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ABSTRACTS

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POSTERS

Poster 1

Automated behavioral phenotyping of ouabain-treated Flinders sensitive line rats: Toward an animal model for the mixed state? A pilot study

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Abstract

Abstract not available.

Poster 2

Predictive utility of artificial intelligence on schizophrenia treatment outcomes: A systematic review and meta-analysis

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Poster 3

Prevention and management of antipsychotics-induced metabolic syndrome via modulation of leucine sensors

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Poster 4

Quasi-tenacious depression (QTD) as an alternative framework to treatment-resistant depression (TRD)

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Poster 5

Sex, estrous cycle, and S-ketamine's rapid-antidepressant action in a genetic animal model of depression: Possible direct interaction of ketamine with membrane steroid receptors

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Poster 6

Feasibility test of intermittent Theta-Burst Stimulation (iTBS) as add-on to Eye Movement Desensitization and Reprocessing (EMDR) in EMDR-treatment-resistant work-related Post-traumatic stress disorder (PTSD)

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Abstract: Post-Traumatic Stress Disorder (PTSD) is a debilitating mental disorder that may have a long-term impact on an individual's emotional regulation, relationships, and functioning. Although recommended therapies, including trauma-focused Eye Movement

Desensitization and Reprocessing (EMDR), do result in meaningful improvement, a significant number of patients do not respond sufficiently to treatment.

As PTSD is considered to be a disorder of neural circuitry, neuromodulatory treatments such as repetitive transcranial magnetic stimulation (rTMS) may serve as an effective add-on to trauma-focused psychotherapy. Specifically, rTMS may improve patients' ability to cognitively engage with trauma-focused treatments and facilitate the processing of traumatic memories. Notably, to date, no studies have examined the therapeutic effect of combined intermittent Theta Burst Stimulation (iTBS) – a subtype of rTMS – and psychotherapy in the treatment of PTSD.

The aim of this open-label study is to investigate the feasibility (compliance, potential therapeutic effect, safety, and tolerability) of adding iTBS to EMDR therapy for patients suffering from EMDR-treatment-resistant work-related PTSD.

A total of 20 patients with work-related PTSD, recruited from the outpatient PTSD clinic at Aarhus University Hospital – Psychiatry, who and do not show a significant response after 7 weekly sessions of EMDR (reduction in CAPS-5 not superior to 10 points or not superior to 30%), will be treated with 4 weeks of daily iTBS as an add-on to their weekly EMDR treatment.

Assessments of wanted and unwanted effects of treatment will be performed by a team of raters with established interrater reliability, at baseline, during, and after the combined EMDR and iTBS treatment.

If this pilot study shows that the add-on treatment of iTBS to EMDR in patients who do not respond sufficiently to EMDR alone appears is feasible, it is our intention to examine the efficacy of iTBS as an add-on to EMDR in a multicentre randomized controlled trial, in collaboration with the other Psychiatric Services of the Central Denmark Region.

Poster 7

Maternal eating disorders and adverse neonatal outcomes: A Danish register-based cohort study

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Abstract:

Objective: We examined the risk of adverse pregnancy neonatal outcomes in children born to mothers diagnosed with eating disorders (EDs), including anorexia nervosa (AN), bulimia nervosa (BN), and eating disorders not otherwise specified (EDNOS).

Design/Methods: This register-based cohort study included 1,517,839 liveborn singletons born in Denmark between 1991-2015. We identified children born to mothers diagnosed with AN, BN, and EDNOS prior to the child's birth. For each ED subtype, we divided the study population into three groups, including children born to mothers with a recent diagnosis (within two years prior to conception up to the child's birth), a past diagnosis (more than two years prior to conception), or no diagnosis of the ED of interest. We estimated relative risk ratios (RRRs) and 95% confidence intervals (CIs) for pre-term and post-term birth, low and high birthweight, small-for-gestational age (SGA) and large-for-gestational age, low Apgar score, Caesarean section (C-section), congenital malformations, postpartum hemorrhage, and preeclampsia.

Results: Across almost all exposure groups, we observed significantly increased risks of preterm birth, low birthweight, SGA, C-section, congenital malformations, and postpartum haemorrhage. However, many relative risks were no longer significant after adjustment for demographic and clinical covariates. Both recent AN and past AN remained associated with increased risk of low birthweight (recent: RRR=2.70 [95% CI=1.87-3.89]; past: 1.22 [1.04-1.43]), SGA (recent: 1.89 [1.17-3.05]; past: 1.37 [1.16-1.62]), and preterm birth (recent: 1.60 [1.07-2.40]; past: 1.17 [1.00-1.36]. Recent, but not BN was associated with increased risk of low Apgar score (1.44 [1.03-2.00]). We observed some negative associations between maternal EDs and adverse neonatal outcomes, though many associations were no longer significant once we adjusted for pre-pregnancy body mass index (BMI).

Conclusions: Children born to mothers with maternal EDs, particularly AN, have an increased risk of several adverse neonatal outcomes. Associations between maternal EDs and adverse neonatal outcomes may be more attributable to maternal characteristics (e.g., pre-pregnancy BMI) than ED diagnoses. These results underscore the need for improved prevention of maternal EDs to mitigate adverse neonatal outcomes. Finally, this study provides valuable data that could be used to develop prediction models and enable clinicians to anticipate risks to both the mother and child.

Poster 8

Establishing a treatment-resistant depression model for studying the resolution of inflammation

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Abstract: Major Depression Disorder is one of the most disabling diseases worldwide, affecting 322 million people and about 30-50% of patients fail to show a substantial clinical response to conventional antidepressant therapy. Individuals who are non-responders or partial responders to antidepressants are defined as suffering from treatment-resistant depression (TRD). Among the various etiological hypotheses of depression, there are the theory of neuroinflammation and the dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis. HPA axis overactivity is often normalized after effective antidepressant treatment and some studies have suggested that failure of antidepressants to normalize the HPA axis may be a predictor of treatment resistance. Plus, data suggests that adrenocortical activation mediates the relationship between IL-1 and stress-induced depression. Specialized lipid pro-resolving mediators (SPM), derived from omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), such as arachidonic acid (AA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) seem to have a very important active profile for ending inflammation and, consequently, improving emotional behaviors related to mood disorders. The SPMs were identified and classified into four categories: lipoxins, resolvins, maresins and protectins. These lipids are agonists of G protein-coupled receptors. However, the underlying mechanisms of these remarkable effects concerning depression remain unclear. To test the interaction between depression and neuroinflammation, it is necessary to have an animal model of TRD in a way to view in different kind of systems. For this first part of the study, it is our hypothesis that a repeated treatment with ACTH (30 or 100 ug/mg for 21 days) can mimic this condition in BALB/c male mice and, in a first moment, have a predictive validity to TRD. Imipramine (IMI, 30ug/kg) was used for positive control for the last 7 days as well as Ketamine (KET, 20 ul/kg) one hour before the first batch of behavioral experiments. For the quantitative analysis, it was performed the forced swim test (FST) and tail suspension test (TST) and the immobility time in both was count as a parameter for depressive-like behavior. For the validation of this model. we expected: 1) A statistic difference of depressive-like behavior between the group treated with vehicle and the group treated with ACTH in the behavioral tests; 2) A classical antidepressant fails to respond in ACTH treated animals; 3) A non-classical antidepressant responds in ACTH treated animals. The data show that the repeated treatment with ACTH: 1) induced a depressive-like behavior with 30ug/mg dose; 2) IMI disrupted this behavior decreasing the immobility time in FST; and 3) KET was not able to disrupted the depressive-like behavior. The repeated treatment with ACTH at 100ug/mg was not able to induce depressive-like behavior. Any difference was observed in locomotor activity during the OFT. Since the aim is to work with TRD, the ACTH strategy for this was not an effective model and it was also corroborated with others experiments from our group. The next step is standardizing the social defeat stress as a TRD model, make the SPMs screening on it and start the treatments.

Poster 9

Investigating social and cognitive effects of Cannabidiol: modulation of medial pre-frontal cortex GABAergic interneurons in non-stress and stress conditions.

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Abstract:

Introduction

Despite significant progress in understanding the neurobiology of depression and its treatment, several critical challenges persist. These include treatment resistance in approximately residual and/or undesirable symptoms and the delayed onset of therapeutic effects with current antidepressants. Thus, there is an urgent and unmet need to understand the neurobiology of

depression and identify novel treatment options with a better therapeutic profile. The medial prefrontal cortex (mPFC) stands out for its involvement in both symptom development and treatment response in depression. Aim of the study. This study hypothesized that Cannabidiol (CBD) could exert antidepressant effects by restoring the hypoactive state of mPFC and that chemogenetic activation of mPFC interneurons would block the antidepressant effects of CBD.

Methods

To test our hypotheses, we did intramPFC injection of adenovirus associated with Dlx promoter (specific to GABAergic interneurons) and the gene encoding receptors binding to Designed Drugs hM3D(Gq)(DREADD+) in male C57BL6Ntac mice. Control groups received adenovirus with only the promoter and a reporter gene (Reporter-tdTomato). Experiment 1 (Non-Stressed Animals): Three weeks after surgery, animals were assigned to treatment groups, including Vehicle or CBD (10mg/kg) administered 1h before behavioural tests, which were: 3chamber test (3CT), Elevated Plus Maze (EPM), Open Field Test (OFT), Tail Suspension Test (TST), and Y-maze. Experiment 2 (Social Defeat Stress): Animals underwent the same protocol as in Experiment 1, but they were subjected to Social Defeat Stress, involving exposure to CD1 aggressors for 10 days, then randomized into different treatment groups based on their behavior in the Social Interaction (resilient or susceptible). Data was analyzed using a two-way ANOVA comparing treatment and DREADD, or stress and DREADD.

Results

In Experiment 1, non-stressed animals, activating mPFC interneurons with DREADD+ reduced time spent in open arms and in the center of the EPM and OFT, respectively ($p<0.05$ compared to the reporter group). There was an interaction of DREADD+ and treatment in the number of entries in closed arms ($p<0.05$ compared to vehicle reporter) but no main effect for DREADD+. CBD rescued animals from cognitive deficits induced by DREADD+ in the Y-maze. There was an increase in errors comparing vehicle reporter and vehicle DREADD ($p<0.05$ in same arm return). Complementary to that, CBD DREADD+ showed higher correct alternation compared to vehicle DREADD+ ($p<0.05$). No significant differences were observed in locomotion, 3CT, or TST. In Experiment 2, Stress significantly reduced the preference for exploring the mice chamber ($p<0.05$ compared to the non-stressed Reporter). In contrast, CBD treatment, increased the preference for mice chamber (*$p<0.05$ compared to vehicle DREADD+). In the TST, there was an interaction of DREADD and CBD treatment, increasing immobility.

Conclusions

Manipulating interneurons in mPFC in non-stressed animals promotes anxiety-like behaviors and cognitive impairment, and the latter was reversed with CBD treatment. Conversely, the stress protocol reduces social preference, and the association of DREADD+ and CBD restores social interaction despite worsening depressive-like behaviours. Financial Support. FAPESP, AUFF, Lundbeck Foundation, and TNU, with no conflict of interest declared.

Poster 10

Can health anxiety be differentiated from other anxiety phenomena in adolescence?

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Abstract:

Background

Health anxiety is characterized by excessive worries about the possibility of having a serious disease or contracting one. There is a substantial phenomenological overlap between health anxiety and other anxiety disorders.

Objective

This study explored if health anxiety differed from other anxiety phenomena in adolescence regarding physical symptoms, symptoms of depression, bodily dissatisfaction, health-related quality of life (HRQoL) and the use of health care services.

Methods

Data from the 16/17-year follow-up (N = 2521, 16-17 years old) from the general population-based Copenhagen Child Cohort 2000 was employed. Self-report questionnaires were used to assess health anxiety (Whiteley Index (WI)), anxiety (Spence Children's Anxiety Scale (SCAS)), physical symptoms (Bodily Distress Syndrome-25 Checklist), depression (The Mood and Feelings Questionnaire), bodily dissatisfaction, and HRQoL (KIDSCREEN-10) together with register data on health care utilization. Based on cut-offs on the WI and SCAS, four groups were created: 1) no health anxiety or anxiety, 2) only health anxiety, 3) only anxiety, and 4) both health anxiety and anxiety. Subsequently, differences between the four groups regarding physical symptoms, depression, bodily

dissatisfaction, HRQoL and health care use were examined using general linear models.

Results

Among the 10.4% adolescents who were defined as having high health anxiety, almost half (4.6%) reported having only high health anxiety without other anxiety symptoms. The health anxiety group (group 2) displayed significantly more physical symptoms, fewer depressive symptoms and higher health care utilization compared to group 3. The health anxiety group reported less favourably on all measures compared to group 1. Adolescents who reported high levels of both health anxiety and other anxiety symptoms (group 4) had the most detrimental clinical profile.

Conclusion

Our results indicate that health anxiety can be recognized as a separate construct in adolescence, associated with several negative health-related aspects. Research is required to ensure adequate identification and treatment of health anxiety in this age group.

Poster 11

Trends in incidence of postpartum depression and depression in women of reproductive age. A comparative population-based register study from 2000-2022

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Abstract:

Background

There are limited evidence on time trends in the incidence of postpartum depression (PPD), and no studies have investigated if time trends of PPD are similar to trends of depression among women in general. Such insight could provide basis for discussing specific features for PPD.

Objective

To describe and compare time trends in the incidence of PPD and depression in women in general.

Methods

We conducted a descriptive longitudinal study using Danish nationwide health registers. We identified a postpartum population, defined as all women who gave birth to at least one liveborn child during 2000-2022, aged 15-49 years at date of childbirth. We sampled a background population by matching five women for each delivery on age (identical birth month and year) and date of childbirth (the index date). Women were excluded if they had filled antidepressant prescriptions or a recorded depression diagnosis within five years before delivery/matching. We measured PPD and depression in two ways; a depression diagnosis or redeemed antidepressant prescription within 180 days from the index date. We described incidence rates (IR) per 10,000 person-years between 2000-2022 of PPD and depression by stratifying risk time into calendar months and fitting a restricted cubic spline with six knots.

Results

The study population consisted of 1,133,947 postpartum women (669,101 unique) matched to 5,669,735 women (1,165,505 unique). Overall IRs of depression diagnoses were 34.3 (95% CI: 32.8-35.8) per 10,000 person-years for PPD and 19.2 (95% CI: 20.5-23.6) for depression, and both IRs increased similarly across time in main analyses but had diverging trends in stratified analyses of age and parity. Overall IR for antidepressant prescriptions was 135.7 (95% CI: 132.7-138.8) per 10,000 person-years for PPD and 209.8 (95% CI: 208.1-211.5) for depression, and both groups had both increasing and decreasing trends over time.

Conclusion and relevance

Diagnosis measures showed that PPD and depression followed similar increasing trends, but stratified analyses suggested distinct increases for primiparous and older mothers, possibly suggesting an increasing impact of motherhood on mental health among specific groups over time. Observed prescription trends were likely driven by external factors such as tendencies in drug prescribing and not a reflection of disease trends.

Poster 12

Genome-wide association study of borderline personality disorder accounting for age at diagnosis and family history in iPSYCH

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Abstract:

Background

Borderline Personality Disorder (BPD) is a psychiatric illness characterized by marked instability in emotions, self-image, and interpersonal relationships. Although the lifetime prevalence of BPD in the general population is only 1–3%, individuals with BPD make up a large proportion of the patient population receiving treatment in psychiatric hospital services. To develop more effective treatment options and aid early intervention, we must improve our understanding of the etiology of BPD. Previous twin and family studies reported a broad-sense heritability of 60–75%. More recently, a genome-wide association study (GWAS) based on ~1000 cases and ~1500 controls has shown that BPD has a polygenic basis and is genetically correlated with depression, schizophrenia, and bipolar disorder.

Objectives

To investigate how common genetic variation influences the likelihood of developing BPD, we will conduct a GWAS of BPD in the iPSYCH2015 sample accounting for age at diagnosis and family history.

Methods

iPSYCH is a nationally representative case-cohort study of all individuals born in Denmark between 1981 and 2008 and diagnosed with a major psychiatric disorder (i.e., affective disorder, attention deficit hyperactivity disorder, schizophrenia spectrum disorder, autism spectrum disorder, or postpartum disorder) by 2015 and ~50,000 individuals randomly selected from the population for the cohort. We will identify individuals diagnosed with BPD within the entire iPSYCH2015 sample using the Danish Psychiatric Central Research Register (ICD-10 code F60.3x, ~7000 expected). Individuals from the iPSYCH2015 cohort without a diagnosis of BPD by the end of the follow-up period will be used as the cohort for this study).

We will estimate the latent genetic liability for BPD for each individual with the extended liability threshold model conditioned on family history (LT-FH++) method. LT-FH++ is an alternative to traditional time-to-event analysis and can account for family history, right censoring, sex, and cohort effects. For our analysis, we will use the age at diagnosis, family history of BPD, and the cumulative incidence proportion of BPD stratified by sex and birth year of the entire Danish population from national register data. We will use the estimated genetic liability as a continuous phenotype to conduct a GWAS of BPD in BOLT-LMM. Ancestry principal components and genotyping array will be included as covariates.

We plan to conduct further sensitivity analyses to investigate cross-trait genetic architectures, especially with other psychiatric disorders such as major depressive disorder, schizophrenia, and bipolar disorder, whilst accounting for the ascertainment method in iPSYCH based on these diagnoses.

Results

This study will be the first GWAS of BPD to use time-to-event information and family history to date, leveraging information from the Danish national registers to increase the power to detect genetic risk factors for BPD. To date, the few small GWAS investigating clinically diagnosed BPD or continuous BPD features have not detected any genetic risk loci.

Discussion

The ascertainment of the cases in iPSYCH presents both a challenge and a unique opportunity to investigate cross-trait genetic architectures in the context of BPD, as BPD is a secondary phenotype.

Poster 13

Novel Ibogaine Analogs for Serotonergic Targets

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Abstract:

Background

Ibogaine is a hallucinogenic and psychedelic drug that has shown anti-addictive effects in human and animal studies. Several legitimate ibogaine clinics in countries where ibogaine is a legal or unscheduled drug offer to treat and cure people with addictions, but unluckily, deaths due to the use of ibogaine have been reported. Therefore, numerous studies investigate the possible therapeutic potential of ibogaine, including Cameron et al. who in 2020 synthesized and tested the ibogaine analog tabernanthalog. This drug did demonstrate a much safer profile while still possessing anti-addictive and antidepressant properties.

Objectives

In order to understand the difference in these drugs' effects on the serotonin transporter (SERT) and the serotonin receptors 5-HT2A and 5-HT2C, analogs representing structural intermediates between ibogaine and tabernanthalog were synthesized and tested.

Methods

Intracellular calcium flux assays, uptake inhibition assays and the substituted cysteine accessibility method was employed to characterize serotonin receptor activation, serotonin transporter inhibition and serotonin transporter conformational changes.

Results

The tetrahydroazepine ring of the ibogaine analogs decreased the efficacy of the compounds on the 5-HT2A receptor, while a further addition of a 1,3- dioxylane ring structure revealed a 5-HT2A receptor antagonist. Five analogs also showed selectivity towards the 5-HT2A

receptor. All ibogaine analogs inhibited SERT while inducing the outward-facing conformation, contrary to ibogaine which inhibits SERT in the inward-facing conformation.

Conclusion

Tabernanthelog and analogs had different serotonin receptor and transporter pharmacology than ibogaine. Despite convergent behavioural effects of tabernanthelog and ibogaine our results suggest that tabernanthelog employs a different mechanism of action than ibogaine.

Poster 14

Reduced synaptic SV2A density in a porcine model of Parkinson's disease and its modulation by deep brain stimulation of the subthalamic nucleus

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Abstract

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Poster 15

Critical assessment of the definition of treatment-resistant depression and treatment with esketamine in Denmark

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Abstract

Background

Nasal esketamine was approved to treat treatment-resistant depression (TRD) in combination with other antidepressants (AND) by the European Medical Agency in 2019, but has not been included in treatment recommendations in Denmark yet, partly due to safety concerns and because there is no consensus on the definition of TRD for identifying eligible patients. Understanding patient characteristics and clinical courses in depression treatment is essential to inform treatment decisions.

Objectives

1) To describe the characteristics and course of treatment with AND in patients (age 25-64 years) with varying definitions of TRD in clinical practice in Denmark; 2) To compare the identified characteristics with characteristics of participants in randomized controlled trials (RCTs) of esketamine.

Methods

We conducted a population-based cohort study of all individuals who initiated AND treatment in Denmark between 2015-2018. Follow-up was one year. For these patients, we identified sociodemographics, clinical characteristics, and course of treatment, i.e. redeemed prescriptions for ANDs and psychiatric hospital contacts, from the national registers. Patients were classified according to the number of different ANDs redeemed during FU to define different levels of TRD. For the comparison of patient characteristics, we conducted a literature review of relevant RCTs.

Results

During the study period, 68,417 individuals started AND treatment for the first time since 1995. During follow-up, 96.7% of patients used ≤2 ANDs, 3.3% used 3 or 4 ANDs, and 0.5% used ≥4 ANDs. Of all AND users, 4,081 (6.0%) were referred to a psychiatric hospital, including 175 (0.26%), who had tried >2 different ANDs. Compared with the participants of the RCTs, individuals from the population-based sample had less than one-year duration of depression, had depression of unknown severity, and included people with psychotic features, substance abuse, or suicidality.

Conclusion

According to the labelled indication of esketamine for TRD of having tried >2 ANDs, 2631 (3.8%) individuals would have been eligible for nasal esketamine during 2015-2018, and 175 (0.26%) individuals among patients with psychiatric hospital contacts. Consideration of depression severity, psychotic features, substance abuse, or suicidality to minimize risk profiles would decrease the number of eligible patients.

Poster 16

Association of psychotropic drug use with uncertain treatment indications and the risk of mortality in older adults: A nationwide population-based cohort study in Denmark

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Abstract

Background

Psychotropic use in older adults (aged ≥65) is frequent. Despite safety concerns, off-label use by indication of these drugs is also common, but its impact is understudied.

Objectives

To investigate whether psychotropic prescriptions with uncertain treatment indications were associated with a one-year risk of all-cause mortality in older adults overall and in subgroups with psychiatric disorders, depression, or dementia.

Methods

This register-based cohort study in Denmark included all older adults who redeemed first-time prescriptions for antidepressants, antipsychotics, or benzodiazepines during 2006-2018. We defined uncertain indications as missing or free-text written indications in the prescription register. We used Poisson regression to estimate incidence rate ratios (IRR) with 95% confidence intervals and controlled for socio-demographics and clinical factors.

Results

We identified 202,067 individuals redeeming their first prescriptions for antidepressants, 97,387 for antipsychotics, and 30,471 for benzodiazepines. The proportion of individuals with uncertain treatment indications was 32%, 37%, and 22% for antidepressants, antipsychotics, and benzodiazepines, respectively. For antidepressants and antipsychotics, no significant differences were observed in the risk of mortality by prescription with uncertain indications. However, for benzodiazepines, uncertain treatment indications were associated with a higher risk of mortality (e.g., for overall population IRR: 1.51, 1.27-1.79), which were attenuated to lower risk (e.g., overall population IRR: 0.76, 0.63-0.92) when we accounted for end-of-life treatment.

Conclusion

This study revealed that psychotropic use with uncertain treatment indications is prevalent in older adults but does not increase the risk of mortality. Future research should investigate further drug-specific outcomes of off-label psychotropic use.

Poster 17

A Feasibility study of the Transdiagnostic Self-injury Interview

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Abstract

Objectives

The Transdiagnostic Self-injury Interview (TSI) is a new measure for non-suicidal self-injury in clinical settings. It assesses onset, frequency, methods, and severity. The aims were to demonstrate the feasibility of a TSI validation study, and to investigate TSI's criterion validity, clinical correlates, and interrater reliability.

Materials and methods

Recruiting sites were in- and outpatient units in adult psychiatry. Feasibility targets included number of participants completing the study, TSI completion time, total participation time, participants experiencing exacerbation of symptoms, along with other targets. Criterion validity was evaluated using the Deliberate Self-Harm Inventory (DSHI). Clinical correlates were examined with the Columbia-Suicide Severity Rating Scale (C-SSRS), the Personal and Social Performance Scale (PSP), the Affective Lability Scale-18 (ALS-18), and the Brief Trauma Questionnaire (BTQ). Interrater reliability was evaluated with video recordings and written material.

Results

Fifty participants were included. The majority were women (76 %) and had a mean age of 31.3 years (SD: 10.4). Schizophrenia (44 %) and schizoaffective disorder (18 %) were the most prevalent diagnoses. TSI took on average nine minutes to complete and the total participation time for the study was on average less than one hour. One participant experienced exacerbation of self-injury ideation without need of intervention. Excellent correlation was found between TSI and DSHI. TSI was correlated to C-SSRS ideation intensity and ideation frequency but not suicidal attempts. TSI was not correlated to PSP, BTQ, and ALS-18. Interrater reliabilities were excellent.

Conclusions

The results support the feasibility of a TSI validation study, which is needed to validate TSI in different settings and across diagnoses.

Poster 18

Reproductive patterns in individuals with epilepsy; a nationwide cohort study

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Abstract

Purpose

We studied sex-specific reproductive patterns in individuals with epilepsy.

Method

We carried out a prospective population-based register study of all individuals of reproduc-tive age (15-45 years) living in Denmark between January 1st 1982 and December 31st 2018. Study participants with epilepsy were identified using diagnostic information (ICD-8: 345 excluding 345.29 and ICD-10: G40) from the Danish National Patient Register. Psychiatric comorbidity was retrieved from the Danish Psychiatric Central Register for all psychiatric disorders (ICD-8: 390-315, ICD-10: F00-F99), including codes specific to intellectual disability (ICD-8: 311-315, ICD-10: F70-F79). Births were identified from the Danish Medical Birth Register. Cohort members were followed from 15 years of age until childbirth, 45 years of age, emigration, death, or end of follow-up (December 31st, 2018), whichever came first. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard models.

Results

We included a total of 2,396,180 individuals (1,227,240 males and 1,168,940 females) of reproductive age, including 48,420 with epilepsy before or during follow-up (24,960 males and 23,460 females) with a mean (SD) age at diagnosis of 15,7 (11,4) years. Compared with the general population, the HR of having children was lower in males with epilepsy (HR 0.59, 95%CI 0.57, 0.60) than in females with epilepsy (HR 0.73, 95%CI 0.71, 0.75), p-value<0.0001. This trend remained consistent in the stratified analyses based on the epilepsy subtypes focal and generalised epilepsy. When stratifying by psychiatric comorbidity, the HR of having children was also lower in males (HR 0.79, 95%CI 0.77, 0.82) than in females (HR 0.91, 95%CI 0.89, 0.94).

Conclusion

We found that individuals with epilepsy of reproductive age are less likely to become parents than individuals in the general population, and that this tendency is more pronounced in males than females with epilepsy. The contrast observed may be due to sex-specific differences in biological and/or social effects of epilepsy on reproduction. However, when stratifying by psychiatric comorbidity, the results revealed a less substantial difference in reproduction between the reference population and individuals with epilepsy, particularly when excluding those without psychiatric comorbidity.

Poster 19

The regulation of mGluR5 and SV2A after chronic mild stress

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Abstract

Background

Major depressive disorder is the leading cause of disability worldwide affecting millions of people and the incidence is still rising. The etiology is still subject to investigation. Recent research speculates in the involvement of glutamate and synaptic density in the pathophysiology of the disorder.

Objectives

In the present study the metabotropic glutamate receptor subtype 5 (mGluR5) and synaptic density will be explored in a chronic mild stress (CMS) model of depression after treatment with agomelatine. Initially, we will focus on core brain areas of depression, the prefrontal cortex (PFC) and hippocampus (HP).

Methods

The CMS rat model of depression was performed for 10 weeks and antidepressant treatment with agomelatine (40 mg/kg) was included in the last 5 weeks. The study included four groups differentiated by the results of the sucrose consumption test: Control, anhedonic-like, agomelatine responders and agomelatine non-responders (n=8/group except n=6 for control).

The mGluR5 level and the synaptic density in the PFC and HP were investigated using autoradiography. The availability of mGluR5 was assessed using the tracer [3H]MPEPy, and the synaptic density was estimated using the radioligand [3H]UCB-J targeting the synaptic vesicle glycoprotein 2A (SV2A).

Results

We found that the level of mGluR5 in the prelimbic cortex (PreL) was increased after CMS. Furthermore, agomelatine treatment decreased the levels of mGluR5 in both PreL and infralimbic cortex (IL) in the responding group. The mGluR5 level in the HP was not affected by CMS or agomelatine, and neither were the synaptic density in the PFC or the HP.

Conclusion

This suggests that mGluR5 in the PFC might be engaged in the pathophysiology of MDD.

Poster 20

Development of a fluorescence life-time based biosensor for imaging of serotonin transport and release in vitro and in vivo

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Abstract:

Background

Serotonin is a monoamine neurotransmitter that plays a pivotal role in modulating mood, cognition, reward, learning and memory. The serotonergic system is therefore an important target in drug development and understanding of pathological conditions. The serotonin transporter (SERT) is a principal target for antidepressants, which inhibit the serotonin transporter, elevating the concentration of serotonin in the synaptic cleft. The organic cation transporters (OCTs) transport several monoamine neurotransmitters, including serotonin, and can undermine- or delay the therapeutic effects of drugs targeting SERT.

For screening of therapeutics targeting SERT or OCTs, a recently developed fluorescence-based biosensor, iSeroSnFR (Unger et al., 2020), can in real-time detect changes in intracellular serotonin concentration as a result of serotonin transport via SERT and OCT2. However, the fluorescent sensor is sensitive to changes in intracellular pH, which may be affected by the therapeutics targeting SERT or OCTs.

Objectives

To overcome this problem, we sought to engineer the pH-sensitive chromophore of iSeroSnFR from sfGFP to resemble mTurquise2 and characterize this novel sensor.

Methods

We employed mutagenesis and structure-based biosensor design to produce novel variants. We characterized the serotonin affinity and pH-sensitivity of the biosensor variants with fluorescence intensity change and fluorescence lifetime change as functional readouts.

Results

We have successfully removed the pH sensitivity of the biosensor but also changed the readout modus of the biosensor from fluorescence intensity to fluorescence lifetime. However, fluorescence lifetime can be a highly useful read-out for fluorescence microscopy since it is stable across different pH levels, sensor expression levels and the instrumentation used.

Conclusions

We were able to make new fluorescent biosensors for serotonin with fluorescence lifetime as the mode of detection. Fluorescence lifetime sensors are useful for studying serotonin dynamics with high spatial and temporal resolution between animals, brain regions, control and disease models of neurological and psychiatric disorders and over longer periods of time. Further characterization is planned with a future goal of an intracellular biosensor which can monitor the transport of serotonin via SERT and OCTs in a pH independent manner and an extracellular biosensor which can detect changes in serotonin levels in wake and behaving animals.

Poster 21

Frontal Gyrus Dysfunction in Understanding Others: Neuroimaging Insights into Cocaine Users' Theory of Mind

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Abstract

Cocaine Use Disorder (CUD) is associated with various social and interpersonal challenges. The effectiveness of social interactions depends on the intricate psychological mechanisms encompassed within social cognition. Among these, Theory of Mind (ToM) stands out as a vital cognitive ability facilitating the comprehension of others' intentions, beliefs, and desires. Previous behavioral investigations have revealed diminished ToM performance in individuals using cocaine compared to healthy controls.

The present study explored distinctions in ToM-related neural activity between female cocaine users and a control group using functional magnetic resonance imaging (fMRI). Our study enrolled 20 cocaine users (CK) and 20 healthy controls (CG).

Data were acquired on a 3 Tesla GE Healthcare Signa HDxt scanner employing an eight-channel radio-frequency coil (RF). Functional MRI (fMRI) entailed the acquisition of 447 Echo-Planar Images during the execution of a ToM task. Participants performed an adapted version of the Reading the Mind Eyes Test (RMET), comprising 36 pairs of eye images. The study encompassed two conditions: participants were tasked with either (1) attributing one of two possible emotions to the eyes or (2) determining whether the eyes belonged to a male or female individual. Responses were recorded using a button box, with participants employing their left or right index finger. All fMRI data was processed using AFNI, incorporating motion, slice-time correction, and spatial normalization to a standardized template space. Employing multiple regression, both task conditions were modeled based on the canonical hemodynamic response function. After model estimation, a t-test was administered for between-group comparisons. The contrast of interest was the difference in neural activity between the emotion attribution and sex attribution conditions.

Results showed activation in the right medial frontal gyrus (RMFG) and the left medial frontal gyrus (LMFG) among the control group relative to cocaine users. Remarkably, no statistically significant differences in response time or accuracy emerged from the behavioral assessments. This outcome suggests an anomalous prefrontal cortex functioning in ToM processes in the context of cocaine use. The implications are noteworthy, implying that targeted interventions should address this prefrontal cortex dysfunction. The RMFG, implicated in decision-making processes, interfaces with neural circuits associated with regulatory control, cost-benefit analysis, and risk assessment - integral components of decision-making. The findings substantiate a potential association between aberrant RMFG activity during ToM processing and the social and interpersonal difficulties characterizing female cocaine users.

Poster 22

Polygenic liabilities and clinical trajectory patterns in individuals diagnosed with early-onset major depressive disorder in Danish psychiatric hospitals

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Abstract

Background

Major depressive disorder (MDD) is a common and burdensome psychiatric disorder. MDD's clinical presentation is heterogenous. Research has shown that differences in genetics between individuals, summarized numerically as a polygenic score (PGS), may influence clinical course.

Objectives

We investigated whether polygenic scores for 6 psychiatric disorders influenced MDD's clinical course in a nationally representative sample of individuals with early-onset MDD (diagnosis <25 years).

Methods

We studied 11,395 individuals from iPSYCH2015 who were treated for early-onset MDD (ICD-10 F32-F33) in Danish psychiatric hospitals (inpatient, outpatient, or emergency). We used Latent Class Growth Analysis (LCGA) to identify distinct trajectory patterns of hospital admission over a 7-year period following the index diagnosis. Using DNA samples taken from bloodspots collected at birth, PGSs were computed for MDD, schizophrenia (SCZ), bipolar disorder (BD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and anorexia nervosa (AN). Using multinomial logistic regressions, we tested associations between PGSs and trajectory class membership. Using logistic regression, we tested associations between PGSs and outcomes for individuals who left the secondary-care system within 6-24 months. These outcomes were: readmission for another psychiatric disorder or continued treatment for MDD in primary care. Sex, age-at-index episode, genotyping platform, and the first 5 principal components were included as covariates

Results

LCGA showed 4 trajectory classes: 1) brief contact (65%) including individuals who left secondary treatment within 24 months (most within 6 months), 2) prolonged initial contact including individuals who stayed in secondary treatment for MDD for 3-4 years (20%), 3) later re-entry (8%) including patients who left and later re-entered treatment, and 4) persistent contact (7%). Compared to individuals with brief contact, PGS-MDD was significantly associated with later re-entry (OR=1.09 [95% CIs=1.02-1.17], p=0.01). PGS-ADHD was associated with decreased odds of prolonged initial contact (0.92 [0.88-0.97], p=0.0008) and persistent contact (0.90 [0.83-0.97], p=0.006). PGS-AN was associated with persistent contact (1.11 [1.02-1.19], p=0.01) and PGS-ASD was associated with later re-entry (1.08 [1.01-1.16] p=0.02). Of those with brief contact, PGS-MDD was associated with continued treatment in primary care (1.11 [1.05-1.17], p=0.0002). Over half (56%) of those with brief contact were treated for another psychiatric disorder in a hospital. PGS-MDD and PGS-ADHD were associated with subsequent treatment for anxiety disorders (ICD-10 F4), which were the most common diagnoses (27%).

Conclusion

It is well known that inherited genetic risk for MDD increases likelihood of developing the disorder. Our study highlights that it also influences the clinical course among those affected, although the effect sizes for PGS associations are currently too small to be of clinical value.

Poster 23

Acute auricular vagus nerve stimulation decreases glucose metabolism measured by 18F-FDG PET uptake in subcortical rat brain

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Abstract

Abstract not available.

Poster 24

Ketamine effects in the endocannabinoid system in a genetic animal model of depression

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Abstract

Introduction

Major depressive disorder (MDD) ranks among the most prevalent and disabling medical conditions worldwide. Several treatment options exist for MDD, but conventional antidepressants typically exhibit a delayed onset of action, ranging from 2 to 4 weeks, and are only effective for 60-70% of patients, with remission achieved in merely 25-30%. Ketamine (KET) has demonstrated a rapid and sustained antidepressant effect in patients resistant to classic monoaminergic treatments, a phenomenon also observed in basic research. There is growing evidence suggesting the

involvement of the endocannabinoid system (ECS) in the neurobiology of MDD, potentially linking it to the effects of KET. However, most of these studies have relied on naïve animal models. In this study, we investigated the effects of KET in Flinders Sensitive Line (FSL) rats, a genetic model of depression, and their control, Flinders Resistant Line (FRL) rats. We assessed the gene and protein expression of various ECS targets in the prefrontal cortex (PFC) and conducted a lipidomic assay to evaluate levels of endocannabinoids and their metabolites in the PFC. Additionally, we explored the possible involvement of CB1 receptors in KET's effects using autoradiography and treated animals with a CB1 antagonist.

Methods

Rats aged 8-11 weeks in the FSL group received either KET (15 mg/kg; i.p) or a vehicle (n=6-10 animals/group). The FRL, of the same age, received a vehicle (n=6 animals). One hour post-treatment, animals underwent a 10-minute Open Field Test (OFT) followed by a 7-minute Forced Swimming Test (FST). We extracted the PFC for subsequent qPCR and Western Blotting analysis to examine endocannabinoid degradation enzymes, FAAH and MAGL, as well as receptors of the endocannabinoid system, CB1, CB2, and GPR55. A lipidomic assay was performed to assess the levels of AEA, DHA-EA, EPA-EA, Linoleyl-EA, Oleoyl-EA, Palmitoyl-EA, 1-AG, and 2-AG. [3H]SR141716A autoradiography was conducted on postmortem PFC tissue. Another group of FSL animals received Rimonabant (RIMO; 1mg/kg), a CB1 antagonist, or a Vehicle, and 30 minutes later, they received KET or Saline. One hour later, the OFT was performed, followed by the FST.

Results

FSL animals treated with a vehicle exhibited increased immobility ($p<0.05$; t-test) and reduced swimming time compared to FRL ($p<0.05$; t-test), with no difference in struggling behavior ($p>0.05$; t-test). KET treatment decreased immobility time ($p<0.05$; t-test) and increased swimming ($p<0.05$; t-test) and struggling ($p<0.05$; t-test) behavior in FSL animals compared to those treated with the vehicle. No differences were observed in the OFT ($p>0.05$; t-test). Gene expression analysis did not reveal any modification in CB1, CB2, GPR55, MAGL, and FAAH ($p>0.05$; t-test) between FSL and FRL animals treated with the vehicle. However, KET treatment decreased the gene expression of CB1 ($p<0.05$; t-test) and FAAH expression ($p=0.0583$; t-test). No differences were observed in protein expression. KET showed a trend towards restored reduced levels of 2-AG in FSL animals ($p=0.08$; t-test) and increased [3H]SR141716A specific binding in the PFC of FSL animals ($p=0.057$; t-test). In the RIMO experiment, KET animals were divided into two groups: High and Low immobility. RIMO-treated animals did not exhibit differences compared to FSL KET animals with Low Immobility ($p>0.05$; One-way ANOVA), but RIMO animals showed lower immobility compared to KET animals with High Immobility ($p<0.05$; One-way ANOVA).

Conclusions

KET demonstrated an antidepressant effect in FSL animals, and its mechanisms of action appear to involve certain components of the endocannabinoid system.

Poster 25

Frontotemporal Cortical Myelin's Relevance for Depression Severity and Working Memory Function During Serotonergic Treatment in Major Depressive Disorder: A NeuroPharm-1 Study

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Abstract

Background and Objective

Major depressive disorder (MDD) is an increasing problem in modern-day society. The complex and heterogeneous nature of the disorder1 makes it challenging to treat likely due to its heterogeneous nature.

To contribute to a better understanding of this, we will examine frontotemporal cortical myelin levels before and after serotonergic treatment in MDD patients to clarify its relevance in depression severity, working memory function and treatment response.

This is based on studies that have found reduced myelin levels2 and fractional anisotropy in multiple brain areas3 in patients with MDD. Furthermore, myelin has been shown to be a semi-specific diagnostic marker for MDD4.

Study Design

The project used data from the NeuroPharm-1 study, a longitudinal, open-label multimodal neuroimaging clinical trial investigating potential biomarkers in the antidepressant treatment of MDD.5

96 unmedicated patients (72% female, mean age 27.2) with a moderate to severe single episode of depression

were measured with MRI and treated with 10-20 mg of escitalopram for 12 weeks.

Measurements and Outcomes

Depression severity was assessed with HAM-D17 and treatment response was defined as a ≥50% reduction in HAM-D17 rating at weeks 8 and 12. Working memory function (Letter Number Sequencing Scores) was assessed before treatment and at week 12. Cortical myelin in frontotemporal regions from the Desikan-Killiany atlas was assessed by the T1- and T2-weighted MRI ratio before treatment and for half of the patients at week 8.

Statistical Methods

We will examine correlations of frontotemporal cortical myelin with depression severity, working memory dysfunction and treatment outcome, using linear regressions adjusted for age and sex. We will use repeated measures ANOVA to examine the putative increase in myelin after treatment. We will use appropriate family-wise error correction to account for multiple tests.

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Poster 26

S-Ketamine acutely increases hippocampal synaptic vesicle glycoprotein 2A density in Flinders Sensitive Line rats

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Abstract

Up to 30% of patients with depression face inadequate treatment. Classically available pharmaceuticals can take 3-6 weeks to reach full effect. Aiming to bridge this gap, S-ketamine is used in patients with treatment-resistant depression, as a fast-acting agent. Ketamine is a synaptic modulator, inducing synaptic plasticity in certain regions of the brain, which is hypothesized to be part of its mechanism of antidepressant action. To investigate this, we treated 8 Flinders Sensitive Line (FSL) rats, considered a genetic model of depression, with an intraperitoneal injection of 15 mg/kg of S-Ketamine and compared them to 6 saline-injected FSL rats. We then performed autoradiography on selected regions of brains removed 1-hour post-injection. Fresh frozen brain sections were processed using [3H]-UCB-J, a radioligand of synaptic vesicle glycoprotein 2A, considered a biomarker of pre-synaptic density. Following results were obtained using two autoradiography methods, a novel and a classic, to ensure validity. The results were consistent across both methods. We found significantly higher [3H]-UCB-J binding in ventral (19% increase, p=0,01) and dorsal hippocampus (14% increase, p=0,05) of ketamine-injected FSL rats compared to the saline group. No significant increases were found in the remaining areas. These findings suggest ketamine's effect to be based in synaptic modulation of the hippocampus. We suggest further investigation at different time points and with left-right discrimination. We are currently investigating the effects of ketamine on post-synaptic density using a ligand of metabotropic glutamate receptor 5.

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Ketamine effects in the endocannabinoid system in a genetic animal model of depression

Poster 25
Frontotemporal Cortical Myelin's Relevance for Depression Severity and Working Memory Function During Serotonergic Treatment in Major Depressive Disorder: A NeuroPharm-1 Study

Poster 26
S-Ketamine acutely increases hippocampal synaptic vesicle glycoprotein 2A density in Flinders Sensitive Line rats