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Title:
T34. THE IMPACT OF ANTIDEPRESSANT USE ON THE TRANSITION TO PSYCHOSIS RATE IN THE NEURAPRO TRIAL

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Background: Schizophrenia (SZ) is a complex and debilitating mental disorder that affects approximately 1% of the world population and, according to the World Health Organization, it is one of the top ten causes of disability in developed countries. Neonatal hypoxia is a well-establish risk factor to SZ development, though little is known about the molecular mechanisms involved. Indeed, animals submitted to neonatal gaseous hypoxia show behavioral alteration and neurochemical changes resembling SZ features. However, the effect of chemical hypoxia induced by cobalt chloride (CoCl2) treatment is poorly understood. Remarkably, hypoxia induces an augmentation of adenosinergic system, an effect that seems to be relevant to neurodevelopment. Indeed, attention is being focused to adenosinergic system in the context of SZ. Thus, our goal was to investigate the effect of neonatal CoCl2 administration in distinct neuronal and behavioral parameters related to SZ. Moreover, we evaluated the role of haloperidol, a typical antipsychotic, and caffeine, an adenosinergic antagonist, in this scenario.
Methods: Wistar rats were treated with CoCl2 (subcutaneous, 60 mg/kg) or saline (NaCl 0.9%) in post-natal day 7 (PND7) – period in which rodent's brain development is equivalent to human's in the moment of birth. At PND50 – corresponding to 18 years-old in humans – locomotion, which correlate with SZ positive symptoms, was evaluated. At PND90 – resembling adulthood in humans – social interaction deficit and contextual fear conditioning were analyzed, as indicator of SZ negative symptoms, and cognitive symptoms and diminished emotional processing, respectively. Immediately after, all animals underwent euthanasia and had their brains removed and dissected. HIF-1α and VEGF gene expression were analyzed through RT-qPCR at pre-frontal cortex. Additionally, total neurons and positive-parvalbumin (PV+) cells were labelled at pre-frontal cortex and amygdala through immunofluorescence. Four groups were also assessed to behavioral parameters: i) animals challenged with Haloperidol (ip; 0.1 mg/kg) or saline, 30 minutes before the experiments, at PND50 and PND90, and ii) rats treated with caffeine (sc; 10 mg/kg) or saline (at PND6); experiments were also conducted at PND50 and PND90.
Results: Our results show that CoCl2 treatment induced hyperlocomotion at PND50, as well as a decrease in social interaction and time of freezing at contextual fear conditioning test at PND90 when compared to control group. CoCl2 treated-rats also showed an increased expression of HIF-1α e VEGF, diminishment in PV+ neurons at pre-frontal cortex and increasing in amygdala in relation to control group. Moreover, haloperidol reversed behavioral deficits induced by CoCl2 treatment in both PND50 and PND90. Interestingly, the previous caffeine exposure also reversed the effect of CoCl2 at PND50 and PND90.
Discussion: In conclusion, our results indicate that chemical neonatal hypoxia induced behavioral alterations and neuronal changes relevant to SZ, reinforcing the hypoxia participation in the development of this disorder. The abolishment of CoCl2-induced effects after haloperidol reinforces the usage of this model to SZ studies. Importantly, caffeine treatment also warned behavioral modification, strengthening the participation of adenosinergic system in SZ development.

T33. NEUROIMMUNE MECHANISMS OF PSYCHIATRIC DISORDERS: LONGITUDINAL EVALUATION OF DIFFUSION MEASURES OF EXTRACELLULAR FREE WATER IN A NON-HUMAN PRIMATE MODEL OF MATERNAL IMMUNE ACTIVATION

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Background: A key finding in developmental neurobiology is a widespread role for immune molecules in normal brain development and synaptic function and evidence has been accumulating for an immune-based developmental pathophysiology in psychiatric disorders, particularly in schizophrenia. Epidemiological studies have revealed an increased incidence of schizophrenia in offspring of mothers who had an infection during pregnancy while GWAS studies have identified genetic links to the major histocompatibility complex and peripheral changes in immune markers are widely reported in the illness. The murine maternal immune activation model system is widely used to investigate the effects of immune activation during pregnancy on brain development in behavior in offspring. Here we report findings from an ongoing study of a unique cohort on non-human primates (NHP) who underwent MIA (compared to controls) on a promising biomarker of neuroimmune perturbation in vivo--extracellular free water--a diffusion magnetic resonance imaging measure obtained with a multi-shell acquisition, which we have shown in multiple studies to be increased in young people with early psychosis.
Methods: Fourteen pregnant rhesus monkeys (Macaca mulatta) received polyICLC and 14 control animals have been scanned prospectively from both to their current age of 3.5 years. The offspring from both groups underwent a diffusion MRI scan on a 3 Tesla Siemens Skyra scanner in which multiple b-value shells were acquired to improve estimation of extracellular free water. Data were collected when the offspring were 1, 6, 12, 24 and 36 months to date. Diffusion images were nonlinearly aligned to individual subject MPRAGE scans, which were segmented and parcellated into regions of interest using multi-atlas techniques. For this preliminary analysis, frontal, cingulate, and temporo-limbic regions were selected as a priori ROIs in addition to whole-brain gray and white matter masks. Group differences were assessed using repeated measures ANOVA and independent samples t-tests.
Results: Results from birth to age 2 years showed a significant main effect of group in both white ($p<.05$) and gray ($p<.001$) cingulate cortex free water, with MIA-exposed offspring showing higher free water. Similar trends were also identified in prefrontal white matter free water ($p=.07$) and whole-brain white ($p=.11$) and gray matter free water ($p=.07$). No significant group by time interactions were identified. Data analysis is currently underway including the 3-year time point.
Discussion: Despite the lack of gross behavioral abnormalities at age 2, extracellular free water values are increased in MIA-exposed offspring, particularly in the cingulate cortex. More global whole-brain free water group differences, however, did not reach statistical significance, which may indicate some regional specificity to these changes early in development. These NHP MIA model complement the human schizophrenia literature in which extracellular free water increases have been repeatedly identified. And show that changes in the brain occur early in life, well before the emergence of atypical behaviors in the NHP model.

T34. THE IMPACT OF ANTIDEPRESSANT USE ON THE TRANSITION TO PSYCHOSIS RATE IN THE NEURAPRO TRIAL

Monika Schlögelhofer*[1], Patrick D. McGorry[2], Barnaby Nelson[2], Maximus Berger[2], Connie Markulev[2], Hok Pan Yuen[2], Miriam R. Schäfer[2], Nilufar Mossaheb[3], Stefan Smesny[4], Ian B. Hickie[5], Gregor Berger[6], Eric Y. H. Chen[7], Lieuwe De Haan[8], Dorien Nieman[8], Merete Nordentoft[9], Anita Riecher-Rössler[10], Swapna Verma[11], Andrew Thompson[12], Alison Yung[13], G. Paul Amminger[2]
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Background: Over the last two decades, several randomised controlled trials (RCTs) have indicated that preventive psychosocial, pharmacologic (Van der Gaag et al. 2013), and nutritional interventions (Amminger et al. 2010) are likely to be beneficial in people at ultra-high risk (UHR) of psychosis, in terms of delaying or preventing a transition to psychosis. Antidepressant medication is commonly prescribed in young people at UHR for psychosis; however, the evidence regarding its efficacy for psychosis prevention is limited (Fusar-Poli et al. 2007; Cornblatt et al. 2007; Fusar-Poli et al. 2015). The main aim of the present study is to investigate the impact of concomitant AD medication on the transition to psychosis rate in young people at ultra-high risk of psychosis who participated in the NEURAPRO trial (McGorry et al. 2017).
Methods: In this secondary analysis, data from 304 participants of a multicenter, double-blind, placebo-controlled, randomized clinical trial (NEURAPRO) of omega-3 polyunsaturated fatty acids (omega-3 PUFAs) were included. During the trial, concomitant antidepressant medication was permitted for treatment of moderate to severe major depressive disorder (a score of ≥ 21 on the Montgomery-Asberg Depression Rating Scale, MADRS) in all participants.
Results: Of 304 participants, 189 (62.2%) were treated with ADs. 98 (64.1%) of those were in the omega-3 group and 91 (60.3%) in the placebo group. The transition rate to psychosis was higher in individuals who received AD treatment (13.2%; 25 of 189) as in individuals without ADs (6.1%; 7 of 115). The Kaplan-Meier survival curve estimated a group difference of X2 = 3.237, P = .072 (log rank test).
Discussion: Antidepressants are widely used in early psychosis. This analysis does not support the view that antidepressants may have reduced the transition to psychosis rate in this cohort. The findings are limited by the fact that antidepressants were prescribed based on clinical discretion. A randomised controlled trial is needed to determine whether antidepressants have a role in prevention of transition to psychosis.

T35. A PHASE 3, MULTICENTER STUDY TO ASSESS THE 1-YEAR SAFETY AND TOLERABILITY OF A COMBINATION OF OLANZAPINE AND SAMIDORPHAN IN PATIENTS WITH SCHIZOPHRENIA: RESULTS FROM THE ENLIGHTEN-2-EXTENSION

Abstract not included.

T36. NEURAL CHANGES FOLLOWING A BODY-ORIENTED RESILIENCE THERAPY WITH ELEMENTS OF KICKBOXING FOR INDIVIDUALS WITH A PSYCHOTIC DISORDER: A RANDOMIZED CONTROLLED TRIAL

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Background: Individuals with a psychotic disorder are at an increased risk of becoming the victim of a crime. A body-oriented resilience therapy with elements of kickboxing ('BEATVIC') aimed at preventing victimization by addressing putatively underlying factors was developed. One of these factors is social cognition, particularly facial affect processing. The current study investigated neural effects of BEATVIC using two face processing tasks.
Methods: Participants were randomized to either BEATVIC or a 'Befriending' control group consisting of social group meetings. Twenty-seven patients (BEATVIC n=14; Befriending n=13) completed an Emotional Faces task and the Wall of Faces task during fMRI, pre and post intervention. General linear model (GLM) analyses and Independent component analyses (ICA) were performed to define networks and investigate group*time effects.
Results: Voxelwise GLM analyses yielded no differences between groups over time. On a network level (ICA) we found overall increased activation of the salience network to angry and fearful faces in BEATVIC compared to Befriending. A trend towards significance (p=0.05) for increased activation of the (medial) visual network to (a group of predominantly) angry faces, and decreased deactivation (p=0.08) in the sensorimotor network in response to fearful faces in BEATVIC was observed.
Discussion: Increased activation of the salience network may suggest an increased alertness for potentially dangerous faces. Trend findings of the visual network and the sensorimotor network which are formally statistically insignificant may be regarded as tentative and strongly warrant further investigation to allow for more definite conclusions. Increased activation of the visual network might suggest more elaborate processing of visual information. Decreased deactivation in the sensorimotor network might indicate a reduced tendency for "freezing" and enhanced action readiness in response to indirect threat.

T37. PREPULSE INHIBITION IN UNAFFECTED SIBLINGS OF SCHIZOPHRENIA AND CLINICAL-HIGH RISK WITHOUT FAMILY HISTORY OF PSYCHOSIS

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Background: It is reported that prepulse inhibition (PPI) deficiency of startle reflex in schizophrenia is associated with positive symptoms and is hereditary. In this study, the perceived spatial separation (PSS) induced-prepulse inhibition paradigm based on the priority effect effectively was used to explore PPI levels of genetically high-risk (GHR) of schizophrenia and clinical high risk (CHR) without family history of psychosis
Methods: We examined startle magnitude and PPI in38 CHR (No family history of psychosis), 28 GHR (Siblings or children of schizophrenia), and 44 healthy controls (HC). Modified acoustic PPI paradigm included PSS-PPI and perceived spatial co-location PPI (PSC-PPI) with inter-stimulus interval (ISI) of 60 or 120ms. The Structured Interview for Psychosis risk Syndromes (SIPS) and MATRICS Consensus Cognitive Battery (MCCB) was used to measure psychotic symptom and neuropsychological state of individuals
Results: Using gender, age, and smoking as covariates, Covariance analysis for modified PPI level results revealed that there were significant differences in PSSPPI60 ($F = 6.25$, $p = 0.03$) and PSSPI120 ($F = 6.57$, $p = 0.03$) paradigm between the three groups. Compared with HC, PSSPPI paradigm detected PPI defects of CHR individuals at 60ms ISI ($F = 14.25$, $p < 0.001$) and 120ms ISI ($F = 14.01$, $p < 0.001$). PPI deficiency was not detected in GHR individuals. PPI level in both groups were unrelated to demographics, clinical characteristics, and cognition. Using GLM analysis, the interaction between grouping and experimental paradigm had no significant effect on PPI level at 60ms ($F = 1.88$, $P = 0.16$) and 120ms ($Z = 1.66$, $P = 0.19$).
Discussion: It seems that mere heritability of psychosis is not enough to produce PPI defects, which may be related to the progression of psychosis