Unit of Clinical Neuroscience, University of Oulu and Oulu University Hospital, Oulu, Finland
2 Department of Radiotherapy, Oulu University Hospital, Oulu, Finland
3 Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Canada
4 Departments of Psychology and Psychiatry, University of Toronto, Toronto, Canada

The development of axonal connections during fetal period is guided by numerous signaling molecules, making it prone to external insults. Prenatal exposure to maternal cigarette smoking (PEMCS) exposes the fetus to nicotine, which is a potent neuromodulator due to the early expression of nicotinic receptors in the developing brain. Nicotine causes abnormalities in cell proliferation, alters neuronal pathfinding and disrupts the functions of sex hormones, with many of the alterations persisting after birth or only emerging later in development. PEMCS is one of the most prevalent harmful prenatal factors in industrialized countries. The exposure has been associated with lower birth weight, smaller head circumference at birth, lower cognition and compromised mental health. In the present report, we focus on an association between maternal smoking during pregnancy and structural properties of the corpus callosum, a major white matter tract connecting the two hemispheres, in adolescents and youth drawn from three community-based cohorts. We use six complementary MRI measures sensitive to structural properties of brain tissue. We observed associations between PEMCS and higher callosal R2, and lower MD in 368 typically developing males of the ALSPAC. Higher FA and lower callosal volume were observed in the exposed (vs. non-exposed) young males from the NFBC1986 cohort (males n=188, females n=259), with an Exposure-by-Sex interaction in the same MRI measures. The findings may relate to a higher fraction of small-caliber axons, as reported in our earlier work. According to the relation between fetal sex hormones and nicotine exposure shown in animal studies, our findings may suggest disruption of masculinization of the male brain due to suppression of testosterone during fetal development. We hypothesize that maternal cigarette smoking during pregnancy disrupts sex hormone-mediated early programming of callosal features characteristic to males or females.

Psychedelic treatment for addiction? Preliminary characterisation of anti-rewarding properties of LSD and 25CN-NBOH

Elsilä, L.[1] & Korpi, E.[1]

1 Department of Pharmacology, Faculty of Medicine, University of Helsinki

Psychedelic drugs, such as LSD and psilocybin, have again become of great interest in neuroscience after several clinical studies have shown promising results in the treatment of psychiatric disorders with psychedelic therapies. There is also data showing that a single dose of psychedelic drug, paired with behavioural therapy, could help alcohol addicts significantly cut down their drinking with the effects lasting for up to six months. The mechanisms behind the therapeutic effects are still unknown as is whether the same effects are present in animal models of addiction. To assess the potential acute anti-rewarding effects a classic hallucinogen LSD and a highly selective 5-HT2A receptor partial agonist 25CN-NBOH, we used drinking-in-the-dark paradigm where C57BL/6J male mice were allowed to drink 20 % v/v ethanol for 2 h for three days a week and 4 h on the fourth day, 3 h after the start of the active circadian phase. A two-bottle choice was incorporated in the design, giving the mice both ethanol and water to choose from. After three weeks of learning to drink, the mice were treated with either vehicle (n=8), 0.2 mg/kg LSD (n=9) or 3.0 mg/kg 25CN-NBOH (n=9) right before giving them access to ethanol for the following 4 h. Both LSD and 25CN-NBOH reduced the amount of ethanol consumed acutely by approx. 40 % during the following hours (relative to baseline; LSD p=0.0014; 25CN-NBOH p=0.0885) but no prolonged effects were observed during the week-long follow-up. While applying a different drinking paradigm, our findings contradict the recently published data on LSD's effects on mouse drinking and therefore highlights the need for more thorough investigation.

Chemogenetic manipulation of the insula alters alcohol consumption in rats

Haaranen, M.[1], Schäfer, A.[1], Kuhlefelt, A.[1] & Hyytiä, P.[1]

1 Department of Pharmacology, Faculty of Medicine, University of Helsinki, Helsinki, Finland

The anterior insula (AI) and its efferent connections are associated with multisensory information processing and goal-directed decision making. Recent data suggests a vital role for AI in voluntary alcohol consumption in both rats and humans. To further elucidate the role of the AI in the regulation of alcohol consumption we employed chemogenetic tools for manipulating AI activity. An excitatory G-protein coupled designer receptor exclusively activated by designer drugs (Gq-DREADD) was expressed bilaterally in the AI. DREADD activation by clozapine-N-oxide administration (CNO,10 mg/kg, i.p.) decreased alcohol consumption in alcohol-preferring AA (Alko Alcohol) rats trained to drink 10% alcohol for 2 hours q.a.d. To characterise the effects of AI activation on its efferent connections, we expressed the Gq-DREADD unilaterally, followed by CNO activation. We then quantified the neuronal activation marker c-Fos expressing puncta in AI-connected brain regions and compared them to the contralateral c-Fos expression count. To characterise further the role of the individual output connections, we injected Cre-dependent DREADDs (excitatory Gq-DREADD, inhibitory Gi-DREADD or control) bilaterally into the AI while applying a retro-Cre to AI terminal areas in the nucleus accumbens (Acb) or the basolateral amygdala (BLA) in order to achieve pathway-specific DREADD expression, followed by CNO DREADD activation. Pathway-specific activation or silencing of AI -> BLA connections as well as silencing of AI -> Acb connections did not influence voluntary alcohol consumption. However, activation of the AI -> Acb pathway induced a statistically significant ($p < 0.01$) increase in voluntary alcohol consumption. Collectively, these experiments show that the AI with its rich interconnectivity modulates alcohol reinforcement and consumption and could therefore serve as a future therapeutic target. Supported by EU's Horizon 2020 program (668863, SyBil-AA).

Maternal prenatal anxiety and infant temperament: moderating effects of the oxytocin receptor genotype

Kajanoja, J.[1], Nolvi, S.[1,2], Paunio, T.[3,4], Kantojärvi, K.[3,4], Karlsson, L.[5] & Karlsson, H.[1]

1 Department of Psychiatry, University of Turku, FinnBrain Birth Cohort Study, Turku, Finland
2 Institute of Medical Psychology, Charité Universitätsmedizin, Berlin, Germany
3 Genomics and Biomarkers Unit, National Institute for Health and Welfare, Helsinki, Finland
4 Department of Psychiatry, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
5 Department of Child Psychiatry, University of Turku, FinnBrain Birth Cohort Study

Introduction: A growing body of research suggests that allelic variability in the oxytocin receptor gene may regulate individual susceptibility to psychosocial stress. Maternal stress during pregnancy has been tied to infant emotional problems, cognitive delays and aberrant brain development, which may affect future mental health. The purpose of this study was to test whether common SNPs (rs53576 & rs2254298) in the oxytocin receptor gene affect the association of maternal prenatal anxiety, and infant negative reactivity and self-regulation.

Methods: In the FinnBrain birth cohort study, we analyzed a sample of 1173 mothers and their children. Prenatal stress was assessed using questionnaires concerning anxiety symptoms during pregnancy. We controlled for the effects of age, education level, Body Mass Index, parity, smoking status during pregnancy, and postnatal depressive symptoms. Infant negative reactivity and self-regulation were assessed at the age of 6 months.

Results: Main effects for genotype were not significant. Both rs53576 ($p=0.045$, partial $\eta 2 =0.005$) and rs2254298 ($p=0.007$, partial $\eta 2 =0.006$) showed a significant interaction with prenatal anxiety in predicting infant self-regulation. There was no significant interaction effect for negative reactivity ($p=0.338$ for rs53576 and $p=0.788$ for rs2254298). Our results suggest a cumulative genetic risk, as the negative association between prenatal anxiety and infant self-regulation was stronger in infants carrying both risk alleles, compared to those carrying 0 or 1 ($p=0.002$, partial $\eta 2 =0.008$)

Conclusions: Our results suggest that previously identified risk alleles in the oxytocin receptor gene may increase vulnerability to the effects of stress already in utero, although effect sized were small. The harmful effects of maternal prenatal stress may at least partially be transmitted via an oxytocinergic mechanism. Our results also highlight the importance of studying the additive effect of several SNPs.

FoxO1 variant rs17592371 modifies the association between maternal distress during pregnancy and offspring psychiatric problems in early childhood

Kero, H.[1], Räikkönen, K.[1], Lahti-Pulkkinen, M.[1], Cattaneo, A.[2,3], Czamara, D.[4], Binder, E.[4,5] & Lahti, J.[1]

1 Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Finland;
2 Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK;
3 Biological Psychiatry Unit, IRCCS Fatebenefratelli S. Giovanni di Dio, Brescia, Italy;
4 Max-Planck-Institute of Psychiatry, Department of Translational Research in Psychiatry, Munich, Germany:
5 Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, USA.

Background: Maternal distress during pregnancy increases the risk for psychiatric problems in the offspring. Genetic variation in FoxO1 was recently found to moderate well-established association between childhood stress and risk for subsequent depression in adulthood with rs17592371 showing the strongest effect. Whether rs17592371 also modifies the link between maternal distress during pregnancy and risk for psychiatric problems in the offspring is not known.

Methods: Study sample comprised mother-child dyads (N=460) of the Finnish Prediction and prevention of preeclampsia and intrauterine growth restriction (PREDO) -cohort. To measure levels of prenatal distress of the mothers, we used the means of the Spielberger State Anxiety Scale (STAI) and Center for Epidemiologic Studies Depression Scale (CES-D) across up to 14 measurements during pregnancy. DNA was extracted from the cord blood samples and rs17592371 was extracted from the Illumina OmniExpress Exome 1.2 array. Early psychiatric problems were reported by the mothers with the Child Behavior Check List (CBCL) at the mean age of 3.5-years.

Results: Association between both maternal STAI and CES-D during pregnancy and CBCL Total Problems and Externalizing scores differed according to the rs17592371 genotypes (p-value for interactions < .05). Maternal distress associated with higher scores in the CBCL Total Problems scale and Externalizing scale in the rs17592371 CT/TT carriers when compared with the CC carriers.

Conclusions: We showed that FoxO1 variant rs17592371 modifies the association between maternal anxiety/depression during pregnancy and offspring psychiatric problems in childhood. This result is in line with earlier study focusing on the modifying role of FoxO1 variation in the relationship between childhood stress and depression and may indicate the role of FoxO1 in the sensitivity to psychosocial distress.

Neural correlates of narrative morphosemantics: a functional MRI study

Kurkinen, K.[1,2], Alho, J.[1], Hulten, A.[1], Jääskeläinen, I.[1], Saalasti, S.[1,3], & Sams, M.[1]

1 Department of Neuroscience and Biomedical Engineering, Aalto University School of Science
2 Faculty of Biological and Environmental Sciences, University of Helsinki
3 Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki

Morphemes are the smallest units of a language carrying a meaning. In Finnish language, words contain a variety of morphemes, most often bound suffixes, which makes Finnish useful when studying morphology. In the current study, we ask how semantic processing of morphological information in a narrative context is reflected in brain activity as measured with functional magnetic resonance imaging (fMRI). We presented an approximately 8 minute long intelligible narrative to subjects (healthy right-handed females, N=29) during fMRI. The narrative was told from a female first-person perspective. As a control, we presented a gibberish version of the narrative, where each word was replaced with a pseudo-word while still keeping the inflectional morpheme similar to the original version. Thus, the main difference between the conditions is that the morphemic constituents can be meaningfully combined in the original story but not in the gibberish version. The semantic content of the narrative was modelled with a Word2vec semantic model based on co-occurrences of words in a large corpora (here the Finnish language internet). Next, we use regularized canonical correlation analysis (rCCA) which allows for estimation of correlation between different-sized matrices, to compare the semantic content of the stimuli with the voxel-wise blood-oxygen-level dependent (BOLD) brain signal time course. We hypothesize that the neural correlates of morphosemantic processing differ between intelligible and gibberish narratives thereby allowing us to better understand how the brain combines morphological information. The current study will introduce a novel method to study impaired comprehension of narrative language, present in many neuropsychiatric disorders.

Gene-environment interaction in myelin plasticity after chronic psychosocial stress

Laine, M.A.[1], Trontti, K.[1], Misiewicz, Z.[1], Sokolowska, E.[1], Rikandi, E.[2,3,4], Kulesskaya, N.[1], Heikkinen, A.[1], Saarnio, S.[1], Balcells, I.[1], Greco, D.[5], Jokitalo, E.[5], Mantere O.6, Kieseppä T.[4,7], Suvisaari, J.[4], Raij, T.T.[3,7] & Hovatta, I.[1,2]

1 Molecular and Integrative Biosciences Research Program, University of Helsinki, Finland
2 Department of Psychology and Logopedics, University of Helsinki, Finland
3 Department of Neuroscience and Biomedical Engineering and Advanced Magnetic Imaging Center, Aalto University School of Science, Espoo, Finland
4 National Institute for Health and Welfare, Mental Health Unit, Helsinki, Finland
5 Institute of Biotechnology, University of Helsinki, Finland
6 Douglas Mental Health University Institute and McGill University, Department of Psychiatry, Montréal, Canada
7 Department of Psychiatry, Helsinki University Hospital, Finland

Genetic and environmental factors, such as chronic psychosocial stress, jointly predispose to anxiety disorders and other psychiatric conditions. We used chronic social defeat stress (CSDS) as a model of psychosocial stress in four inbred mouse strains [129S2/SvPasCrl, BALB/cAnNCrl, C57BL/6NCrl (B6) and DBA/2NCrl (D2)] to investigate the role of genetic background in stress resilience and -susceptibility. We found that these strains differed notably in behavioural response to stress, with at the extremes 95 % of D2 mice but only 31 % of B6 mice displaying susceptibility. To survey neurobiological pathways affected by stress we conducted mRNA-sequencing on three stress-associated brain regions [medial prefrontal cortex (mPFC), ventral hippocampus (vHPC), and bed nucleus of the stria terminalis (BNST)] of CSDS-exposed and control D2 and B6 mice. Using gene set enrichment analysis we found strong enrichment of myelin-related genes. Electron microscopic analysis validated that myelin thickness varied between behaviourally different mice (resilient, susceptible or control) and genetic backgrounds. For example, B6 susceptible mice had thicker myelin sheaths and higher myelin-related gene expression in the BNST compared to same-strain controls, while resilient D2 mice had thinner sheaths in the mPFC compared to susceptible mice. We additionally demonstrated that myelin-related gene expression was not affected by stress in the dorsal hippocampus or cortex excluding the mPFC, and that corpus callosum thickness was unaffected. This suggests that observed myelin-related differences occurred specifically in stress-associated regions. Lastly, in healthy humans we showed higher mean diffusivity, a proxy of potentially sparser myelination as measured by diffusion tensor imaging, in frontal white matter of participants with subclinical anxiety compared to participants without. Our findings suggest that plasticity in CNS myelin has a critical role in response to psychosocial stress.

Testing the effects of chronic ethanol exposure on anxiety-related behaviors in an animal model

Mugantseva, E.[1], Hyytiä, P.[2] & Latvala, A.[1]

1 Institute for Molecular Medicine Finland, University of Helsinki, Finland
2 Department of pharmacology, University of Helsinki, Finland

Alcohol use disorders and anxiety disorders often co-occur but whether heavy alcohol use is causally related to the development of anxiety remains unknown. While several/experimental studies have focused on acute exposures corresponding to the effects of binge-like intake of ethanol, the effects of long-term voluntary consumption of ethanol have not been studied extensively. We aimed at studying the effects of long-term alcohol use on the development of anxiety-related behavior using two groups of alcohol-preferring adolescent and adult female rats (Alko, Alcohol, Helsinki, Finland) starting at the age of 6 and 16 weeks, respectively. Animals/belonging to the experimental groups (n=12, each) were given 10% alcohol as their only drinking fluid during the first 4 days to habituate them to the taste of alcohol. After that, the rats were allowed a two-bottle choice between alcohol and water, which represents a widely used paradigm for voluntary alcohol consumption. The control groups (n=12, each) were given only water during the entire experiment. We conducted behavioral experiments to study anxiety-like behavior using the elevated plus maze, open field, light/dark box, stress-induced hyperthermia, and social behavior (the dominance tube test). After eight weeks, all animals in the experimental groups had developed a consistent and physiologically meaningful alcohol consumption pattern with a preference for choosing alcohol above 90%. There were no consistent differences in anxiety-related behaviors between the groups. In contrast, we found differences in the social dominance/behavior: the adult drinking rats showed less dominant behavior than the control group ($p < 0{,}001$). In conclusion, our preliminary results with a follow-up corresponding to approximately 10 years in humans provide no evidence of long-term effects of early and late-onset alcohol use on the development of anxiety.

Joint factorial structure of psychopathology and personality

Rosenström, T.[1,2], Gjerde, L.C.[1,3], Krueger, R.F.[4], Aggen, S.H.[5], Czajkowski, N.O.[1,3], Gillespie, N.A.[5], Kendler, K.S.[5,6,7], Reichborn-Kjennerud, T.[1,8], Torvik, F.A.[1,3] & Ystrom, E.[1,3,9]

1 Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway
2 Department of Psychology and Logopedics, University of Helsinki, Finland
3 Department of Psychology, University of Oslo, Norway
4 Department of Psychology, University of Minnesota, USA
5 Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA
6 Deparment of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA
7 Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA
8 Institute of Clinical Medicine, University of Oslo, Norway
9 PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Norway

While many studies have focused on specific psychiatric disorders, researchers are increasingly recognizing that they may reflect a non-specific shared dimension of risk, dubbed ‘p factor’ or ‘general psychopathology factor’. Despite long-standing interest in their potential etiologic role, normative and pathological personality traits have rarely been integrated into the large-scale structural analyses of psychiatric disorders. We report findings from a joint factor structure of 11 psychiatric disorders, five personality-disorder trait domains (DSM-5 Section III), and five normative personality trait domains (the ”Big Five”) in a population-based sample of 2796 Norwegian twins, aged 19-46 (Psychol Med, http://doi.org/10.1017/S0033291718002982). Covariation (‘comorbidity’) among these variables could be interpreted to reflect three factors: (i) general psychopathology factor (heritability h2 = 0.48 with 95% CI = 0.41-0.54); (ii) a risk factor specific to internalizing disorders and traits (h2 = 0.35, CI = 0.28-0.42); (iii) a risk factor specific to externalizing disorders and traits (0.37, CI = 0.31-0.44). This pattern suggests that many findings on specific disorders may reflect a general behavioral liability instead of, or in addition to, specific etiology. Future research should investigate joint etiologic and transdiagnostic models for normative and pathological personality and other psychopathology.

Autism in females

Saure, E.[1], Castrén, M.L.[2] & Salmi, J.[3,4]

1 Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland
2 Physiology, University of Helsinki; Faculty of Medicine, Helsinki, Finland
3 Department of Psychology and Speech-Language Pathology, University of Turku, Turku Finland
4 Turku Institute for Advanced Studies, University of Turku, Turku Finland

Background: Autism spectrum disorder (ASD) is 2-5 times more common in males than in females. In recent years, researchers have found, that there are differences between females and males in ASD symptoms, neuropsychological characteristics, comorbid problems, neurobiology and genetics. The purpose of this systematic review is to give a comprehensive picture about the role of female sex/gender in ASD. To establish this, the review covers ASD symptoms, neuropsychology, neurobiology, comorbidity, neurogenetics and neuroendocrinology.

Methods: Literature search was conducted using the Medline and PsychINFO as search engines. Search terms were 1) autism spectrum disorder or Asperger syndrome and 2) sex differences or gender differences or sex-specific. The final sample consisted of a total of 129 articles. Data was extracted on all relevant variables of the study, that were the number of participants, age of participants, specific diagnoses, methods and results.

Results: Sex/gender differences in ASD were found in all areas included in this systematic review. Females with high function ASD (HFASD) were found to have less problems in social communication and interaction and less repetitive and restricted behavior and interests than males with HFASD. However, females with ASD were found to have more sensory processing problems, mental health problems and epilepsy than males with ASD. Females with ASD were also found to have lower full-scale intelligence quotient than males with ASD. In the context of etiology, it has been found that there are sex/gender differences in neuroanatomy, susceptibility genes and hormone levels.

Conclusions: Results from this systematic review suggest that females with HFASD are underdiagnosed. This results from etiological sex/gender differences that cause partially different clinical presentation of ASD between females and males. ASD research has also ignored females with ASD. In the future, it is crucial to pay attention to females with ASD in the clinical work and scientific research.

Mouse strain specific gene and miRNA expression responses to chronic stress

Trontti, K.[1,2] & Hovatta, I.[1,2]

1 Molecular and Integrative Biosciences Research Program, University of Helsinki, Finland
2 Department of Psychology and Logopedics, University of Helsinki, Finland

Inbred mouse strains differ vastly both in their innate and psychosocial stress-induced anxiety levels, but the genetic mechanisms underlying the strain variation are not known. We investigated gene expression differences associated with chronic social defeat stress (CSDS) in two mouse strains, mostly stress-resilient C57BL/6NCrl (B6), and mostly stress-susceptible DBA/2NCrl (D2). We carried out RNA-sequencing (RNA-seq) and microRNA-sequencing (miRNA-seq) of medial prefrontal cortex (mPFC) and ventral hippocampus (vHPC) from stress-susceptible and control mice of the two strains. To identify differentially expressed genes and miRNAs, we discretized gene expression levels using supervised Discriminant Fuzzy Patterns (DFP). Genes expressed at a higher or lower levels in susceptible mice compared to the controls, in one or both strains, were analyzed for enriched Gene Ontology (GO) terms. In addition, to identify the predicted targets of miRNAs with differential expression, we used the Ingenuity MicroRNA Target Filter. B6 mice had a larger number of differentially expressed genes after CSDS in both brain regions (mPFC n=1496, vHPC n=4501) than D2 mice (mPCF n=258, vHPC n=593). Most genes responding to stress showed a gene-environment interaction and were either private to the strain (mPFC 95.4%, vHPC 90.0%) or shared, but differentially expressed in opposite directions (mPFC n=2, vHPC n=1). Similarly, the 41 stress-responding miRNAs in both brain regions were mostly strain specific (mPFC 95.1%, vHPC 90.2%) and only six miRNAs were differentially expressed in both strains. Comparison to test whether genes private to the strain coalesce in the same GO terms showed common enrichment only for glucocorticoid receptor binding between B6 mPFC and D2 vHPC. The expression levels of 48 differentially expressed miRNAs anticorrelated with several differentially expressed mRNAs in both strains (mPFC: B6 n=254, D2 n=15; vHPC: B6 n= 289, D2 n=46) of which three anticorrelated with a gene annotated to glucocorticoid receptor binding.

Comorbidity of substance misuse with anxiety-related and depressive disorders: A genetically informative population study of 3 million individuals in Sweden

Virtanen, S.[1,2], Kuja-Halkola, R.[2], Mataix-Cols, D.[3], Jayaram-Lindström, N.[3], Rück, C.[3], Suvisaari, J.[4], Lichtenstein, P.[2] & Latvala, A.[1,2]

1 Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
2 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
3 Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
4 National Institute for Health and Welfare, Helsinki, Finland

Importance: Substance misuse and anxiety-related and depressive disorders (ADs) are among the most common psychiatric conditions and often co-occur. Despite adversities associated with the comorbidity, its causes remain unclear.

Objective: We used Swedish nationwide register data aiming to (1) estimate associations of substance misuse and ADs in the population, (2) investigate gender differences in comorbidity, and (3) test the associations while accounting for genetic and shared environmental factors in stratified analyses within twin pairs and siblings.

Design, Setting, and Participants: Individuals born in Sweden between January 1968 and December 1997 (n=2,996,403) were followed-up with register-based data for 1997-2013. Main Outcomes and Measures Substance misuse was defined using ICD-10 diagnoses of substance use disorders (F10-F16, F18-F19) and drug-related criminal convictions. ADs included anxiety (F40-F43) and depressive disorders (F32-F34, F38-F39). Confounding by sex, birth year, personality disorders (F60.0-F60.9), socioeconomic covariates, and parental history of psychopathology was adjusted for.

Results: Risk of ADs was substantially increased in individuals with substance misuse (Risk Ratios (RR): 2.5-4.5). Of the AD diagnosis clusters derived from exploratory factor analysis, generalized anxiety/depression had the strongest association with substance misuse (RR=4.46, 95% CI 4.42-4.50). Similarly, those with substance misuse had a 4.6-fold (95% CI: 4.52-4.60) risk of generalized anxiety/depression and a 4.7-fold (95% CI: 4.65-4.84) risk of panic disorder/social phobia as compared to those without substance misuse. The associations were stronger in women than in men, and were attenuated in within-family analyses. However, elevated risks were found even among MZ twins suggesting the comorbidity was not fully explained by familial factors.

Conclusions and Relevance: Risk of ADs is elevated in individuals with substance misuse, and vice versa, and these associations are partially confounded by familial liabilities. However, the results are also compatible with a partially causal relationship between substance misuse and ADs.

PSYCHIATRIA FENNICA
Foundation for Psychiatric Research
Publication Series