TELOMERES SHORTENING IN ACUTELY-ILL FEMALE ADOLESCENTS WITH ANOREXIA NERVOSA, AND FOLLOWING WEIGHT RESTORATION

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Background: People with psychological distress, including anxiety and depression, might suffer from accelerated cellular aging, manifested by shortened telomere length (TL).

Aim: To compare TL in acutely-ill malnourished patients with anorexia nervosa (AN), an illness characterized by considerable physiological and psychological distress, to healthy controls. Second, to assess whether correction of malnutrition would be associated with correction of putative TL shortening

Methods: we measured TL in 44 acutely-ill female adolescents with AN and in 22 controls. Eighteen patients with AN were also assessed for TL at discharge.

Results: No differences in TL were found between acutely-ill hospitalized patients with AN and controls, and from admission to discharge, at a mean of 4 months later, despite an increase in body mass index (BMI). By contrast, 18 patients with AN-binge/purge type showed shorter TL on admission than 26 patients with AN-restricting type, despite showing higher BMI. Age at admission and at the onset of AN, BMI, cholesterol levels and thyroid function tests were not correlated with TLs.

Conclusion: The negative findings of the study are likely associated with methodological inconsistencies and with the relatively short duration of AN in adolescent patients. Nonetheless, the shorter TL in patients with AN-Binge/Purge type might indicate it to being a more severe variant of the disorder than AN-R, even relatively early in the course of the illness.

EFFICACY AND SAFETY OF ATYPICAL ANTIPSYCHOTICS TREATMENT IN CHILDREN AND ADOLESCENTS WITH AVOIDANT/RESTRICTIVE FOOD INTAKE DISORDERS

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Introduction: Little is known about the efficacy and safety of pharmacological treatment for avoidant and restrictive food intake disorder (ARFID), a challenging feeding disorder associated with marked impairment and developmental arrest.

Objectives: The present study aimed to assess the efficacy of atypical antipsychotics in promoting weight gain and height in children and adolescents diagnosed with ARFID in a long follow-up period of 18 months.

We secondarily aimed to assess the safety and the occurrence of adverse events.

Methods: We retrospectively evaluated the computerized medical records of 21 children and adolescents treated with atypical antipsychotics for ARFID. Clinical Global Impressions scores were recorded.

Results: There was a statistically significant increase in BMI, weight, and height during the 18 months study period (Mean change from the beginning of treatment to the last follow-up was: Weight 9.66 ±9.24 Kg; Height 10.23±11.54 cm; $p<.001$).

Weight increase over time was significant for both males and females ($p < .001$). BMI and height increase over time was significant for males but not for females.

Patients with high BMI gained more in the first 6 months as compared to those with low BMI 7.11Kg vs 3.48kg, respectively). However, in the following 6 months, the trend was the opposite (high BMI 1.69 Kg vs low BMI 3.99 Kg). The mean height increased over time for patients with low BMI percentile (Friedman's $\chi2(7)=19.8$, $p = .006$) but with high BMI percentile (Friedman's $\chi2(7)=12$, $p = .10$). Global Impressions scale scores indicated a marked improvement in patients treated with atypical antipsychotics.

Conclusion: The present study illustrates that long-term treatment atypical antipsychotics when used as an adjunct to other treatment modalities, may facilitate growth in terms of weight gain and height in children with ARFID.

WFSBP GUIDELINES UPDATE 2023 ON THE PHARMACOLOGICAL TREATMENT OF EATING DISORDERS

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Objectives: The first World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders (EDs) were published in 2011. Since then, numerous studies have been conducted on various psychopharmacological agents for EDs. Additionally, improved methods for grading of the level of evidence (LoE) and the grade of recommendation (GoR) have been adopted by the WFSBP. Thus, a timely update of the guidelines was performed.

Methods :A new WFSBP Eating Disorders Task Force was assembled with experts from all over the world. The relevant literature was reviewed and evaluated according to the Scottish Intercollegiate Guidelines Network (SIGN) standards. Finally, in discussion LoE and GoR were provided.

Results: For anorexia nervosa (AN) there is strong evidence for effectiveness on weight. For bulimia nervosa (BN), there is strong LoE for the fluoxetine and topiramate. For binge eating disorder (BED), lisdexamfetamine (LDX) and topiramate have yielded the most evidence. There is little evidence for the drug treatment of avoidant restrictive food intake disorder, pica and rumination disorder.

Conclusion: IRecommendations include fluoxetine and topiramate for BN, and in LDX and topiramate for BED. Despite published evidence, olanzapine and topiramate have not received authorization for use in EDs from any medicine regulatory agency. Newer directions for AN include dronabinol and hormonal treatments including growth hormone, ghrelin agonist and oxytocin.

BRAIN-MEDIATED REGULATION OF GUT IMMUNITY IN MICE

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Introduction: Immune cells in the gut are exposed daily to a range of harmless foreign antigens. Thus, the intestinal immune system has to suppress unnecessary immune responses to innocuous antigens while protecting from pathogens. Sensory information encoded by the brain during feeding (e.g., taste, odor, etc.) can predict the safety of the ingested food to direct the immune response. These feeding-related external sensory cues are received and processed by the insular cortex (IC), a multimodal brain region that is also interconnected with limbic areas, allowing the integration of sensory modalities (e.g., taste) with affective, anticipatory, and reward-related information. Moreover, neurons in the IC have visceromotor functions. Namely, they can affect cell activity in visceral organs (e.g., the gut) by modulating the autonomic nervous system, thereby regulating oral tolerance.

Results: We show that neurons in the mid-IC (mIC) that respond to oral consumption of appetitive substances are anatomically connected to the gut-draining mesenteric lymph nodes, a key site for oral tolerance formation. Accordingly, chemogenetic inhibition of neural activity in the mIC while mice were licking a novel food antigen affected immune cell populations in the gut and impaired the ability to suppress the immune response to the antigen.

Conclusions: Disruption of oral tolerance is critical in food allergy formation and gut inflammatory disorders. Our results reveal the involvement of the brain and specifically the insula and mesolimbic system in this key physiological process.

ASSOCIATIONS BETWEEN SENSORY AND INTEROCEPTIVE INFORMATION ARE MEDIATED BY A CIRCUIT WITHIN THE INSULA IN MICE

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The underlying mechanisms of association between different types of sensory information of the outside world (e.g. fear conditioning) are studied extensively in the last 100 years. In addition, we understand better the formation and stabilization of internal representations of the external world. At the same time, we know very little about internal representations of our inner world, the different organs within our body and their association with external information. The insular cortex, an elongated, atypical, hidden cortex was identified as playing major role in internal homeostasis body states. The insula can be segregated in human to different functional subdomain, some are contributing to emotional tagging of experiences and feeling of someone self. Here, using mice model, viral vectors, DREADs, electrophysiology, IHC and behavior, we show that different circuits within the insula play different roles in associative paradigms of taste and interoceptive information. Moreover, different cell types and connectivity differentially encodes anticipation, acquisition and retrieval of such association.

RECOVERY FROM ACUTE STRESS IN HUMANS INVOLVES ENHANCED COHESION BETWEEN SOMATO-SENSORIMOTOR AND SALIENCE NETWORKS

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Introduction: Stress perturbs our mental and physical homeostasis and individuals greatly differ in their ability to recover and stay healthy despite adversity (i.e. stress resilience). One candidate for physical health resilience mechanism is the Somato-SensoriMotor Network (SMN); a core network in processing body sensation and interoceptive awareness. This network was shown to be involved during the response to stress, though its role in response recovery from stress is yet unknown. This study aimed to depict changes in resting-state network dynamics of the SMN after an induced lab stress, and assess their relation to individual differences in recovery.

Methods: Fifty healthy male participants (ages 18-65) underwent fMRI resting-state scans (RS) before and after lab stress task known to induce distress as indicated by psychological and physiological measures. Network dynamics during RS was computed by the network-cohesion-index (NCI) analysis; a metric that calculates the degree to which pairs of nodes within or between networks fluctuate together. In comparing before to after stress scans, we expected to observe increased cohesion (i.e., more integration) with other RS-networks such as the Salience, Default Mode and Executive Networks (SN, DMN, CEN).

Results: Paired t-test yielded a significant increase in NCI between SMN and all networks in post stress scan ($t(47)=-3.21$, $p=0.002$). To examine which of the networks drives these results, we computed comparisons of NCI between each pair of networks. While all pairs of networks showed the same trend of NCI increase in post stress scan, only SMN-SN pair was significant ($t(47)=-3.59$, $p=0.001$).

Conclusions: These findings demonstrate a specific stress induced neural trace involving the SMN and SN, networks involved in body representations, interoception and emotional embodiment. Enhanced integration between these networks in the aftermath of acute stress, might point to a neural mechanism that underlies individual differences in physical health following stress adversity.

EMPOWERMENT OF IMMUNE FUNCTIONS IN HUMANS THROUGH FMRI NEUROFEEDBACK OF THE MESOLIMBIC REWARD CIRCUIT

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Recent animal studies have demonstrated that targeted stimulation of a core mesolimbic reward processing region of mice boosted peripheral antibacterial activity and inhibited tumor growth. In humans, such a causal association between motivation and immune functions, have not yet been demonstrated. Our study aimed to investigate whether up-regulation of the mesolimbic reward circuit via functional Magnetic Resonance NeuroFeedback (fMRI-NF) results in enhanced peripheral immune functions in humans. In a pre-registered, randomized, triple-blinded controlled design,85 healthy individuals (age 18-45) were assigned to one of three groups: (1) mesolimbic reward circuit NF (ML-NF; N=34), (2) a NF of a Control region (NF-C; N=34), or (3) No-NF group (No-NF; N=17). NF participants underwent four fMRI-NF up-regulation training sessions (TP1-4). Following NF sessions (or a waiting period for No-NF group), all participants received an HBV vaccination to challenge their innate and adaptive immune system. To assess immunological effects, blood samples were collected before the 1st and 4th NF session as baseline assessments, and 3, 14, 28 days following vaccination. Our primary hypothesis was that compared with both control groups, ML-NF group would exhibit stronger immune responses as reflected by blood cytokines and HBV antibodies. Results approved our hypotheses, demonstrating a significant interplay between levels of reward mesolimbic activations during NF training, and post vaccination immune effects. By combining a customized fMRI-NF procedure with longitudinal immunological assessments, we revealed new causal motivation-immune links in humans, which could pave the way for non-invasive neuromodulaiton interventions for the empowerment of immune functions.

PURSUING PERSONALIZED MEDICINE FOR DEPRESSION: A MULTICENTER STUDY TARGETING LATERAL VERSUS MEDIAL PREFRONTAL CORTEX WITH DEEP TMS

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Major depressive disorder (MDD) can benefit from novel interventions and personalization. Deep transcranial magnetic stimulation (Deep TMS) targeting the lateral prefrontal cortex (LPFC) using the H1 Coil, was FDA-approved for treatment of MDD, however recent preliminary data indicate that targeting medial prefrontal cortex (MPFC) using the H7 Coil might induce as good or even better outcomes. This prospective multicenter randomized study explored whether Deep TMS targeting the MPFC is non-inferior to targeting LPFC in MDD patients (N=169) who failed antidepressant treatments in the current episode, and whether electrophysiological or clinical markers for patient selection can be identified. Both treatment protocols included 24 Deep TMS sessions over 6 weeks and resulted in similar clinical efficacy and safety profiles, with response rates of 60.9% for the H1 Coil and 64.2% for the H7 Coil. Moreover, brain activity measured by EEG during the first treatment session correlated with clinical outcomes in a coil-specific manner, and a cluster of baseline clinical symptoms as identified in the current multicenter study, distinguished between patients who can benefit from each Deep TMS target. This multicenter study has led to FDA approval of the H7 Coil for treatment of MDD, providing a new treatment option for MDD patients, and provides initial guidance to differentiate between patients likely to respond to lateral versus medial prefrontal cortex stimulation location.

INTRANASAL OXYTOCIN AS AN ADJUNCT TREATMENT IN PATIENTS WITH MAJOR DEPRESSION WITH AND WITHOUT COMORBID BORDERLINE PERSONALITY DISORDER

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Introduction: The mechanisms leading to Oxytocin's differential effects among patients with borderline personality disorder have thus far been elusive. This study was aimed to explore the differential effect of OT administration among depressive patients with or without comorbid borderline personality disorder, and to explore the mediating role of attachment in these differential patterns.

Methods: Patients treated with psychotherapy in an inpatient setting (N=58) were randomized and double-blindly allocated to receive oxytocin or placebo for a period of four weeks. The effect of OT on therapy process and outcome was examined among patients with (n=35) and without (n=23) borderline personality disorder. Moderated mediational models were estimated to explore whether attachment differentially affected the association between oxytocin and treatment outcomes.

Results: patients without BPD showed significantly larger improvements following OT administration (B=-8.32, p=.001) as compared to placebo in OQ-45. On the other hand, patients with BPD showed no significant improvement following OT (B=0.61, p=.76). The same pattern was observed in the HSCL, where patients without BPD demonstrated significantly larger improvements following OT administration (B=-0.29, p=.0009) as compared to placebo, while patients with BPD demonstrated no significant improvement (B=-0.04, p=.55). Moderated mediational models indicated no significant moderated indirect effect, however, a significant trend of indirect effect only in the BPD group was observed, whereby the no-BPD group showed a stronger direct effect (β=-0.19, t=-1.30, p=.20), whereas the BPD group showed a stronger indirect effect (β=-0.72, SE=0.45, CI= -1,71, -0.00).

Conclusions: Patients with depression and comorbid BPD benefit less from OT administration as compared depressive patients without such comorbidity. It is possible that the involvement of the attachment system may be associated with the attenuation of OT's effect.

DISCREPANCY IN THE REPORTS ON LIFE EVENTS BETWEEN PARENTS AND THEIR DEPRESSED/ANXIOUS CHILDREN LEADS TO SEVERER PSYCHOPATHOLOGY AND LOWER RESPONSIVENESS TO SSRI TREATMENT

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Introduction: Exposure to a range of stressful life events (SLE) is implicated in youth psychopathology. Discrepancy between parents'/children's' reports (especially regarding SLE) is a major concern in child psychiatry. This study was designed to assess parent–youth discrepancies regarding SLE and its association with severity of psychopathology at baseline and response to treatment. Additionally, we assessed the association between three plasma pro-inflammatory cytokine levels and SLE.

Methods: SLE were assessed in children/adolescents suffering from depressive/anxiety disorders using the life events checklist (LEC), a self-report questionnaire measuring the impact of negative life events (NLE) and positive life events (PLE), as reported by the children and their parents. Severity of depression/anxiety disorders and response to antidepressant treatment were evaluated and correlated with both measures of LEC. We also correlated SLE with levels of three pro-inflammatory cytokines (TNF-α, IL-6, IL-1β).

Results: Participants were96 parent-child dyads (39 boys, 57 girls) aged 6-18(mean=13.90, SD=2.41y). Parents reported higher severity of NLE than their children. Discrepancy in PLE was associated with more severe psychopathology and reduced response to treatment. No association with cytokine levels was found.

Limitations: Lack of data on differences between mothers and fathers on the perception of SLE who may exhibit different patterns of consensus and disagreement.

Conclusions: Discrepancy in informant reports regarding life events in depressed/anxious youth, especially regarding PLE, is associated with more severe psychopathology and reduced response to pharmacotherapy. It is important to increase congruency regarding SLE between parents and children to improve response to treatment.

EXAMINING LOW-GRADE INFLAMMATION AS A POTENTIAL SHARED MECHANISM OF DEPRESSION AND OBESITY ACROSS ADOLESCENT DEVELOPMENT

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Introduction: Depression and obesity frequently co-occur, yet, the causal mechanisms are poorly understood. Research with adults suggests low-grade inflammation as a potential shared mechanism connecting these two health conditions. However, few studies examined this hypothesis in a prospective longitudinal manner in younger populations, and current findings are inconsistent.

Method: We examined concurrent and bidirectional associations between adiposity, inflammation, and depressive symptoms from pre-adolescence to early adulthood (at ages 9, 15, 17, and 24) using data from ALSPAC (*N*=6,558). Depressive symptoms were assessed by the Short Mood and Feelings Questionnaire. Fat Mass Index (FMI) was used as a proxy for general adiposity, and C-reactive protein (CRP) was used as a marker of systemic inflammation. Hypotheses were tested in a 3-level, 4-wave cross-lagged panel model, followed by multiple-groups comparison analysis to examine sex differences.

Results: We found positive longitudinal associations between FMI and CRP across all waves, demonstrating that adiposity is a robust predictor of CRP during adolescence. CRP was not clearly linked with depression across adolescence; in fact, for both boys and girls, CRP was inversely associated with depression at different points in development. Considering associations with adiposity, our findings suggest that preadolescents with elevated depressive symptoms may be at greater risk for increasing adiposity, and for girls, increasing inflammation in the transition into adolescence. However, this pattern did not continue in the later phases of adolescence and emerging adulthood.

Conclusion: These findings demonstrate that the mechanisms underlying the link between adiposity, inflammation, and depression differ in adolescents compared to adults. There is no evidence that systemic inflammation increases the risk for obesity and depression during adolescence. Instead, adiposity appears to drive later inflammation, and both seem to be consequences rather than antecedents of adolescent-onset depression. Further research is needed to elucidate when, how, and for whom these associations emerge.

ANTI-OBSESSIONAL EFFECTS OF PSILOCYBIN IN THE MARBLE BURYING PARADIGM; RELATIONSHIP TO PSYCHEDELIC EFFECTS

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Background: There is increasing interest in the role of psychedelic compounds in treating psychiatric disorders including obsessive compulsive disorder (OCD). Pre-clinical and preliminary clinical findings suggest that the psychedelic compound, psilocybin, has anti-obsessional attributes. The aim of this research was to study (i) the role of 5-HT2A and 5-HT1A receptors in the anti-obsessional effects of psilocybin in mice using the marble burying (MB) paradigm, a preclinical screening test for anti-obsessional effects, and; (ii) the role of the psychedelic effects induced by psilocybin in its putative anti-obsessional properties.

Methods: Male ICR mice were injected intraperitoneally with psilocybin (4.4 mg/kg), escitalopram (5mg/kg), the 5-HT2A antagonist M100907 (2mg/kg), the 5-HT1A agonist 8-OH-DPAT (2mg/kg), the 5-HT1A partial agonist buspirone (5mg/kg), the 5-HT1A antagonist WAY 100635 (2mg/kg) or their combinations. Mice were tested for MB 30 min after pharmacological treatment. Head twitch response (HTR) induced by psilocybin alone or combined with buspirone was measured using a magnetometer-based assay.

Results: Both psilocybin and its positive control, escitalopram, significantly reduced marble-burying ($p<0.01$). Psilocybin's effects on MB were not affected by the 5-HT2A antagonist, M100907. Buspirone and 8-OH-DPAT both significantly reduced MB (8-OH-DPAT effect that was additive to psilocybin). WAY100635 attenuated the effects of buspirone and 8-OH-DPAT on MB. Co-administration of buspirone with psilocybin did not block the latter's MB effects. Buspirone significantly attenuated the effect of psilocybin on HTR

Conclusions: Our results indicate that the effects of psilocybin on MB are not induced via 5-HT1A or 5-HT2A receptors. Buspirone administered with psilocybin blocked the latter's psychedelic effects (in the head twitch response test) while its anti-obsessional attributes in MB were retained. Therefore, the combination of buspirone and psilocybin can be further developed for treating OCD in the clinical setting.

LONG-TERM EFFECTS OF EXPOSURE TO CHRONIC STRESS IN HEALTH AND DISEASE: MODULATION OF SIRTUIN-1 EXPRESSION

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Background: Stressful unpredictable life events have been implicated in numerous diseases. It is now becoming clear that some life periods are more vulnerable than others. As adolescence is a sensitive period in brain development, the long-term effects of stress during this period could be significant. On the other hand, People with Alzheimer's disease (AD) and other dementias are disproportionately likely to suffer from several forms of anxiety, and anxiety also constitutes a well-established biomarker for AD to the extent that some have suggested it constitutes a prodrome. This is especially relevant nowadays, as apart from social isolation, one of the major causes of stress during the Covid-19 pandemic is the uncertainty and the sense of lack of control. We investigated the long-term effects of exposure to unpredictable chronic stress in adolescent mice on alternative splicing of Sirtuin-1.
Methods: 1-months old WT or AD-model mice (5xFAD) were exposed to chronic unpredictable stress and examined for anxiety and cognition at the age of 2, 4 and 6 months. Following the behavioral examination at each timepoint, qPCR and Western blot were used to examine alternative splicing of Sirtuin-1 and TrkB receptor in the hippocampus and cortex.
Results: In WT mice we found a rise in anxious behavior immediately after the exposure to stress. Importantly, there was a long-term impairment of performance in cognitive task and an imbalance in Sirtuin-1 and TrkB receptor alternative splicing, in the stress-exposed mice compared with controls. In AD mice we found that exposure to stress hastened the AD-related cognitive decline.
Conclusions: Our results show that exposure to unpredictable stress during adolescence affects cognition in adulthood and influence the development of AD-related cognitive decline.

CIRCADIAN DISTURBANCES AND STRESS: OBJECTIVE AND SUBJECTIVE MEASURES OF STRESS IN STUDENTS WITH MORNING OR EVENING CHRONOTYPES

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Chronotype is a trait that determines the morningness-eveningness preference of individuals over a 24-h period. Significant data indicate meaningful differences between evening types (ET) and morning types (MT) in behavior, personality traits, health and well-being. The aim of the current study was to investigate the cortisol response and the subjective perceived stress of MT and ET individuals in response to an acute common stressor. Fifty-two (N=52) undergraduate college students - 26 definite MT and 26 definite ET were recruited for this study. Participants were instructed to evaluate their perceived subjective stress and to provide saliva samples for the cortisol response measurement in four time points: Morning of regular school day versus morning of a final exam, and afternoon of a regular school day versus afternoon of a final exam. For general mood assessment, the participants were also asked to fill out the Positive and Negative Affect Schedule (PANAS) questionnaire. The most outstanding finding of this study was a blunted cortisol response in ET in response to acute stress in the morning. While in MT salivary cortisol levels were higher before a morning exam compared to a morning of a regular school day, in ET the acute stressor – A final exam, did not induce significant elevation in cortisol levels. Our results suggest dysregulation of the HPA axis in ET possibly due to their daily struggle to function in a morning-oriented society. These results further highlight the challenges faced by ET individuals and raise the question of possible interventions to assist them in overcoming these challenges.

INSIGHTS FROM PRECLINICAL STUDIES ON THE IMPACT OF CANNABINOIDS ON DEPRESSION AND PTSD

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A large body of evidence, including our own findings, points to the endocannabinoid (ECB) system as a possible therapeutic target to treat the emotional dysfunction characterizing PTSD and depression. Using rat models, we found that cannabinoids that increase anandamide levels [the FAAH inhibitor URB597, cannabidiol (CBD)] prevent depression- and PTSD-like behaviors and the associated brain dysfunction.

In many cases, drugs are used in clinical settings without a full understanding of the molecular mechanisms through which they function. Understanding the mechanism of action for a given drug in greater detail has the potential to support further pharmacological development efforts and mitigate the risk of failed clinical trials by stratifying patients to focus on subpopulations most likely to respond to such treatment.

In a series of studies, we present a potentially novel mechanism for the therapeutic effects of cannabinoids that involves the activation of CB1 receptors, the Wnt/β-catenin pathway, and microRNAs in the PFC. Overall, our findings suggest that administering cannabinoids such as URB597 and CBD may be viable for treating stress-related neuropsychiatric disorders.

CANNABIS AND PTSD FIFTEEN YEARS OF ACHIEVEMENTS AND A LOT OF CHALLENGES

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Post-Traumatic Stress Disorder (PTSD) is a common disability with a treatment challenge with disappointing outcomes and frustrating results.
I aim to present the results of open study of about two thousand PTSD patients that were treated by Medical Cannabis (MC) in my clinic since 2008.
The PTSD diagnosis was made upon DSM5 symptoms checklist. All the patients received the treatment approval from The Israeli Ministry of Health (MoH) to smoke between 30-50 gram/m of MC or the same amount of Cannabis oil. The cannabis strain was selected for the personal needs of the patient, until 20% THC for PTSD patients or based mainly on rich CBD oil. MC was added on their regular treatment. The precondition of MC approval were two conventional antidepresant trials failure and one psychotherapy. The PTSD patients described a significant clinical improvement: a better sleep continious and without nightmares, less hyperarousal, less anxiety, anhedonia and traumatic recollections. Almost 80% of the patients stoped all conventional medication and about 68% returned to work or studies. Only 29% worked somehow before cannabis treatment. The patient's condition remaind stable with cannabis during time.
There are a lot of challange questions about the maching of the cannabis strain and the specific kind of PTSD symptoms. A lot of future research options will be discussed.

CANNABIS FOR PTSD – INTERNATIONAL EXPERIENCE CANNABIS FOR PTSD – INTERNATIONAL EXPERIENCE

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Posttraumatic stress disorder (PTSD) is a debilitating condition characterized by re-experiencing, avoidance, and hyperarousal symptoms that have developed following a traumatic experience. Recently, there has been an increased interest in the use of cannabis and cannabinoids for the treatment of PTSD. A cross-over RCT showed that patients using cannabis and its derivates had a significant reduction in overall PTSD symptoms. Data from observational studies demonstrated a significant reduction in overall PTSD symptoms and improvement in functional outcomes such as quality of life, social function, and family function. In most studies, cannabis was administered in combination with other pharmacological agents, in varying potencies and through different routes such as direct smoking or evaporation as well as tablets, oral sprays, or powder form. The duration of response to cannabis was also variable among the studies. Seemingly, inhaled cannabis was acutely effective in reducing PTSD symptoms, and higher doses were associated with reduced anxiety and a lower frequency of intrusive thoughts.

It is speculated that active ingredients in cannabis, such as THC and CBD, potentiate the memory processing and endocannabinoid systems in the brain and thus, reduce sleep impairment, nightmares, and overall PTSD symptoms. However, it is still unclear whether the THC/CBD ratio or global (so-called entourage) effect and route of administration and potency played a significant role in treating PTSD patients.

Much still needs to be assessed concerning the efficacy and safety of cannabis in treating PTSD. Questions remain concerning effective doses for different conditions, how long the cannabis needs to be taken before positive effects can be expected, potential sex differences in the effectiveness of cannabinoid action, and to what extent adverse outcomes can be expected. Future studies should investigate the long-term effectiveness of cannabis use, the possible influence of entourage effect, the route of administration, and its overall potency in managing PTSD.

CHELATION ON LABILE BRAIN IRON IN SCHIZOPHRENIA

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Schizophrenia is a devastating neuropsychiatric disorder. The hypothesis that a disturbance of brain iron is involved in schizophrenia pathophysiology has been largely overlooked, despite the long-held recognition that brain iron homeostasis is critical. Iron serves as a major cofactor for tyrosine and tryptophan hydroxylases and *c*-aconitase, which are, respectively, the rate limiting enzymes in the synthesis of dopamine, serotonin and glutamate. Accordingly, iron chelators, which have been shown to inhibit synthesis and turnover of these key neurotransmitters, could offer a mechanism-based treatment approach. Our (unpublished) data indicate that iron is elevated in schizophrenia postmortem brain tissue and that in mice, deferiprone, a clinically used, orally available iron chelator, targeted a range of psychotic-like symptoms induced by dopaminergic (amphetamine, cocaine), glutamatergic (ketamine) and serotonergic (5-HTP) agents. Consistent with deferiprone's anticipated mode of action, a preliminary targeted metabolome analysis revealed that deferiprone could reverse amphetamine-induced frontal hyperglutamatergia and hyperserotonergia. In the proposed project, we intend to extend these findings by performing metabolome analyses in larger samples, while testing several psychomimetics and focusing on additional brain regions. By bolstering the behavioral findings with mechanistic insights, we expect that data emanating from this project could be readily translated into a deferiprone add-on clinical trial.

MECHANISMS OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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The negative symptoms of schizophrenia are strong prognostic factors but remain poorly understood and treated. At least two distinct cluster of negative symptoms have been identified: (1) motivation and pleasure; and (2) emotional expressivity deficits. Across patients, there is a varying degree of severity of each cluster, but deficits in motivation and pleasure pose the most significant risk for poor functional outcome. Here, we set out to examine the brain mechanisms of motivation and pleasure deficits in patients. Patients performed a series of cognitive neuroscience tasks that assess distinct motivational processes in a goal-directed action. Preliminary data from 40+ patients will be presented. Our overarching goal is to map these mechanisms onto behavioural and clinical phenotypes, in order to facilitate the testing of more specific interventions.

NEONATAL KETAMINE MODEL OF SCHIZOPHRENIA – COGNITIVE DEFICITS, AFFECTIVE AND SOCIAL ABNORMALITIES

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Schizophrenia is a widespread psychiatric disorder that affects 0.5-1.0 percent of the world's population and induces significant, long-term disability that exacts high personal and societal cost. Negative symptoms, which respond poorly to available antipsychotic drugs, are the primary cause of this disability. Preclinical translational models of schizophrenia are powerful tools in the development of novel and effective treatments for the disease. The present study tested the effect of neonatal ketamine treatment on cognitive, affective, and social phenotypes of the adult mice.

ICR male mice were treated with either saline (n=16) or 40mg/kg ketamine (n=15) on PNDs 6-9, 12-13. Behavioral phenotyping started when mice were 3-month-old, and was consisted of cognitive (Y-maze, radial arm water-maze, fear conditioning), social (social exploration, social interaction in pairs, tube dominance test, male sexual behavior), and affective (forced-swim test, open field, elevated plus maze) tests. In addition, response to acute ketamine and amphetamine injection were tested.

Ketamine-treated mice displayed cognitive impairments compared with saline-treated mice, demonstrated in the Y-maze test of working memory ($t[29]=2.105$, $p=0.0441$) and in the RAWM test of spatial navigation ($F[1,28]=6.727$, $p=0.0149$); lower social dominance ($t[25]=2.085$, $p=0.0471$), and lower interest in hedonic social behaviors demonstrated in the social exploration ($t[20]=2.235$, $p=0.037$) and male sexual behavior ($t[29]=3.209$, $p=0.0033$) tests; and higher anxiety, demonstrated both in higher permeance of the wall area in the open field ($t[29]=2.476$, $p=0.0194$), and higher freezing rate in a novel context in the fear conditioning test ($t[29]=2.075$, $p=0.0469$). interestingly, ketamine-treated mice displayed lower response to acute amphetamine ($F[1,28]=7.396$, $P=0.0409$).

Taken together, these results indicate that neonate ketamine treatment induces long-lasting deficits and may serve as a powerful tool in the development of novel treatments to schizophrenia and psychosis.

NON-REPLICATION IN NEUROBEHAVIORAL RESEARCH - CHALLENGES AND OPPORTUNITIES

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Non replication in biomedical research is a growing concern, amplified by the inherent complexity of neurobehavioral disorders and their weak and unstable phenotype delineation. We have repeatedly used data driven "machine learning" and artificial intelligence tools to palliate these weaknesses towards increasing findings' replicability and translational potential. Following a recent and careful of cross-samples non-replication fMRI study of early PTSD (Ben Zion et al., AJP 2022), this presentation offers an open and critical examination of diverging findings throughout the presenters' research career - and those of others. It annotates specific difficulties to achieve replicable findings, and offers ways to address such difficulties in study design, implementation and publication. It is argued that human neuro-behavioral research is inherently local and therefore neither advanced bioinformatic tools nor traditional statistical significance testing can overcome reliability and generalizability constraints emanating from data collection, sampling, measurements, implicit assumptions underlying study design, study execution context, and varying phenotype definitions. Ways to better examine, document and report studies' 'local' features are exemplified and discussed as opportunities to acknowledge, estimate and explicitly report the boundaries of one's studies' contribution to knowledge.

INTERHEMISPHERIC TRANSFER OF VISUAL INFORMATION: MEANINGFULNESS AND RESPONSE FORMATION

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We examined whether Redundancy Gain (RG) can be dissociated from the response stage of a Go/NoGo paradigm, and whether the meaningfulness of a stimulus modulates the stage at which information relevant to the response crosses from one hemisphere to the other. In Experiment 1, using a simple match-to-category paradigm, we found that meaningfulness had an effect on RG, such that the higher the meaningfulness of an object, the more efficiently information was transferred between the hemispheres. In Experiment 2, trials consisted of two stages, designed to separate the redundant stimulus from the response-eliciting stimulus in time. We show that RG occurs even when response is made to a centrally presented stimulus which is matched to a previously shown peripheral stimulus. This effect was modulated by the interval between the two stages of the trial. Additionally, Meaningfulness interacted with Presentation Order (responding to centrally or peripherally presented stimuli), suggesting that there are differences in information sharing between the hemispheres that result from bilateral and central presentation of visual stimuli. We interpret these differences such that bilateral presentation biases the brain towards separate processing in the two hemispheres, whereas central presentation biases the brain towards shared processing.

INTERMITTED FASTING REGIME INDUCES NEUROPROTECTION VIA CHROMATIN REORGANIZATION

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DNA double-strand breaks (DSBs) and reactive oxygen species were shown to accumulate in the early stages of several neurodegenerative and neuropsychiatric disorders, suggesting them to be a cause of said disorders rather than a consequence. The beneficial effects of intermitted fasting (IF) on various brain-related insults are well established, thus we seek to unveil the molecular mechanisms of these improvements. Under IF regime, the liver supplies the energy demands by producing glucose and ketones. In longer fasting periods, ketones such as β-hydroxybutyrate (BHB), become the principal fuel source for the brain, as well as regulating many pathways that are associated with neuroprotection. Interestingly, BHB was found to alter chromatin organization, thus we aim to explore whether the effect IF has on the brain, is mediated through ketones-induced epigenetic regulation.

In our experiment, mice went under an acute 24h fasting period. Half of the group was euthanized right after the fasting period (Fast-Ac) and the other half were euthanized after additional 24 hours of ad libitum access to food (Refed-Ac). Moreover, mice had ad libitum food access for 24 hours followed by 24 hours of fasting, for 15 cycles. Half were euthanized right after they fasted (Fast-Ch) and half were euthanized after they were fed (Refed-Ch). Additionally, we exposed induced human neurons (iNs) to BHB to explore whether these mechanisms could be recapitulated in *in vitro* model, without the fasting bouts.

In vivo, we found upregulation of genes related to oxidative stress (*GPx1*), and DNA damage response (*RAD50*) in the Fast-Ch group. Moreover, chronic IF regimes resulted in chromatin conformation, where we observed dynamic crosstalk between BHB binding to histone 3 lysine 9 tail (H3K9) and H3K27ac, on promoter sites.

Our data suggest that BHB is a key driver in chromatin modulation associated with the positive effect witnessed in the brain.

THE IMPACT OF RUNNING THERAPY ON MENTAL HEALTH OF YOUTH IN THE INPATIENT AND DAYCARE CENTERS: A PILOT RANDOMIZED CONTROLLED TRIAL

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There is a growing interest in the influence of physical activity on mental health. Among adults, it has been shown that physical activity is a promising treatment for depression and other mental health issues. For adolescents, the research on this issue has been developing in recent years and becoming more established. Despite methodological differences, measured mental health outcomes, types of physical activity, and age, the overall trend is similar. It indicates that physical activity positively affects mental health and should be combined with mental care. To our knowledge, only one scoping review on the relationship between running and mental health is available. While the evidence reported above supports running therapy as an effective way of improving mental health, there is a need for future research, especially in clinical under-18 populations, and a need to test the effect of running on more mental health outcomes other than depression, like anxiety. The current study was conducted on patients in the inpatient and daycare centers of the psychiatric adolescent department at Ziv Medical Center. This study assessed the effectiveness of combining a group-based running therapy as part of the treatment program provided in the inpatient and daycare centers of the psychiatric ward. To our knowledge, it is the first time that a randomized control trial of this kind has been conducted. Positive outcomes of this and future studies on the topic could lead to a policy change in which running therapy would be an integral part of the routine treatment program in adolescent psychiatric wards. In addition to the innovation of combining this kind of therapy in psychiatric adolescent wards, the study will also address the lack of sufficient evidence regarding the effect of running therapy on the adolescent clinical population, especially in-patients with the most complex and severe mental health states.

INITIAL MEDICAL WORKUP OF FIRST PRESENTATION OF PSYCHOTIC SYMPTOMS IN CHILDREN AND ADOLESCENTS: RESULTS FROM A TERTIARY MEDICAL CENTER

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Introduction: Psychosis is categorized into primary and secondary disorders. Secondary psychotic disorders include substance-induced psychosis or psychosis due to underlying medical condition, mainly neurologic, autoimmune, infectious, metabolic, and chromosomal disorders.

Evaluation of patients who present with psychotic symptoms requires comprehensive assessment including thorough history, physical examination, and decision of further laboratory tests, EEG and neuroimaging tests. Full medical investigation in cases of first presentation of psychotic symptoms is neither practical nor cost-effective. Therefore, identifying the cases in which full investigation is required is of utmost important.

Objective: To describe the medical workup of children and adolescents presenting with psychotic symptoms in a large tertiary medical center and to search for predictive variables for further medical investigation.

Methods: A review of computerized medical charts of children and adolescents, admitted to a tertiary medical center, with first presentation of psychotic symptoms, from February 2011 to May 2021, was conducted. Data regarding full medical investigation was retrospectively analyzed. This data includes physical and neurological examination, blood tests for CBC, chemistry analysis, inflammation markers and tests for autoimmune, infectious, and metabolic disorders. Additional data was included regarding urine toxicology screen, EEG, fundus examination, imaging tests and lumbar puncture.

Results: The study sample included 68 patients with mean age of 13.7± 3.7. Sixteen (23%) patients were diagnosed with secondary psychosis and the other fifty-two (76%) patients were diagnosed with primary psychosis. Secondary psychosis cases included medical diagnoses such as multiple sclerosis and autoimmune encephalitis. The main factors that were found in association to a higher risk to secondary psychosis are: early onset psychosis (<13), catatonia, classification of atypical psychosis and absence of prodromal symptoms.

Conclusion: Basic medical investigation should be performed in children and adolescents with psychotic symptoms. Further tests are recommended only in appropriate cases.

THE ASSOCIATION BETWEEN THE USE OF COMMUNITY REHABILITATION SERVICE PATHWAYS AND RE-HOSPITALIZATION AMONG PEOPLE WITH CHRONIC PSYCHOTIC DISORDERS

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Background and Hypothesis: Community rehabilitation is an essential element in the treatment of people with schizophrenia. In Israel, the Community rehabilitation law, enacted in 2000, enabled funding and development of various services. We aimed to assess the effect of different types of community rehabilitation services and their combinations on re-hospitalization days of people with schizophrenia in a long-term follow-up.

Methods: Data from the National Psychiatric Case Register on 18,684 adults with schizophrenia was merged with data from the Israeli Mental Rehabilitation Services Register. There were three follow-up periods: 1991-2000 - pre-rehabilitation; 2001-2009 - exposure to rehabilitation; 2010-2017 - outcome period. Associations between type of rehabilitation and annual re-hospitalization days (ARHD), adjusted for demographic and clinical characteristics, were analyzed using ANCOVA.

Results: Mean time to re-hospitalization prior to the first rehabilitation service was 512 days, while it increased to 1329 days following its implementation ($p<0.0001$). Types of rehabilitation were independently associated with ARHD ($p<0.0001$): after rehabilitation, those who received both residential and vocational rehabilitation had a decrease of 20 ARHD; Residential or vocational rehabilitation alone were associated with a decrease of 2 and 5 ARHD respectively; whereas those without any such rehabilitation had a mean increase of 9 ARHD. The more the residential rehabilitation provided higher level of support, the greater the decrease in ARHD (hostel – 20 days, enhanced supported housing – 11 days, supported housing – 7.5 days). Of the vocational rehabilitation types, supported employment and sheltered workshops were associated with the highest decrease in ARHD (17 days).

Conclusions: Rehabilitation should start as soon as possible, preferably combining residential and vocational services, as this may have the greatest impact on reducing mental exacerbations and hospitalization days. Sheltered workshops can be a good alternative for those whose level of functioning is not high enough for supported employment.

EFFECTS OF INHIBITION CONTROL ON DECISION MAKING AND CHECKING IN UNCERTAINTY

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Difficulty tolerating uncertainty is a central deficit in psychopathologies and one of its common responses is checking. inducing inhibition improves resolution of uncertainty. However, it is unclear whether inducing inhibition improves the resolution of uncertainty or checking. In this study we evaluated how inducing inhibition affects resolution of uncertainty with and without checking. Healthy adults (N=34) completed three blocks which combined a Stroop task with a novel Visual-Matching task, that dissociated resolution of uncertainty and checking. In Block 1 the Visual Matching task included only "certainty" trials and allowed unlimited checking. In Block 2, the task featured "certainty" and "uncertainty" trials, with no checking allowed. In Block 3 the task featured only "certainty" trials, with no checking allowed. Our results indicate that inducing inhibition minimizes unnecessary checking in "certainty" trials (Block 1, $F1,30 = 4.37$, $p < 0.05$) when checking is possible. Inducing inhibition also improves accuracy in uncertainty trials when checking is impossible by limiting the propagation of uncertainty (Block 2, $t30 = 2.78$, $p < 0.01$; Block 3, $t30 = -0.79$, $p = 0.43$). Propagation of uncertainty was linked to depression ($r = 0.43$, $p = 0.01$), and checking was linked to OCI-R ($r = 0.38$, $p = 0.03$). We show here that inducing inhibition improves the ability to tolerate uncertainty and reduces redundant checking. Interestingly, the harmful propagation of uncertainty is linked to depression severity. Our results have implications for our understanding of how difficulty enduring uncertainty psychopathologies, and the mechanisms inhibition affects.

EXPECTANCY AND ATTENTION BIAS TO SPIDERS: DISSECTING ANTICIPATION AND ALLOCATION PROCESSES USING ERPS

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Studies suggest that there exists an interaction between a-priori expectancies and attention bias toward threat, as threat detection can override endogenous attention control driven by expectancy. Specifically, while expectancy influences the detection of neutral stimuli, it does affect the detection of spiders. The current study focuses on the temporal dynamics of the relationship between expectancy and attention toward threat, to better understand the mechanisms underlying the prioritization of threat detection. In this accepted-in-principle (Stage 1) registered report, an event-related potentials (ERP) experiment was conducted. Specifically, we manipulated a-priori expectancy and measured attention bias, using a well-validated paradigm: a visual search array was presented, with one of two possible targets: spiders (threatening) or birds (neutral). A verbal cue stating the likelihood of encountering a target preceded the array. Following cue presentation, preparatory processes were examined using the contingent negative variation (CNV). Following target presentation, two components were measured: early posterior negativity (EPN) and late positive potential (LPP), as these components reflect early and late stages of natural selective attention toward emotional stimuli, respectively. In line with our hypotheses, preliminary results suggest main effects of emotion during early processing (at the CNV and EPN levels) and later effect of expectancy (at the LPP level). These results may suggest that attention is firstly directed by the emotional value of the stimulus, beginning from cue presentation. Understanding the temporal dynamics of expectancy-attention interactions may help in targeting these processes using cognitive trainings, which could reduce attention bias levels and subsequently specific phobia symptoms.

THE DYNAMICS OF PHYSIOLOGICAL SYNCHRONY IN SMALL HUMAN GROUPS

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Despite the critical importance of groups to achieving goals, shaping identity, and creating social change, little is understood about the biobehavioral foundations of social interactions and social synchronization in groups. Face-to-face interactions give rise to interpersonal synchrony, the spontaneous temporal coordination of actions, emotions, and physiological processes between two or more individuals. Synchrony is a ubiquitous phenomenon thought to function as "social glue", with a biological basis in neural networks, genes, and physiological markers of social function. One of the main characteristics of synchronization is its dynamical nature, continuously shifting in and out of synchrony throughout social exchanges. Face-to-face interactions have been one of the most important settings in which dyadic synchrony has been researched, and yet they have rarely been utilized when studying synchrony in groups or teams. We will present data from four large studies (N=350) that examined group face-to-face interactions in the lab. We will provide examples of physiological group synchrony and show how these multimodal markers of synchrony predict group outcomes, such as cohesion and efficacy. We will go further to present the dynamics of synchrony during group face-to-face interaction to explore its meaning and emphasize the importance of examining changes in synchrony as predictors of adaptive social function. Our data highlights the theoretical importance of addressing dynamical and multimodal factors in the study of synchronization in face-to-face group interactions.

INNOVATIVE NOVEL DISCOVERIES IN AUTISM

Illana Gozes[1], Haitham Amal[2], Shlomo Wagner[3], Shani Stern[4]

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Selected Israeli autism researchers will present psychiatric, biological, cellular, molecular, electro-physiological and behavioral modelling, from the laboratory bench toward clinical development:
Chair: Professor (Emerita) Illana Gozes, Tel Aviv University
Lectures:
1] Prof. Shlomo Wagner, University of Haifa:
Beyond the three-chamber test: toward a multimodal and objective assessment of social behavior in rodents.
Selected Publication: Jabarin R, Netser S, **Wagner S.** Mol Autism. 2022 Oct 25;13(1):41
2] Dr. Haitham Amal, Hebrew University of Jerusalem:
Nitric oxide: from systems biology to diagnostic models and therapeutic targets for autism spectrum disorder
Manish Tripathi, Maryam Kartawy, Wajeeha Hamoudi, Shashank Ojha, Huda Soluh, Shira Mencer, Shelly Ginzburg, Igor Khaliulin, and **Haitham Amal**
Selected Publication: Free Radic Biol Med. 2022 Aug 1;188:83-91
3] Professor Illana Gozes, Tel Aviv University
Discovery of shared mechanisms by mutations in different genes associated with autism and schizophrenia
Selected Publication: Ivashko-Pachima Y, Ganaiem M, Ben-Horin-Hazak I, Lobyntseva A, Bellaiche N, Fischer I, Levy G, Sragovich S, Karmon G, Giladi E, Shazman S, Barak B, **Gozes I.** Mol Psychiatry. 2022 May 10.
4] Dr. Shani Stern, University of Haifa:
IQSEC2 mutation associated with epilepsy, intellectual disability, and **autism** results in hyperexcitability of patient-derived neurons and deficient synaptic transmission.
Selected Publication: Brant B, Stern T, Shekhidem HA, Mizrahi L, Rosh I, Stern Y, Ofer P, Asleh A, Umanah GKE, Jada R, Levy NS, Levy AP, **Stern S.** Mol Psychiatry. 2021 Dec;26(12):7498-7508.

NITRIC OXIDE: FROM SYSTEMS BIOLOGY TO DIAGNOSTIC MODELS AND THERAPEUTIC TARGETS FOR AUTISM SPECTRUM DISORDER

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by abnormalities in social interactions, deficits in communication, restricted interests, repetitive behavior, and sensory anomalies. ASD is a life-long disability that can be devastating for the patients and their families. Neither clinical diagnostics assisted by laboratory tests nor effective pharmacological treatment or preventive measures have been established forASD to date. Recently, we showed that *Shank3* human-mutation based in a mouse model of ASD led to a dramatic increase of nitric oxide (NO) formation. NO is a multifunctional signaling molecule and a neurotransmitter that plays an important role in physiological and pathophysiological processes including neuronal signaling. Pioneering work shows that NO can engender nitrosative stress in the nervous system, contributing to neurodegenerative diseases. In the case of ASD, there is no much evidence for a link with NO.We hypothesize that mutations in synaptic genes such *SHANK3* and *CNTNAP2* lead to nitrergic signalling alterations resulting in synaptic and behavioral dysfunctions. To test this hypothesis, we looked into the S-nitroso-proteome of brain samples of both *Shank3* and *Cntnap2* ASD mouse models. We generated the data and defined possible molecular targets for ASD treatment. The nitrergic targets were validated in the animal ASD models, and the pharmacological interventions against these targets were selected. Inhibition of the nitrosative stress reversed the synaptic and behavioral ASD phenotype. The proposed study enabled us to carefully dissect the nitrergic mechanisms involved in the development of the ASD phenotype in the *Shank3* and *Cntnap2* mutant mice. The findings of this project will open new avenues in the search for novel therapeutic targets for ASD.

IQSEC2 MUTATION ASSOCIATED WITH EPILEPSY, INTELLECTUAL DISABILITY, AND AUTISM RESULTS IN HYPEREXCITABILITY OF PATIENT-DERIVED NEURONS AND DEFICIENT SYNAPTIC TRANSMISSION

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Mutations in the *IQSEC2* gene are associated with drug-resistant, multifocal infantile and childhood epilepsy, autism, and severe intellectual disability. We used induced pluripotent stem cell (iPSC) technology to differentiate dentate gyrus (DG) hippocampal neurons to investigate the neuropathology of *IQSEC2*-mediated disease. The neurons were measured at several time points during the differentiation to assess the developmental trajectory. We showed that immature *IQSEC2* mutant DG granule neurons were extremely hyperexcitable early in the development, and exhibited increased sodium and potassium currents compared to those of CRISPR-Cas9-corrected isogenic controls. They displayed a dysregulation of genes involved in differentiation and development. Immature *IQSEC2* mutant cultured neurons also exhibited a marked reduction in the number of inhibitory neurons, which contributed further to the hyperexcitability. As the *IQSEC2* neurons aged, they became hypoexcitable, exhibited reduced sodium and potassium currents, and a reduction in the rate of synaptic and network activity. The *IQSEC2* mutant neurons showed a dysregulation of genes involved in synaptic transmission and neuronal differentiation. Mature *IQSEC2* mutant neurons were less viable than *wild-type* mature neurons and had reduced expression of surface AMPA receptors. Our studies provide mechanistic insights into severe infantile epilepsy and neurodevelopmental delay associated with this mutation and present a human model for studying *IQSEC2* mutations in vitro.

CORTISOL AND PSYCHOLOGICAL CHARACTERISTICS AS PREDICTORS OF DEPRESSIVE SYMPTOMS IN PARENTS OF CHILDREN WITH CANCER

Or Ben Simon Cohen[1], Shimrit Daches[1], Tamar Natanzon[2], Meital Avishai[3], Noa Tsuk Ram[1], Adi Moka[1], Noa Benaroya-Milshtein[3,4]

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Pediatric cancer affects the entire family; however, little is known about the trajectories of parents' adjustment. We conducted a cross-sectional examination that aimed to (1) understand the relationship between the time that has passed since the initial diagnosis and depressive symptoms and (2) determine what psychological process and\or level of cortisol may underlie the experience of depressive symptoms among parents. Specifically, we focused on the effect of parental sense of coping and ruminative thinking style as possible underlying psychological processes. Forty-four parents (32 mothers) of forty-four children participated with a median of three months since their cancer diagnosis were included in the current analysis. Parents completed a set of questionnaires including the Beck Depression Inventory-II (BDI-II), the Parenting Sense of Competence (PSOC), and the Ruminative Response Scale (RRS), which includes the brooding subscale, known to be the maladaptive component of ruminative thinking. Indices of psychological distress included a physiological marker of longer-term stress (hair cortisol concentration). A hair sample was taken from parents at the time of assessment. Findings suggest that time since initial diagnosis did not predict a decrease in depressive symptoms as expected. However, time since initial diagnosis did predict a greater tendency to use ruminative brooding in response to negative mood, which in turn predicted more depressive symptoms in parents. Parental sense of competence predicted lessened use of ruminative brooding in response to negative mood, as well as less depressive symptoms. Our results provide support for the clinical significance of parental sense of competence and ruminative thinking style in response to negative mood as possible underlying psychological mechanisms that can explain the distress of parents of ill children and can be the focus of interventions. Our results encourage future investigation of parental psychosocial factors that may impact parental adjustment to child illness.

PARENTING PRETERM INFANTS: CHALLENGES AND AN INTERVENTION PATH

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Preterm birth presents challenges to children and families, firstly due to associations with an increased risk for major medical conditions, neurodevelopmental shortfalls, and psychiatric diagnoses. Further, stressogenic experiences with the preterm child are highly prevalent peripartum – during the primary and very first steps of bonding – in ways that often interfere with the formation of the child's attachment security and the parent's well-being. Parents' basic needs concerning sleep, intimate relations, and mental hygiene are significantly strained. Further, support networks such as job security and peer friendships are often disrupted and augment parental stress. This talk will comprise three parts. The first will delineate the psychological strains related to prematurity. The second will present the rationale and characteristics of an 8-session group intervention protocol we are developing for parents of preterm infants, commenced in a sensitive period (6 to 24 months) for children's emotional, cognitive, neurological, and behavioral development. The intervention aims to expand mindful parenting skills while addressing specific themes related to prematurity, involving a higher likelihood of a child with a difficult temperament or chronic medical conditions, elevated parental stress, difficulties in forming a secure attachment, and the possibility of familial trauma around childbirth or early life. The intervention consists of five core skills, including (1) psychoeducation on risk and resiliency factors associated with prematurity and the dynamic interplay between biological predisposition and care; (2) General mindfulness skills; (3) Interpersonal mindfulness skills (*e.g.*, contingent responsiveness); (4) Interpersonal distress tolerance skills (*e.g.*, validation and dyadic soothing skills); and (5) Consolidation of birth- and NICU-related trauma. Finally, a demonstration of its clinical implications on two pilot groups of parents of preterm infants (*N* =17). concerning peripartum trauma group processing and interpersonal mindfulness training will be discussed, along with a preliminary analysis of pre-post intervention outcomes.

PARENT-TRAINING IN NON-VIOLENT RESISTANCE FOR CHILDREN WITH ADHD: A CONTROLLED OUTCOME STUDY

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ADHD is a neurodevelopmental disorder whose development and intensity are closely dependent on the child's environment. This is why parental guidance is considered the most effective psychological treatment for ADHD disorder among children (NICE, 2018).
Current forms of parent training (PT) are often insufficient. Many families drop out of training, and treatment gains are often not maintained. Nonviolent resistance (NVR) PT focuses on helping parents resist the child's externalizing symptoms and improve child and parent well-being. NVR serves the anchoring function, supporting the child through presence, self-regulation, and support network. This study applied a randomized controlled trial to assess the efficacy of NVR PT in the treatment of child ADHD.
Method: Participants were parents of children with ADHD (N=101; 5-13 years old) randomly assigned to one of two groups. Measures were administered before and after treatment and at a 4-months follow-up. ADHD outcomes included the Conners and CBCL. Parenting outcomes included parental helplessness, emotional regulation, anchoring function, and family chaos.
Results: Participants in the NVR group reported significant improvements in the child's internalizing, externalizing, and ADHD symptoms, as well as parental helplessness, anchoring, and emotional regulation. The results at follow-up revealed maintenance of change in the child's externalizing and internalizing symptoms, in all of the parent measures, and significant improvement in family chaos. Dropout rates in the treatment group were low (5%), and fathers' engagement was close to 100%.
Conclusion: NVR is an efficient treatment for childhood ADHD, with benefits extending beyond the child's symptoms to the entire family. NVR's special focus on parental distress may have contributed to low dropout, high paternal engagement, and maintenance of change.

REDUCING STRESS AND ENHANCING WELL-BEING OF PARENTS OF CHILDREN WITH CHRONIC TIC DISORDERS VIA VIRTUAL GROUPS TRAINING

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Background: Parents of children and adolescents with chronic tic disorders (CTD) frequently lack knowledge on CTD. They also suffer from caregiver burden, high levels of parenting stress and more psychiatric difficulties compared to parents of children with typical development. Moreover, it is clinically well known that children's well-being regarding living with CTD is tremendously affected by their parents' functioning and perceptions. Surprisingly, parental training was not assessed in clinical guidelines and no recommendation regarding its use has been made. We have developed a virtual-open ended training group: "Parents living well with tics". This pilot study evaluated the feasibility of this new intervention.
Methods: Participants were parents of children and adolescents (age range 6-17) diagnosed with CTD (n=18). Pre and post participation questionnaires were administered: Yale Global Tic Severity Scale (YGTSS); Clinical global impression (CGI); The Child Tourette Syndrome Impairment Scale (CTIM); The Beliefs About Tics Scale (BATS); strength and difficulties questionnaire (SDQ). Brief Mental Health Outcome Measure (Parental well-being); Perceived stress scale adult self-rating (PSS-C); Covid impact questions; satisfaction from intervention and change in attitudes and knowledge about tics.
Results: Pre-intervention well-being was 40.67 out of 60 (±8.43), perceived stress was 20 (±10.2) out of 40. Tic impairment (YGTSS) was 35 (±8.37) out of 50 while impairment caused by other comorbidities (CTIM) was 15.33 (±7.99) out of 36. Most parents reported gaining new knowledge on CTD and felt more capable in their ability to help their child. Most parents reported high satisfaction from the intervention, and that they would recommend it to other parents of patients with CTD.
Conclusions: These preliminary results show both the necessity and the feasibility of the newly developed virtual-open ended training group: "Parents living well with tics". Further study is needed in order to evaluate its efficacy.

REDUCED DYNAMIC FUNCTIONAL CONNECTIVITY BETWEEN THE ANTERIOR AND POSTERIOR COMPONENTS OF THE TEMPORAL PARIETAL JUNCTION MAY UNDERLIE THE ASSOCIATION BETWEEN ATYPICAL ATTENTION AND MENTALIZING IN AUTISM

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Background: Atypicalities in mentalizing and in orienting, disengaging and reorienting of attention have been consistently demonstrated in ASD. These abilities have respectively been linked to the right anterior and posterior subdivisions of the Temporal Parietal Junction (raTPJ/rpTPJ). It has been suggested that attention reorienting is intrinsically linked to difficulties in mentalizing as the ability to disengage and shift attention to new stimuli could be needed for the development of mentalizing abilities. Thus, rTPJ is likely an important interaction point between mentalizing and attention orienting, and specifically the interaction between the raTPJ (attention) and rpTPJ (mentalizing).
Objectives: We examined dynamic resting-state Functional Connectivity (FC) between the raTPJ and rpTPJ in ASD compared to TD adults, and in relation to symptomatology in ASD.
Methods: Dynamic independent component analysis (dyn-ICA) was used to assess FC of the raTPJ and rpTPJ in two resting-state fMRI adult datasets from the ABIDE database: one serving as an exploratory (ASD = 14; TD = 15) and the second (ASD = 29; TD = 29) as replication. We also assessed specific connectivity states (from highly negatively to highly positively correlated) in the larger replication dataset using a sliding-window approach to explore the associations between connectivity states and ASD symptom severity (measured with the Social Responsiveness Scale; SRS).
Results: Results revealed reduced dynamic FC in ASD compared to TD adults in both the exploratory and replication datasets. In ASD, increased dynamic FC predicted decreased behavioural symptoms. More specifically, symptom severity was negatively predicted by engagement of the highly negative state, and positively predicted by engagement of the highly positive state.
Conclusions: Reduced dynamic FC between the raTPJ and rpTPJ is evident in ASD and it is plausible that their increased positive connectivity and reduced alterations and changes of connectivity states underlie attention and mentalizing atypicalities in ASD.

BACTEROIDES ABUNDANCE IS INCREASED IN AN ISRAELI COHORT OF AUTISM AND DEVELOPMENTAL INCREASE OF BACTEROIDES IN MICE INDUCES AUTISM-LIKE BEHAVIOR AND MOLECULAR CHANGES

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Autism Spectrum Disorder (ASD) is a neurodevelopmental condition which is defined by decreased social behavior and the presence of stereotypic behaviors. Recent evidence has suggested that changes in the gut-brain axis may be important in neurodevelopment in general, and may play a role in ASD in particular. Several human and mouse studies have been performed to understand specific microbiome changes that may be associated with ASD. In the current study, we present a study of the gut microbiome in 97 individuals diagnosed with ASD in Israel, compared to 42 neurotypical individuals. We determined differences in alpha and beta diversity in the microbiome in individuals with ASD, and further determined that the phylum bacteroidetes and genus bacteroidetes was the baceterial taxa that most significantly increased in individuals with ASD. To understand the possible functional significance of these changes, we further treated newborn mice one time with Bacteroides Fragilis at birth. B. Fragilis treated mice displayed social behavior dysfunction, increased repetitive behaviors, gene expression dysregulation in the frontal cortex, and changes in serum serotonin levels. These findings suggest that changes in Bacteroides, particularly in early life, may be have functional consequences for individuals with ASD.

DYNAMIC DNA METHYLATION ALTERATIONS IN SOCIALLY DOMINANT AND SUBMISSIVE MICE DURING POSTNATAL DEVELOPMENT

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Aims: Impaired maternal care was shown to have long-lasting effects on the adult offspring behavior through altered hippocampal DNA methylation. However, it is less clear what changes in the DNA methylation landscape occurs throughout the early postnatal developmental stages while offspring are cared by their dams.
Methods: We used mouse models of social dominance (Dom) and submissiveness (Sub), who show innate features of high and low maternal care behaviors, respectively. For genome-wide DNA methylation analysis we used reduced-representation bisulfite sequencing (RRBS-Seq) of hippocampal DNA from 7- and 21-days-old Sub and Dom pups.
Results: Sub mice showed low maternal care behaviors accompanied by reduced DNA methyltransferases expression. We found robust alterations in the DNA methylation landscape for both between-group and between timepoint analyses; with significant enrichment of differentially methylated CpGs in genes associated with behavior, and neuronal development. Cross fostering of Sub pups with Dom dams restored many of the behavioral and molecular alterations observed between Dom and Sub pups.
Conclusion: we conclude that altered methylome previously reported in the hippocampus of adult offspring of dams providing poor maternal care is perceived by early and time-dependent postnatal changes in DNA methylation patterns.

PREMATURE BIRTH, MATERNAL CARE, AND ANXIETY RISK: INSIGHTS FROM A CROSS-FOSTERING MICE MODEL

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Introduction: Premature birth confers a high risk for psychiatric conditions, including anxiety disorders. These risks were found to be moderated by parental caregiving, which can enhance or reduce infants' initial risk conditions. In order to deepen findings from human studies, we used a mouse model of preterm birth in which we manipulated preterm birth and maternal care. We examined whether preterm birth is associated with an increased risk for behavioral and biological manifestations of anxiety and whether this risk can be reduced by nurturing maternal behaviors.

Method: Pregnant mice at day 17 of gestation were injected with either anti-progesterone RU486, which caused preterm parturition at day 18, or with a placebo which was followed by term parturition (day 19.5-20).

Preterm-born (PTB) and term-born (TB) mice were then cross-fostered and raised by either BALB/c dams (typically show low-quality maternal care) or C57BL/6 dams (typically show high-quality maternal care). We assessed the offspring's anxiety-like behaviors in childhood. and measured several biological anxiety indicators in the amygdala.

Results: PTB mice raised by C57BL/6 demonstrated significantly less anxiety-like behaviors in comparison to PTB mice raised by BALB/c, and did not differ from TB mice. A biological examination of the amygdala showed that among mice raised by BALB/c, PTB had higher expression of TrkB.FL compared to TB mice, indicating increased amygdala activity. Contrarily, among mice raised by C57BL/6, PTB had lower BDNF and CRH expression compared to TB mice, suggesting lower amygdala activity.

Conclusions: Results provide support for the notion that high-quality caregiving can attenuate the risk associated with prematurity. In the context of poor caregiving, prematurity increased anxiety-like behaviors and anxiety-related biological indices in the amygdala, whereas in the context of high-quality caregiving, PTB mice were no different from their TB in anxiety-like behavior and showed decreased anxiety-related biological indices.

DAGSY: A NOVEL CLINICAL FRAMEWORK TO ADDRESS A CURRENTLY UNMET NEED IN CHILD PSYCHIATRY

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Many genes simultaneously impact the development and function of multiple organ systems (pleiotropy). Relevant for psychiatry are genes whose pleiotropic functions include brain development, increasing the risk for adverse neurodevelopmental and psychiatric outcomes. Pathogenic variants in such pleiotropic genes, discovered upon genetic testing prompted by physical indications (e.g., congenital heart defects, cleft lip and palate, hearing loss), are increasingly identified. As the utilization of genetic testing continues to be applied earlier in the diagnostic workup, younger children are identified as at risk for atypical developmental trajectories. This provides an opportunity for proactive, anticipatory psychiatric care, which contrasts with traditional ('reactive') psychiatric care models indicated primarily by the presence of symptoms or behavioural concerns.

The DAGSY (Developmental Assessment of Genetically Susceptible Youth) Clinic at the Hospital for Sick Children, Toronto, Canada, was established to fill this emerging unmet clinical need. DAGSY is set up as a multidisciplinary clinic staffed by professionals with backgrounds in child psychiatry, psychology, psychometry, and genetic counselling. Any child with a confirmed genetic risk variant for neurodevelopmental or psychiatric disorders can be referred to DAGSY for a comprehensive standardized assessment of psychiatric, cognitive, social, language, adaptive and academic status using standardized instruments.

Parents and referring physicians receive a comprehensive report in which results are interpreted in the context of what is known about the specific genetic variant identified in the child. In this presentation, I will discuss the DAGSY clinical model and describe the outcomes and feedback for over 140 children seen to date.

THE LATENT VULNERABILITY OF WOMEN WITH CHILDHOOD TRAUMA TO PMAD THROUGH PSYCHOLOGICAL AND NEUROBIOLOGICAL PATHS

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Introduction: Perinatal mood and anxiety disorders (PMAD) affect 15-20% of women, with significantly higher rates in women who have a history of childhood trauma (CT) 1. According to latent vulnerability theory, CT may impact neuronal and psychological development during childhood. This may embed enduring vulnerability to psychopathology later in life 2, especially at sensitive times 3 such as the perinatal period4**.**

Methods: longitudinal research. 104 healthy women (age m=25.9, sd=4) who planned their first pregnancy were recruited. Before pregnancy, participants filled out questionnaires about childhood trauma (CTQ), depression (PHQ-9), and anxiety (GAD-7), and a resting-state functional magnetic resonance (fMRI) scan. DMN maps 5 were identified using independent component analysis (ICA). After birth, they filled out depression and anxiety questionnaires again.

Correlations between CTQ, depression, and anxiety scores, and DMN functional connectivity parameters were calculated before pregnancy and after birth.

Results: 18 women (17.3%) reported CT history, with different abuse and neglect CTQ sub-scales.

Before pregnancy, no significant associations between CTQ total score / other sub-scales with PHQ-9 ($r = .109$, $p > 0.05$), and GAD-7 scores ($r = .043$, $p > 0.05$). No significant associations between DMN functional connectivity parameters and any scores before pregnancy.

After birth, significant associations between PHQ-9 and CTQ total score ($r = .543$, $p < 0.05$), no significant associations between CTQ total score / other sub-scales with GAD-7 scores ($r = .213$, $p > 0.05$). No significant associations between DMN functional connectivity parameters and any scores after birth.

Conclusions: women with CT carry a latent vulnerability to psychopathology, particularly to depression, which may come out during stressful times such as the perinatal period. No findings indicated that this vulnerability is explained by neurobiological changes in the DMN network. Findings highlight the need for early identification of women with CT in the perinatal period.

SMOKING CESSATION AMONG PEOPLE WITH SERIOUS MENTAL ILNESS - THE GAP BETWEEN PHYSICIAN & PATIENT PRACTICE

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Introduction: People with serious mental illness (SMI: schizophrenia, bipolar disorder, schizoaffective disorder) have a threefold higher rate of both smoking and heavy smoking than the general population. Physicians have been skeptical about this group's desire and ability to quit smoking, yet people with SMI are just as motivated to quit and are more likely to present to smoking cessation services.

Methods: A telephone survey was carried out among psychiatrists and primary care physicians in a large HMO (Israel) to measure attitudes and practices regarding smoking cessation promotion for people with SMI. Using the HMO database, registration, participation and successful abstinence were measured for all members that smoked between the years 2013-2019, comparing rates by SMI status.

Results: Sixty percent of physicians agreed that most patients with SMI had little desire or ability to quit. Most physicians (80%) would ask about smoking status, recommend that the patient quit and assess motivation to quit. However, rates of referral, smoking cessation medication prescription and timely follow-up were lower (30-60%), particularly among psychiatrists.

Persons with SMI were 1.8 times more likely to register for smoking cessation services. Of those who participated in at least one session, 30% had quit by the end of the smoking cessation program; 60% among those that had completed the program. The factors most strongly associated with successful abstinence were program completion and smoking cessation medication purchase.

Discussion: Smoking cessation guidelines for people with SMI among physicians should be promoted and routinely evaluated.

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EXTRINSIC EMOTION REGULATION CHOICE: THE ROLE OF DEPRESSION SYMPTOMS

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Extrinsic emotion regulation (EER) is the provision of emotion regulation support to another person. An important question is what factors influence peoples' choice of EER strategy. The present study examined the role of depression symptoms in EER strategy use. Fifty-one women who reported high levels of depression symptoms and 48 women who reported low levels of depression symptoms participated in the study. They were asked to read texts that described negative emotional situations ostensibly written by another participant. They were then asked to help the other participant by writing a supportive letter. They reported the degree to which they believe the other person feels bad, how much they are similar to that person, and the degree to which they used two emotion regulation strategies: distraction and reappraisal. They rated their emotions before and after providing support. Results showed that depressed and non-depressed participants reported more positive and less negative mood after providing support. Furthermore, depressed and non-depressed participants reported higher use of reappraisal compared to distraction when providing support. The level of depression symptoms was positively correlated with the perceived negativity of the events and the perceived similarity to the other person. These findings are consistent with previous findings showing that EER benefits support providers. Together, these findings imply that EER may be a good way to improve mood and that people choose to provide support to others using reappraisal more than distraction. These findings have implications for understanding the role of EER in depression and other psychopathologies.

SUICIDE IN BIPOLAR DISORDER PATIENTS IS ASSOCIATED WITH HIPPOCAMPAL MICROGLIA ACTIVATION AND REDUCTION OF LYMPHOCYTES-ACTIVATION GENE 3 (LAG3) MICROGLIAL CHECKPOINT EXPRESSION

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Bipolar disorder (BD) is associated with marked functional impairments along with severe loss of quality of life and increased rate of suicide, which is the highest compared to all other psychiatric illnesses. Although there is ample evidence for the involvement of inflammatory processes in the pathophysiology of BD, the role of microglia and the mechanisms that regulate these cells in BD patients is still unclear. To examine the BD-associated microglial status, we conducted immunohistochemical analyses of hippocampal sections from post-mortem brains of 15 BD patients and 12 control, assessing microglial density and activation by staining for the microglia-specific receptor P2RY12, and the activation marker MHC II. Given our recent finding on the involvement of the microglial checkpoint molecule lymphocyte-activating gene 3 (LAG3) in depression and electroconvulsive therapy, we assessed the expression levels of LAG3 and their correlations with microglia density and activation status. We found that BD patients who committed suicide displayed a significant elevation in the overall microglia density and the density of MHC II-labeled microglia (but not other MHC II-labeled cells), compared with non-suicidal patients and controls. Furthermore, the percent of microglia expressing LAG3 was significantly reduced only in suicidal BD patients, with significant negative correlations between microglial LAG3 expression levels and the density of microglia, in general, and activated microglia, in particular. In conclusion, suicidal, but not non-suicidal BD patients exhibit microglia activation, which is possibly mediated by reduced LAG3 checkpoint expression, suggesting that anti-microglial therapeutics, including LAG3 modulators, may be beneficial for this subgroup of patients.

SEX DIFFERENCES IN THE ANTI-DEPRESSANT-LIKE EFFECT OF CANNABIDIOLIC ACID METHYL ESTER IN A GENETIC RAT MODEL OF DEPRESSION

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The pathophysiology of major depressive disorder (MDD) is diverse, yet treatment strategies remain limited. Cannabinoids and the endocannabinoid system are linked to depression in clinical and pre-clinical studies. Cannabidiolic Acid-Methyl Ester (CBDA-ME; EPM-301) demonstrated more potent anti-nausea/anti-emetic effects than Cannabidiol (CBD) *in vitro* and *in vivo*. We explored acute and chronic properties of CBDA-ME using male and female Wistar-Kyoto (WKY) rats, which present MDD-like behavioral and physiological endophenotypes. First, rats underwent the Forced swim test (FST) following acute CBDA-ME oral ingestion (1,5,10 mg/kg). Next, rats underwent the FST, Open Field test and Saccharine Preference Test after chronic (14 days) oral ingestion of CBDA-ME (0.5 mg/kg-males; 1/2.5/5 mg/kg-females) or 15 mg/kg of imipramine. Corticosterone blood serum levels and hippocampal mRNA gene expression of CB1/CB2 receptors, Fatty Acid Amid Hydrolase (FAAH), Serotonin transporter (SERT), Corticosterone Releasing-Hormone (CRH) and CRH Receptor type 1 (CRHR1) were evaluated. Finally, rats were injected with CB1 (AM-251) and CB2 (AM-630) receptor antagonists 30 min before acute CBDA-ME ingestion (1 mg/kg-males and 5 mg/kg-females) followed by FST. Brain-Derived Neurotrophic Factor (BDNF) and endocannabinoids levels in blood serum and hippocampal FAAH were measured. Results indicated sex differences in drug effects; lower dosages produced a larger anti-depressant-like effect in males (1 mg/kg acutely and 0.5 mg/kg chronically) compared to females (5 and 10 mg/kg acutely and no chronic effect at any dose). The chronic drug effect in males was accompanied by lower corticosterone levels and upregulated hippocampal mRNA expression of CB1R, FAAH, SERT and CRHR1. Furthermore, AM-630 blocked the anti-depressant-like effect in females, when elevated BDNF and some endocannabinoids serum levels and low hippocampal FAAH expression were detected in the CBDA-ME treated group compared to the other groups. These findings expand the knowledge on the antidepressant effects of CBDA-ME, opening a path for cannabinoid-mediated treatment in MDD and related disorders.

RESTING STATE EEG AND ERPS CAN BE USED AS BIOMARKERS OF RESPONSE TO SSRIS IN MAJOR DEPRESSIVE DISORDER

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Introduction: Major Depression Disorder (MDD) is a highly prevalent and disabling disorder that carries significant morbidity. Up to date, there are no useful objective measures that can help therapists to predict response to SSRIs. This study aims to develop EEG and ERP biomarkers as predictors for responsiveness to SSRIs.
Methods: MDD patients who received zero to two antidepressants were recruited. All patients were diagnosed using the Mini-International Neuropsychiatric Interview (MINI). Depression was evaluated using the Inventory of Hamilton Rating Scales for Depression (HAM-D) and the Montgomery Asberg Depression Rating Scale (MADRS). Cognitive functions were evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB). BNA technology was used to extract resting-EEG, and ERP measures at baseline, 2 weeks and 8 weeks after. EEG/ERP measures were transformed into z-scores following standardization based on Elminda's large normative database.
Results: Out of 36 MDD patients enrolled in the study, 30 patients returned for a second visit 2 weeks later and 22 patients completed the study. MDD patients were matched to 29 normal controls. At the end of 8 weeks of follow-up, 11 (50%) of the depressed patients responded. The EEG analysis, expressed in Z-scores, showed increased left frontal alpha asymmetry (electrodes F3-F4) in MDD patients compared to healthy controls ($F=4.71$, $p=0.093$, partial Eta-squared=0.07, N=56), with a 2-week reduction in left-dominance responders (electrodes F7-F8; $p=0.06$). Baseline central theta relative power was significantly lower in MDD patients compared to healthy controls ($F=5.9$, $p=0.01$, partial Eta-square=0.09, N=60).
After 2 weeks of treatment, baseline relative theta power was significantly increased in responders compared to non-responders ($p=0.02$). In addition, responders exhibited faster P200 at baseline ($r=0.49$, $p=0.04$), and a 2-week reduction in individual alpha peak frequency (Pz; $p=0.007$).
Conclusions: This study shows that a single ERP/EEG has a potential to be used as a predicting marker for SSRI response.

Oral microbiota signatures in post-traumatic stress disorder (PTSD) veterans

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Background: Post-traumatic stress disorder (PTSD) represents a global public health concern, affecting about one in twenty individuals. The symptoms of PTSD include intrusiveness (involuntary nightmares or flashbacks), avoidance of traumatic memories, negative alterations in cognition and mood (such as negative beliefs about oneself or social detachment), increased arousal and reactivity with irritable reckless behavior, concentration problems and sleep disturbances. PTSD is also highly comorbid with anxiety, depression and substance abuse.

Aim and Methods: To advance the field from subjective, self-reported psychological measurements to objective molecular biomarkers while considering environmental influences, we examined a unique cohort of Israeli veterans who participated in the 1982 Lebanon war. Non-invasive oral 16S RNA sequencing was correlated with psychological phenotyping.

Results: A microbiota signature (i.e., decreased levels of the bacteria *sp_HMT_914, 332 and 871* and *Noxia*) was correlated with PTSD severity, as exemplified by intrusiveness, arousal and reactivity, as well as additional psychopathologies, including anxiety, hostility, memory difficulties and idiopathic pain. In contrast, education duration correlated with significantly increased levels of *sp_HMT_871* and decreased levels of *Bacteroidetes* and *Firmicutes*, and presented an inverted correlation with adverse psychopathological measures. Air pollution was positively correlated with PTSD symptoms, psychopathology, and microbiota composition. Arousal and reactivity symptoms were correlated with reductions in transaldolase, an enzyme controlling a major cellular energy pathway, that potentially accelerates aging.

Conclusions: The newly discovered bacterial signature, whether an outcome or a consequence of PTSD, could allow for objective soldier deployment and stratification according to decreases in *sp_HMT_914, 332, 871* and *Noxia* levels, coupled to increases in *Bacteroidetes* levels. These findings also raise the possibility of microbiota pathway-related non-intrusive treatments for PTSD. A better understanding of objective biomarkers for PTSD and related psychopathologies is crucial for optimizing resource allocation for diagnosis, therapy and rehabilitation

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A GLIMPSE INTO THE BIOLOGICAL MECHANISM OF WITHDRAWAL RUPTURES - DYADIC PATTERN OF OXYTOCIN MODERATED BY ANXIOUS ATTACHMENT

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Despite widespread clinical, theoretical, and empirical support linking alliance ruptures to treatment process and outcome, little is known about their underlying biological mechanisms. the overarching goal of the present study was to investigate dyadic patterns between oxytocin (ot) change of patients and therapists (e.g. patient ot increases while therapist ot does not increase) as markers of withdrawal ruptures. hypothesis 1 construed that patient exclusive increase in ot (specifically without therapist increase) will mark the occurrence of withdrawal ruptures. hypothesis 2 construed that this effect will emerge only when anxious attachment orientation is low. surface analysis of 628 saliva samples that were gathered before and after therapeutic sessions of 53 patients and therapist dyads enrolled in a randomized control trial treating major depression. findings suggest that only hypothesis 2 received empirical support. Meaning that only when anxious attachment orientation was low, there were significantly more withdrawal ruptures when patients exhibited ot increase exclusively (without a therapist ot increase). this is consistent with the literature, suggesting that when a withdrawal rupture is initiated, the patient and therapist are in an incongruent state. Findings suggest that this incongruence is mirrored at the biological level, only when that anxious attachment orientation is low. Results shed light on what is happening during a withdrawal rupture, and suggest the benefits of training therapists to attend to signals of distress by their patients. In turn, therapists can help patients learn how to better communicate their needs, first in therapy, and later to significant others in their life.

AUTOMATIC AND OBJECTIVE SYMPTOM ASSESSMENT OF TIC DISORDERS AND TOURETTE SYNDROME

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Background: Tourette syndrome (TS) and other tic disorders are characterized by the expression of motor and vocal tics. The most prevalent measures used for assessing tic expression are subjective qualitative measures based on self-reports. The goal of current study is to create an automatic measure for quantifying tic expression.

Methods: We used a custom-developed smartphone application to record data from children and adolescents with chronic tic disorders. Each recording session included tasks on the smartphone, while the patient's facial tics were simultaneously recorded by the frontal camera and kinematic sensors. Trained experts annotated the videos offline, marking the precise times of tic onset and tic completion, 98-point facial landmarks were extracted from each frame. The landmarks representing the whole video were segmented to short clips, each labeled "tic"/"non-tic" based on the annotations. Finally, a tandem of custom deep neural networks for extracting the spatial and temporal were used for classifying the segments.

Results: We recorded 45 sessions from 13 TS patients (7-18 years old, 1-4 sessions per patient). Preliminary results show that our model achieves over 97% precision recall within patients and 88% precision across patients. Applying the trained model on the whole video, by using a sliding window and then classifying each segment along the video, resulted in detecting roughly 90% of all the tics in the video.

Conclusions: This work has the potential to provide clinicians a powerful tool for diagnosis and follow-up of their patients, and for evaluating the efficacy of different behavioral and pharmaceutical treatments.

HARNESSING CANNABIS MOLECULES TO FIGHT INFLAMMATION-ASSOCIATED DEPRESSION

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When asked about their reasons for using cannabis, most users cite depression as one of the most important reasons, however, there are still no RCTs on the antidepressant effects of cannabis or specific cannabis molecules, and the results of cross-sectional and longitudinal studies are inconclusive. Studies in experimental animals demonstrated that some cannabinoids, particularly CBD, have antidepressant potential. The current study aimed to further elucidate the antidepressant effects of CBD and the possibility to potentiate these effects by administering CBD together with additional cannabis molecules or adjunctive therapeutics in mice. Given previous findings from our laboratory, showing that microglia activation can underlie the development of some forms of depression, we focused on the mediation of the behavioral effects of CBD-based therapeutics by modulation of microglia activation. We report that in cultures of BV-2 microglia cells, stimulated *in vitro* by various immune challenges (LPS, Poly I:C or a-synuclein), CBD induced marked suppressive effects on the secretion of proinflammatory cytokines. Combinations of CBD with specific terpenes or flavonoids indued synergistic microglia-suppressive effects. *In vivo*, CBD treatment in mice attenuated the development of depressive-like symptoms induced by administration of the inflammatory/microglial stimulator LPS. This effect was particularly demonstrated in mature (8 months old) as compared with young (2.5 months old) male mice, with almost no effects in female mice. In contrast, a microglia-suppressive combination of CBD with the flavonoid kaempferol produced significant antidepressant effects also in female mice. Combinations of CBD with the NSAID celecoxib also produced synergistic suppressive effects in BV-2 microglia cultures *in vitro*, as well as potentiated antidepressant effects in the LPS model and the chronic social defeat stress model of depression in mice. Together, these studies suggest that microglia-suppressive cannabis-based formulations may serve as efficacious antidepressants, particularly in depressed patients with an elevated inflammatory status.

PRENATAL CANNABIS EXPOSURE AND THE RISK FOR NEUROPSYCHIATRIC ANOMALIES IN THE OFFSPRING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: As cannabis use becomes more common worldwide, an increase in its use is also observed among women of reproductive age, including during pregnancy. Several studies examined the possible impact of prenatal cannabis exposure on children's psychiatric and neurobehavioral development. However, the variability and inconsistency in the associations observed make it difficult to fully evaluate the risks and potential harm of in-utero cannabis exposure. Therefore, our objective is to evaluate the existing data and assess the association between cannabis exposure during pregnancy and the risk for neuropsychiatric outcomes in the offspring.

Methods: We followed the PRISMA 2020 guidelines for systematic review and meta-analysis. MEDLINE, EMBASE, and Cochrane databases were searched up to August 2022. Data were independently screened for eligibility and extracted by two reviewers. Studies were eligible for inclusion if they reported quantitative data on long-term neuropsychiatric outcomes in the offspring prenatally exposed to cannabis versus control. Data were pooled using random-effects models.

Results: Fourteen eligible observational studies were included in the review, and twelve were included in the final quantitative analysis. The pooled odds ratio (OR(for ADHD was 1.12 (95% confidence interval (CI): 1.00-1.27); for ASD, the pooled risk ratio (RR) was 1.18 (95% CI 0.7-1.97); for psychotic symptoms, the pooled RR was 1.18 (95% CI 0.95-1.45); for anxiety, the pooled OR was 1.63 (95% CI 0.78-3.40); and for offspring's marijuana use the pooled OR was 1.2 (1.01-1.42).

Conclusions: Prenatal cannabis exposure was associated with a mildly increased risk for ADHD and cannabis use in the offspring. These results should be interpreted with caution, given the observational nature of the studies and the potential for residual confounding.

MEDICAL CANNABIS USE AMONG PATIENTS WITH POST-TRAUMATIC STRESS DISORDER (PTSD) IN ISRAEL AND THE RISK FOR PSYCHIATRIC ADMISSION: A NATIONWIDE DATABASE STUDY

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Although the efficacy and safety of medical cannabis in PTSD have not been established, its use among PTSD patients has become widespread. Our study aimed to characterize patterns of use and risk for psychiatric admission in a large group of PTSD patients using medical cannabis.

Data were acquired from the national database comprising all patients licensed to use medical cannabis from January 2014 to December 2021, and the Ministry Health database containing all psychiatric admissions. Data on monthly dispensing of medical cannabis were available from 2018. Self-controlled case series method based on Poisson regression were constructed to calculate the rate ratios and 95% confidence intervals.

12,977 PTSD patients were licensed to use medical cannabis during the study period, constituting 8.2% of all users and making it the 3rd most common indication for consumption of medical cannabis. PTSD patients were significantly younger than non-PTSD patients (40.9 years vs. 52.9 years), and 70% were men. Over two years of usage, there was an increase in the monthly amount and THC concentration consumed by PTSD patients, reaching the maximal available THC concentration of 20%. 885 PTSD patients (6.8%) had a lifetime history of psychiatric admission before using medical cannabis. 244 patients (1.9%) had a psychiatric admission while using medical cannabis, of whom 83 (0.6%) it was the first lifetime admission. Among 352 PTSD patients who used medical cannabis and had a psychiatric admission between 2018 and 2021, medical cannabis use was associated with a rate ratio of 11.7 (95%CI 1.92–60.22) for psychiatric admission.

Medical cannabis was associated with an increased risk for psychiatric admission among PTSD patients. These findings emphasize the need for further study in cannabis usage in PTSD before approving its routine administration.

DISCOVERY OF SHARED MECHANISMS BY MUTATIONS IN DIFFERENT GENES ASSOCIATED WITH AUTISM AND SCHIZOPHRENIA

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Discovered in our laboratory, activity-dependent neuroprotective protein (ADNP) is essential for brain formation/function. Thus, de novo heterozygous mutations in ADNP cause autistic ADNP syndrome. Mechanistically, ADNP mutations impair microtubule (MT) function, essential for synaptic activity and protective against the MT associated protein Tau deposition (tauopathy). The ADNP MT-associating fragment NAPVSIPQ (called NAP) contains an MT end-binding protein interacting domain, SxIP. We hypothesized that not all ADNP mutations are similarly deleterious and that the NAPV portion of NAPVSIPQ is biologically active. Using the eukaryotic linear motif resource, we identified a Src homology 3 (SH3) domain-ligand association site in NAP responsible for controlling signaling pathways regulating the cytoskeleton, namely NAPVSIP. Comparisons of the effects of multiple ADNP mutations on MT dynamics and Tau interactions revealed SH3-binding motif involvement in ADNP/NAP normalization of MT activities in the face of ADNP mutations. Furthermore, SH3 and multiple ankyrin repeat domains protein 3 (SHANK3), a major autism gene product, interact with the cytoskeleton through an actin-binding motif to modify behavior. Similarly, we identified an actin-binding site on ADNP, suggesting direct SH3 and indirect SHANK3/ADNP associations. Actin co-immunoprecipitations from showed NAP-mediated normalization of Shank3-Adnp-actin interactions. NAP treatment ameliorated aberrant behavior in mice homozygous for the *Shank3* ASD-linked InsG3680 mutation, revealing a fundamental shared mechanism between ADNP and SHANK3. Additionally, SHANK3 mutations, ADNP dysregulation and NAP protection are also shown in schizophrenia. Together, these results impact basic understanding of autism spectrum disorders and psychiatric disorders. Protected by orphan drug and rare pediatric designations, NAP (davunetide) advances as a drug candidate for the ADNP syndrome and beyond by ATED Therapeutics Ltd (IG, Chief Scientific Officer).

Reference: Ivashko-Pachima Y, Ganaiem M, Ben-Horin-Hazak I, Lobyntseva A, Bellaiche N, Fischer I, Levy G, Sragovich S, Karmon G, Giladi E, Shazman S, Barak B, Gozes I. Mol Psychiatry. 2022 May 10.

BEYOND THE THREE-CHAMBER TEST: TOWARD A MULTIMODAL AND OBJECTIVE ASSESSMENT OF SOCIAL BEHAVIOR IN RODENTS

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In recent years, substantial advances in social neuroscience have been realized, including the generation of numerous rodent models of Autism Spectrum Disorder (ASD). Still, it can be argued that those methods currently being used to analyze animal social behavior create a bottleneck that significantly slows down progress in this field. Indeed, the bulk of research still relies on a small number of simple behavioral paradigms, the results of which are assessed without considering behavioral dynamics. Moreover, only few variables are examined in each paradigm, thus overlooking a significant portion of the complexity that characterizes social interaction between two conspecifics, subsequently hindering our understanding of the neural mechanisms governing different aspects of social behavior. We demonstrate these constraints by discussing the most commonly used paradigm for assessing rodent social behavior, the three-chamber test. We also discuss current evidence supporting the existence of pro-social emotions and emotional cognition in animal models. We further suggest that adequate social behavior analysis requires a novel multimodal approach that employs automated and simultaneous measurements of multiple behavioral and physiological variables at high temporal resolution in socially interacting animals. Finally, we address several behavioral and physiological variables that can be used to assess socio-emotional states in animal models and thus elucidate the intricacies of social behavior so as to attain deeper insight into the brain mechanisms that mediate impaired social behavior in animal models of ASD.

THE ROLE OF BELIEFS IN SHAPING DAILY EXPERIENCES: FROM COGNITION TO WELL-BEING

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Our beliefs construct a template through which we perceive ourselves, other people, and the world around us. As such, beliefs shape the way we process information and guide our behaviors. One of the most prominent examples is the placebo effect: Beliefs regarding a treatment, rather than the treatment itself, can induce a robust improvement in symptoms. With such a dramatic impact, beliefs ought to have a similar influence in everyday situations. **Our new lab at the Bar-Ilan Faculty of Medicine strives to elucidate the behavioral and physiological mechanisms by which our beliefs shape our daily experiences and influence well-being.** Understanding when and how beliefs influence behavior is imperative to our understanding of the human brain, both in healthy and clinical populations.

In this talk, I wish to talk about our past research and future plans. In brief, building on placebo research, cognitive neuroscience and clinical psychology, our lab studies the role of the mind, namely beliefs, expectations and conceptions we hold, in shaping information processing and well-being. I will discuss these topics as they apply to clinical disorders, in particular depression and autism.

CANNABIS IN POST-TRAUMATIC AUTISTIC INDIVIDUALS

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There is early evidence that cannabidiol (CBD) can bring remarkable benefit to the quality of life of autisitc individuals across the entire "spectrum" of severity. The same is true of THC for individuals suffering CPTSD. There is increasing awareness of the significant incidence of CPTSD as the result of social traumatization of many autistic individuals. The raises an interesting challenge with ragrd to treatment of such individuals with the various straines of cannabis. The author will present an emerging approach to such treatment based on extensive direct clinical experience in his practice.

CANNABIS AND CANNABINOIDS IN POST-TRAUMATIC STRESS DISORDER (PTSD)

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Increased attention has focused on the potential use of cannabis in the treatment of posttraumatic stress disorder (PTSD). However, as we all know, the treatment of PTSD has been a hard nut to crack. Nevertheless, accumulated during last decade clinical data suggests that cannabinoids modulate anxiety, and new emerging data demonstrate therapeutic potential in PTSD in different populations. An enhanced understanding of cannabis and its derivate effects on various aspects of trauma may lead to the identification of novel therapeutic targets and approaches. This symposium will present and discuss the latest findings from local and international basic & clinical research in this area.

MIRTAZAPINE AND TRAZODONE: A POSSIBLE OPIOID INVOLVEMENT IN THEIR USE (AT LOW DOSE) FOR SLEEP?

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The efficacy of each antidepressant available has been found equal to that of amitriptyline in double-blind studies. However, a few of them are being prescribed (at very low, non-therapeutic doses) for sleep, in non-depressed persons, when there are relative contraindications for hypnotics (i.e., history of addiction). Following studies regarding the antinociceptive mechanisms of various antidepressants, we speculate that the involvement of the opioid system in some of the antidepressants' mechanism of action may contribute to these medications use for the induction and maintenance of sleep. The mostly prescribed antidepressants for sleep are trazodone (a weak, but specific inhibitor of the synaptosomal uptake of serotonin, that also binds to alpha-1 and alpha-2 adrenoreceptor sites) and mirtazapine (a postsynaptic drug which enhances noradrenergic and 5-HT1A-mediated serotonergic neurotransmission via antagonism of central alpha-2-auto- and hetero-adrenoreceptors). When mice were tested with a hotplate analgesia meter, both trazodone and mirtazapine induced, naloxone-reversible antinociceptive effect following i.p administration. Summing up the various interactions of trazodone and mirtazapine with opioid, noradrenergic and serotonergic agonists and antagonists, we found that the antinociceptive effect of trazodene is influenced by the opioid receptor subtypes μ and lass d (and a clear 5-HT mechanism of antinociception), whereas the antinociceptive effect of mirtazapine is mainly influenced by *κ* and d opioid receptor subtype (combined with both serotonergic and noradrenergic receptors). This opioid profile of the two drugs may be one of the explanations to their efficacy in the treatment of insomnia, when sedatives (either benzodiazepines or the non-benzodiazepines "Z-compounds) cannot be prescribed.

SEX DIFFERENCES IN THE ANTI-DEPRESSANT-LIKE EFFECT OF CANNABIDIOLIC ACID METHYL ESTER IN A GENETIC RAT MODEL OF DEPRESSION

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The pathophysiology of major depressive disorder (MDD) is diverse, yet treatment strategies remain limited. Cannabinoids and the endocannabinoid system are linked to depression in clinical and pre-clinical studies. Cannabidiolic Acid-Methyl Ester (CBDA-ME; EPM-301) demonstrated more potent anti-nausea/anti-emetic effects than Cannabidiol (CBD) *in vitro* and *in vivo*. We explored acute and chronic properties of CBDA-ME using male and female Wistar-Kyoto (WKY) rats, which present MDD-like behavioral and physiological endophenotypes. First, rats underwent the Forced swim test (FST) following acute CBDA-ME oral ingestion (1,5,10 mg/kg). Next, rats underwent the FST, Open Field test and Saccharine Preference Test after chronic (14 days) oral ingestion of CBDA-ME (0.5 mg/kg-males; 1/2.5/5 mg/kg-females) or 15 mg/kg of imipramine. Corticosterone blood serum levels and hippocampal mRNA gene expression of CB1/CB2 receptors, Fatty Acid Amid Hydrolase (FAAH), Serotonin transporter (SERT), Corticosterone Releasing-Hormone (CRH) and CRH Receptor type 1 (CRHR1) were evaluated. Finally, rats were injected with CB1 (AM-251) and CB2 (AM-630) receptor antagonists 30 min before acute CBDA-ME ingestion (1 mg/kg-males and 5 mg/kg-females) followed by FST. Brain-Derived Neurotrophic Factor (BDNF) and endocannabinoids levels in blood serum and hippocampal FAAH were measured. Results indicated sex differences in drug effects; lower dosages produced a larger anti-depressant-like effect in males (1 mg/kg acutely and 0.5 mg/kg chronically) compared to females (5 and 10 mg/kg acutely and no chronic effect at any dose). The chronic drug effect in males was accompanied by lower corticosterone levels and upregulated hippocampal mRNA expression of CB1R, FAAH, SERT and CRHR1. Furthermore, AM-630 blocked the anti-depressant-like effect in females, when elevated BDNF and some endocannabinoids serum levels and low hippocampal FAAH expression were detected in the CBDA-ME treated group compared to the other groups. These findings expand the knowledge on the antidepressant effects of CBDA-ME, opening a path for cannabinoid-mediated treatment in MDD and related disorder.

ENHANCING ANANDAMIDE SIGNALING RESTORES EARLY STRESS-INDUCED DEPRESSION-LIKE PHENOTYPE ASSOCIATED WITH ALTERATIONS IN CORTICAL MICRO-RNAS

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Introduction: Early life stress (ELS) significantly increases predisposition to psychopathologies, including depression. Here, we compared the effects of treatment with URB597, which increases anandamide levels, and the SSRI, paroxetine, on depressive-like behavior and the expression of microRNAs (miRs) in the medial prefrontal cortex (mPFC) of rats exposed to ELS.
Methods: Male and female rats were exposed to ELS using the "Limited Bedding and Nesting" paradigm, from postnatal day (P)7 to P14. During P45 to P60 (late-adolescence) URB597 (0.4 mg/kg) or paroxetine (5mg/kg), were administered i.p. for 2 weeks. On P90 (adulthood) rats were tested for depressive-like behavior and the expression of mPFC miR-16 and miR-135a.
Results: Adult male and female rats demonstrated depressive-like behavior, such as decreased social behavior and increased learned helplessness. Chronic treatment during late-adolescence with URB597, but not paroxetine, restored these behaviors. In the mPFC, ELS males demonstrated a decrease in miR-16 and ELS females demonstrated a decrease in miR-135a. Importantly, URB597, which restored depressive-like behavior in both sexes, also normalized mPFC miR-16 and miR-135a expression abnormalities in males and females, respectively.
Conclusions: Our findings show for the first time that enhancing anandamide signaling can prevent ELS-induced decrease in mPFC miRs and the associated depression-like phenotype in both sexes. This may advance our knowledge of pathways dysfunctional in depression in cortical areas and suggest a mechanism for the beneficial effects of enhancing endocannabinoid signaling.

COVID-19 PANDEMIC HAS CHANGED THE WAY DISTANCE IS PERCEIVED, BUT NOT THE DISTANCE ACTUALLY MAINTAINED

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Since COVID-19 is easily transmitted in close physical proximity, the focus of the epidemiological policy during COVID-19 crisis included restrictions on the distance people maintained from one another (i.e. interpersonal distance). People were obligated to comply with these restrictions, which included using extreme measures to restrict proximity such as quarantine and lockdown. Nevertheless, the long-term psychological effects of COVID-19 on preferred interpersonal distance are still largely unknown. In the current study, we examined COVID-related changes in preferences and perception of interpersonal distance. Specifically, we conducted two analyses: first, we compared data that was collected two years following the COVID-19 outbreak with data collected just before the outbreak, in order to examine the average change in distance preference and perception. In the second analysis, we coded each individual according to the infection rate that day (R value) and according to the number of days that had passed since the outbreak, in order to examine changes in interpersonal distance preference and perception as the pandemic evolved. Contrary to what we expected, COVID-19 was not associated with an increase in preferred interpersonal distance. However, COVID-19 was associated with an overestimation of interpersonal distance (i.e., perceiving other people as further away than they actually are). In other words, individuals perceive the distance from others as larger but in practice, do not keep larger distance. Furthermore, these effects were stronger among individuals with social anxiety disorder. To the best of our knowledge, this is the first evidence showing COVID-related changes in distance perception, hence providing insight into the pandemic's impact on spatial processing and behavior.

COVID-19 RESTRICTIONS AND VISITATIONS TO AN ISRAELI PSYCHIATRIC EMERGENCY DEPARTMENT: A FOUR-LOCKDOWNS RETROSPECTIVE STUDY

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The Coronavirus disease 2019 (COVID-19) pandemic and its associated governmental restrictions has led to profound mental health consequences. The psychiatric emergency department (ED) plays a key role during such mental health crisis.
In this talk, we examine the volume and characteristics of psychiatric ED visitations through a perspective of four COVID-19 lockdowns.
All adult visitations to the ED of Shalvata Mental Healthcare Centre (Israel) during 2020-2021 were retrieved and statistically analysed. Data from 2017-2019 was considered as control. Voluntary and involuntary ED visitations were considered.
We find that the significant decrease in the volume of voluntary ED visitations during the 1st lockdown was quickly overturned, roughly returning to the pre-pandemic state following its conclusion. In parallel, the volume of involuntary ED visitations has dramatically increased, with the most striking levels observed during the second and third lockdowns. Elapsed time since the first occurrence of COVID-19 in Israel and the level of governmental restrictions is significantly associated with the increase in the volume of ED visits and admissions, the admission rate and the rate of involuntary visits.
The prolonged consequences associated with the pandemic and the measures taken to control it suggest that it is unreasonable to expect a return to normal ED utilization in the near future. As such, alternatives to strict lockdowns should be favored when possible and urgent strengthening of psychiatric care is warranted.

NON-REPLICATION IN NEUROBEHAVIORAL RESEARH - CHALLENGES AND OPPORTUNITIES

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Non replication in biomedical research is a growing concern, amplified by the inherent complexity of neurobehavioral disorders and their weak and unstable phenotype delineation. We have repeatedly used data driven "machine learning" and artificial intelligence tools to palliate these weaknesses towards increasing findings' replicability and translational potential. Following a recent and careful of cross-samples non-replication fMRI study of early PTSD (Ben Zion et al., AJP 2022), this presentations offers an open and critical examination of diverging findings throughout the presenters' research career - and those of others. It annotates specific difficulties to achieve replicable findings, and offers ways to address such difficulties in study design, implementation and publication. It is argued that human neuro-behavioral research is inherently local and therefore neither advanced bioinformatic tools nor traditional statistical significance testing can overcome reliability and generalizability constraints emanating from data collection, sampling, measurements, implicit assumptions underlying study design, study execution context, and varying phenotype definitions. Ways to better examine, document and report studies' 'local' features are exemplified and discussed as opportunities to acknowledge, estimate and explicitly report the boundaries of one's studies' contribution to knowledge.

PREVENTING POSTPARTUM DEPRESSION AND POST-TRAUMATIC STRESS DISORDERS: ANALYSIS OF COGNITIVE BIASES DURING PREGNANCY TO PREDICT THE DEVELOPMENT OF PSYCHIATRIC DISORDERS FOLLOWING DELIVERY

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Postpartum Depression (PPD) and Postpartum Post-Traumatic Stress Disorder (PP-PTSD) are psychiatric disorders, which result in severe difficulties1 and, in extreme cases, may even provoke suicide or neonatal murder2, 3, 4. Women in High-Risk Pregnancy (HRP) are more vulnerable to developing these disorders5, 6. In this study, which is still in progress, we employ Structural Equation Modelling (SEM) statistical analysis to predict the chances of developing PPD and PP-PTSD based on measurements during and after pregnancy. The cohort includes HRP women during the third stage of their pregnancy (HR Group), women pregnant without diagnosis HRP (Normal Pregnancy), and non-pregnant women matched for age (Control Group). All participants performed three tasks examining attentional10, 11, and interpretation biases12 and filled in questionnaires assessing their level of current anxiety13 and intolerance of uncertainty14. The Pregnant Groups took part in a second session, two months after delivery, when they filled in questionnaires assessing their levels of depression and PTSD symptoms and attachment to the child. Preliminary findings show that women in the Pregnant Groups exhibited an attention bias towards happy faces compared to controls. Furthermore, the HR Group experienced higher arousal for happy babies' and neutral pictures. They also rated all the babies' pictures as more positive. Preliminary findings show differential cognitive performance and emotional tendencies among women at HRP, compared to controls. These findings support the hypothesis that cognitive and emotional features will predict the future development of PPD and PP-PTSD after delivery. We hope that this research can allow us to scan possible future mothers who may develop these disorders. Furthermore, the cognitive biases found in this study may result in difficulties for the mothers to react to the different emotions that their baby evokes, causing the baby, over time, to only evoke the emotion the mother is going to react to.

THERAPEUTIC MECHANISM OF PSILOCYBIN IN THE TREATMENT OF DEPRESSION AND OTHER PSYCHIATRIC DISORDERS

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Background: In the current study, we explored the effect of psilocybin on the mouse head twitch response (HTR) which is correlated with psychedelic effects in humans, tested for antidepressant-like effects using the tail suspension test (TST) and examined the effect of psilocybin on proteins implicated in synaptogenesis in 4 brain areas.Methods: Male C57Bl/6j mice were used in all experiments. Psilocybin (98.75% purity, 4.4 mg/kg) was provided by Usona Institute.

HTR was measured over 20 minutes in a magnetometer-based system using ear clip magnets. The tail suspension test (TST) was conducted using a Noldus Ethovision system 48 hours after drug administration. Mice were sacrificed 9-11 days post injection, and synaptic proteins (PSD-95, synaptophysin, GAP-43, and SV2A) were measured by Western blot in 4 brain areas (frontal cortex, amygdala, hippocampus, and striatum). Two-way ANOVA was used for HTR and unpaired t-test for TST and synaptic protein assays.Results: Psilocybin induced a significantly greater HTR response compared to vehicle (Time x Treatment $F [9,198] = 16.11$, $p<0.0001$). Effects on the TST were examined 48 hours post injection. The results of the TST show that compared to vehicle, psilocybin significantly reduced the non-active time ($t=2.888$, $df=12.57$, $p=0.0131$) and increased the moderate + highly active time ($t=2.88$, $df=12.2$, $p=0.0136$). Compared to vehicle, psilocybin significantly increased the synaptic proteins GAP-43 in the frontal cortex ($t=2.825$, $df=21$, $p=0.01$) and SV2A in the hippocampus ($t=2.756$, $df=10$, $p=0.02$). A trend was observed for SV2A increase in the amygdala ($t=2.048$, $df=10$, $p=0.0678$) and striatum ($t=1.881$, $df=8$, $p=0.0967$).

Conclusions: We have shown that on the TST, a screening test for antidepressant potential, psilocybin (at a dose that significantly induced HTR) induced a strong antidepressant-like effect 48 hours post injection. Our synaptic protein findings suggest that this antidepressant effect may be related to the effect of psilocybin on synaptogenesis.

PLACENTAL DERIVED MESENCHYMAL LIKE ADHERENT STROMAL CELLS AS AN EFFECTIVE CELL THERAPY FOR COCAINE ADDICTION IN A RAT MODEL

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Aims: Cocaine addiction is defined as the compulsion to consume a drug while losing control over the amount consumed. However, no treatment have yet been shown to be effective in maintaining abstinence. Mesenchymal stromal cells (MSCs), migrate to pathological brain regions, promote neurogenesis and increase new cells survival and connectivity by reducing inflammation, preventing oxidative stress, and secreting various neurotrophic factors. Cell therapy application faces limitations such as poor knowledge of final cell fate post-transplantation, poor cell survival and tissue integration, tumoring risk, and restriction on administration route. Here, we present a new approach for treating cocaine addiction by using of placenta derived mesenchymal-like cells (PLX-PAD cells), that answer all these short comes.

Methods: Rats were trained to self-administer cocaine (1.5 mg/Kg; FR1) or saline daily (1 hour) until stable maintenance levels were attained. Then they underwent extinction until abstinence. Before the extinction phase, ~106 viable PLX-PAD cells or GNPs labeled PLX-PAD cells were administrated INA or ICV. The rats were monitored behaviorally for craving. For neurogenesis estimation, rats were BrdU injected i.p. before extinction. At the end of the experiment, brains were removed and stained for BrdU & Neun. For tracking the migration and exact localization of the GNPs labeled PLX-PAD cells, we conducted in vivo CT scans at several time points post-transplantation. For a quantitative determination, GNPs concentration number was measured in tissues from different brain regions and analyzed using the Inductively coupled plasma - optical emission spectrometry.

Results: We found that PLX_PAD significantly lowered cocaine seeking behavior by decreasing active lever presses in the relapse test, compared to untreated group. In addition, cells were found to navigate and home to addiction related sites in the brain. Moreover, cocaine self-administration can attenuate neurogenesis in the hippocampus and the PLX-PAD INA treatment normalized it to sham group.

MULTIDIMENSIONAL ADAPTIVE EMPATHY: EMPATHIC RESPONSE SELECTION IN A COMPLEX ENVIRONMENT

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Empathy allows us to respond to the emotional state of another person. Considering that an empathic interaction lasts beyond the initial response, learning mechanisms are involved in this dynamic adaptation. Yet, how empathic response adapts in complex, multidimensional, real-world environments is currently unknown.

Here we address this gap by focusing on adaptive empathy, defined as the ability to learn and adjust one's empathic responses based on feedback, in a multidimensional environment. For this purpose, we developed an empathic-learning experimental paradigm. During instant messaging communication, participants observed a distress situation and chose an empathic response (reappraisal or distraction). After each choice, participants received feedback about the success of their chosen strategy which they could use to inform their future decisions. Distress situations were multidimensional regarding the person in distress (who), the target's mood (what), and the distress reason (why). Unbeknown to the participant, only one interaction dimension was relevant to predicting reward. We also used computational models of reinforcement learning to characterize the learning process.

Our initial results show that the participants tended to learn mostly from the person (who) dimension, i.e., they assumed that the success of their adaptive response in alleviating distress was person dependent and not mood or reason dependent. We also found that participants had a strong prior regarding the effectiveness of reappraisal compared with distraction as an empathic response.

Our findings provide a lab-based model for studying the dimensionality of adaptive empathy and help to understand how learning is done based on the dimensions of interaction.

FROM INTERNAL SENSATION TO BEHAVIOR: UNCOVERING THE NEUROBIOLOGICAL BASIS OF EATING AND EATING DISORDERS

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Brain-body communication requires interoception, the perception of internal bodily signals. Seminal experiments identified the insular cortex (InsCtx) as the primary visceral (interoceptive) cortex, which can modulate visceral function and is important for visceral sensations. InsCtx is implicated in feeding, drinking and social behaviors, as well as in pathological conditions, from anorexia nervosa and obesity to addiction, anxiety and major depression. Our working hypothesis is that InsCtx contributes to these diverse behaviors through its role in interoception. We thus investigate internal sensations and predictions using a novel experimental approach that combines specific and precisely-timed stimulation of internal sensing, with well-controlled behavioral paradigms and large-scale neural recordings in mice. Using this approach, we create specific interoceptive predictions by associating external cues (e.g., smells, tastes) with a specific internal stimuli, while imaging InsCtx activity. Recent advances in gastrointestinal genetics and optogenetics now allow us specific genetic access to manipulate the activity of nutrient sensing cells in the intestine and sensory neurons of the vagus. We have thus developed a novel non-invasive paradigm in behaving mice, in which red light from outside the abdomen activates specific nutrient sensing intestinal cells, nutrient sensing vagal neurons, and gastric-stretch sensing vagal neurons. Our preliminary results validate our approach by showing that activation of intestinal sugar sensing cells enhances artificial sweetener consumption in behaving mice. We are currently working to combine this system with two-photon imaging of InsCtx activity, and with optical recordings of dopamine signals. In the future, we aim to use this experimental system in combination with existing models of eating disorders including anorexia nervosa and diet induced obesity. This will allow us to test the hypothesis that these patients have a different interpretation of interoceptive signals, leading to aberrant interoceptive predictions, which may contribute to clinical symptoms and disease progression.

INTERGENERATIONAL RESILIENCE FACTORS AND THEIR ASSOCIATION WITH PSYCHOPATHOLOGY IN YOUTH PSYCHIATRIC OUTPATIENTS AND THEIR PARENTS

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Background: Understanding variability in youth mental health trajectories from risk to resilience is critical to parse heterogeneity in clinical populations. Resilience factors, such as emotion regulation and self-reliance, are traits associated with adaptive outcomes. Little is known regarding intergenerational transmission of resilience factors. The current study aimed to investigate the associations between resilience factors with psychopathology in mental health seeking youth and their parents.

Methods: Dyads of children and their parents (N=99) treated in a child and adolescent psychiatry outpatient clinic completed assessments for resilience factors, and for psychopathological symptoms-anxiety (GAD-7) and depressive (PHQ-9). We employed multivariate regression models to test associations of resilience factors with psychopathology and tested intergenerational effects. The models were controlled for age, sex, and household income.

Results: Youth's emotion regulation and self-reliance were inversely associated with youth's psychopathology (emotion regulation, β=-0.5, $p < .0001$; self-reliance, β=-0.27, $p = 0.001$). Parental emotion regulation was inversely associated with parent psychopathology (β=-0.70, $p < .0001$), but parental self-reliance was not (β=0.04, $p=0.67$). No correlation was found between parent-child anxiety or depression nor between parent-child resilience factors. Lastly, neither parental psychopathology nor resilience factor were found to have an association with child psychopathology.

Conclusions: these results strengthen the evidence that resilience factors, specifically emotion regulation and self-reliance are associated with less psychopathology in youth. We found no evidence for intergenerational associations of resilience factors and psychopathology in our clinical study population. More research is needed to better understand intergenerational transmission of resilience.

HELPING A FRIEND IN NEED: BEHAVIORAL AND NEURAL MECHANISMS OF PROSOCIAL BEHAVIOR IN RATS

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Prosocial behavior is influenced by both external and internal factors. The mechanisms underlying the execution of helping behavior are not well known. Using the Helping Behavior Test (HBT), we examined behavioral and neural differences between rats who released trapped cagemates from a restrainer to those who did not. In the first experiment, 32 rat pairs were tested in the HBT along with boldness, social interaction, and open field tests. Brains and plasma were collected after the behavioral tests ended. In the second experiment, we focused on neural activity associated with helping behavior. For this, 13 pairs were tested in the HBT, and c-Fos+ cells were quantified over 137 brain regions. After the experiments ended, rats were classified as 'openers' (helpers) and 'non-openers' according to their performance during the HBT. In the first experiment, 14 rats consistently released their trapped cagemate (and classified as 'openers'), and 18 rats did not. Additionally, openers showed affiliation to their trapped cagemate, as expressed in more social interactions before and after the HBT, and synchronization in corticosterone levels and peeking latencies during the boldness test. RNAseq for the Nucleus Accumbens identified several transcription factors that were differentially expressed between the groups and increased Oxytocin receptors levels in the openers. In the second experiment, analysis of brain-wide neural activity revealed increased activity in the brains of openers compared to non-openers. Interestingly, multiple brain regions significantly contributed to the contrast between openers and non-openers, including Orbitofrontal regions, Anterior Cingulate Cortex, Mediofrontal regions (Infralimbic, Prelimbic), Insular regions, Nucleus Accumbens, lateral Habenula, and others. We also found functional connectivity between main social brain regions based on correlations between the c-Fos expressions. These findings demonstrate that social closeness (Exp 1) and several brain regions are associated with helping behavior and suggest future targets for the mechanisms underlying prosocial behavior.

PRESCRIPTION OPIOIDS AND THE DISEASE OF ADDICTION

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More than 27 million people worldwide suffer from opioid use disorder (OUD – formerly addiction) and the subsequent negative consequences including damage to their physical and mental health, lost productivity, and a huge toll on families and communities. Between 1999-2021, more than 500,000 people in the United States died because of an opioid overdose, whether prescribed or illegal. This crisis has not been confined to the United States—rates of opioid prescribing and OUD have risen dramatically in many countries around the world, including Israel.

Several factors contribute to the development of OUD. The biopsychosocial model of addiction has been based upon risk factors including genetics, underlying untreated psychiatric disorders and a history of childhood trauma. But, due to the vast increases in opioid prescribing of mainly oxycodone and fentanyl for months, years and even decades by physicians, exposure alone to opioids from a long-term, high-dose medical prescription has superseded this model and resulted in OUD.

OUD can be diagnosed by the Diagnostic and Statistical Manual of Mental Disorders Version 5 (DSM-5). Depending upon how many of the 11 diagnostic criteria a person suffers from during the previous year, an individual can be diagnosed with mild, moderate or severe OUD.

In Israel, there are two medications used to treat OUD, namely methadone and buprenorphine. Patients undergoing medication-assisted treatment receive psychosocial support as part of treatment and often remain on a treatment regimen for many years since OUD is a chronic relapsing-remitting disorder. Medication-assisted treatment helps an individual stop using illicit opioids by stabilizing their brain receptors so they do not suffer from cravings and physical withdrawals. The overall goal of treatment is to help an individual go back to work, reconnect with their family and become a contributing member of society.

PRESCRIPTION OPIOIDS AND THE DISEASE OF ADDICTION

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AGONISTIC PEPTIDE OF DELTA OPIOID RECEPTOR AS A NOVEL MEANS TO ATTENUATE COCAINE USE DISORDER

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Substance use disorder (SUD), and particularly cocaine use disorder (CUD), is a complex disease that affects societal, economic, and psychological factors. Opioids are endogenous pain-relieving substances that bind to variety of receptors, one being the delta opioid receptor (DOR). β-endorphin is an endogenous opioid that primarily lies in brain regions associated with mechanisms of reward and development of addiction. Endogenous β-endorphin released after prolonged cocaine withdrawal activates accumbal DOR, leading to attenuated cocaine seeking; albeit can not penetrate the BBB when given exogenously. Therfore,a use of a phage display peptide library to isolate biomimetics with similar biological properties to β–endorphin. PEP1 was used in vitro experiments that demonstrate specificity for DOR and function as receptor agonists. In this research we exaime the ability of PEP1 to be a potential treatment for CUD.

PEP1 was conjugated to gold-nanoparticle (NCP) and was examined in Conditioned Place Preferance (CPP). The result presented PEP1 attenuated cocaine-CPP and didn't show CPP itself. Administration of PEP1 during sucrose self administration not effected on sucrose intake - the reward system is not hindered. PEP1 attenuated cocaine craving in two models of addiction, self-administration and incubation of craving. Inductively Coupled Plasma Mass Spectroscopy (ICP-MS) concluded that PEP1 preferably accumulates in the brain than in the periphery organs. These results indicate safety of PEP1 and the ability to be a novel alternative treatment for CUD and possible therapy for drug use disorder.

DIETARY RESTRICTION RESCUES ADAPTIVE BEHAVIORS IN STRESS-VULNERABLE PHENOTYPED RATS

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Owing to stress, animals can respond and survive in a threatening environment by activating various neural and endocrine systems (allostasis). Stress, however, can also cause a range of physical and mental pathologies if it persists (allostatic load).

A salient aspect of stress relates to its impact on metabolism and energy balance. An adaptive stress-response regulates energy mobilization to meet the coping demands imposed by stressors. Consequently, a deregulated stress response impairs energy homeostasis and vice versa.

Dietary restriction (DR), by contrast, improves bioenergetics, and stimulates stress resistance pathways. However, very few neuro-behavioral studies have explored the beneficial effects DR outside models of age-related neuro-pathologies. Therefore, here, we set out to explore DR's-therapeutic potential for stress-induced psychopathologies, by utilizing the "behavioral profiling method".

Towards that end, after exposing the animals to stress, “individual Behavioral Profiling” tool was used to identify, prior to the DR-intervention, the stress-affected (vulnerable) population, which were then subjected to 5-weeks of DR.

The DR-intervention induced a robust recovery rate; by rescuing adaptive behaviors in 61 % of the stress-affected rats. The DR-induced recovery was not associated alterations of functional plasticity, nor in local circuits activity of the Hippocampus. Due to the fact that animals were challenged in the behavioral settings, while in the electrophysiological settings-a challenging stimulus was absent; we interpret these findings as the fallowing: what separates the DR-recovered animals, from the unrecovered, is not how they function at baseline conditions; but rather, how they adapt when they are challenged.

In conclusion, here, to the best of our knowledge, we have shown for the first time that DR holds therapeutic potential for stress-related psychopathologies. These results, although preliminary, set the stage for further research to utilize the behavioral profiling method so that peripheral and central biomarkers for DR-induced recovery could be identified.

HIGH-RESOLUTION TRACKING OF UNCONFINED ZEBRAFISH BEHAVIOR REVEALS SENSORY-LIKE STIMULATORY EFFECTS OF PSILOCYBIN

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Serotonergic psychedelics are promising therapeutic candidates for mental disorders, yet their pharmacological actions in the brain remain mostly elusive. Zebrafish have evolutionary conserved serotonergic circuits and their downstream targets in the brainstem, making it a promising model for testing the effects of serotonergic drugs in these deep brain areas. Here we developed a wide-field behavioral tracking system for larval zebrafish and investigated the effects of Psilocybin, a psychedelic agonist for excitatory serotonin receptors. Multidimensional analyses of swim patterns and tail motions identified behavioral states during spontaneous exploration, non-threatening sensory stimuli, and stress exposure. Acute Psilocybin treatment had a facilitative effect on spontaneous exploration in a similar manner to non-threatening sensory stimuli. This effect is distinct from the suppressive effects of other serotonergic drugs such as serotonin-selective reuptake inhibitors. This finding indicates that serotonergic psychedelics may modulate animal behaviors based on subcortical mechanisms that are conserved across vertebrates.

THE CLINICAL COURSE OF INDIVIDUALS WITH 22Q11.2 DELETION SYNDROME CONVERTING TO PSYCHOTIC DISORDERS: A LONG-TERM RETROSPECTIVE FOLLOW-UP.

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22q11.2 deletion syndrome (22q11.2DS) is the most known microdeletion in humans occurring in 1 out of 3000–6000 live births. This syndrome is characterized by a broad spectrum of physical manifestations. Moreover, 22q11.2DS individuals are at higher risk for psychiatric diseases such as anxiety, depression, autism-spectrum-disorders, and attention-deficit-hyperactivity-disorder. Furthermore, 22q11.2DS is associated with extremely high rates (25%) of psychotic disorders, predominantly schizophrenia.

Longitudinal studies over the years aspired to understand risk factors for conversion to psychosis among 22q11.2DS individuals. However, most of the studies had only two-time-points - posing a limitation on observation of the conversion process, some of them present relatively young cohort that is below the age of risk for conversion to psychosis.

This study aims to investigate the clinical course of a relatively large international cohort (from Israel, USA, and Switzerland) with 22q11.2DS from years before the onset to years following the onset of psychosis. Our specific aims are: 1. To identify baseline psychiatric disorders and cognitive deficits associated with later onset of psychosis. 2. To characterize the change in psychiatric symptoms (prodrome) close to the conversion to psychotic disorders. 3. To portray the course of psychosis and cognitive deficits after the conversion.

Preliminary results suggest that most patients (85%) suffer from an anxiety disorder before conversion, 50% suffer from ADHD, and had a high rate of OCD. The most common prodromal symptoms were social avoidance, anxiety, and suspiciousness. The most common symptoms of psychosis were delusions, hallucinations, and grandiosity. We found that after conversion most individuals are unemployed, unmarried, and live with their parents. We will also present data regarding the decline in cognitive functions following the conversion.

This longitudinal study follows up with the patients from before the psychosis to the present day and sheds a light on the course of psychosis in 22q.11DS.

SALIVARY CORTISOL CONCENTRATION AND PERCEIVED STRESS MEASURE IN RESPONSE TO ACUTE COMMON STRESS: THE ROLE OF MORNINGNESS-EVENINGNESS PREFERENCE.

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Introduction: The circadian system is a major regulator of human physiology and behavior. Chronotypes are the innate sleep/wake timing preferences of individuals. Significant research indicates that late chronotypes (LC) are in disadvantage compared to early chronotypes (EC) in physiological, mental, behavioral, and social parameters and suffer more from more somatic and psychiatric diseases. One suggested mediator of these affects is the HPA axis. We explored the interaction between chronotype and subjective and physiological measures of stress in response to an acute common stressor.
Methods: 52 students with clear LC or EC were selected from a larger cohort using the Morningness-Eveningness questionnaire. Participants indicated their subjective stress level and gave a saliva sample at four timepoints: morning/afternoon regular day/just before a final exam. Cortisol levels were determined from saliva using ELISA. Data for was analyzed using mixed ANOVAs followed by post-hoc analyses.
Results: Subjective stress for the entire cohort was higher before exams compared with regular days [$F(1,176)=49.4$, $p<0.001$] and higher in morning compared with afternoon [$F(1,176)=8.74$, $p=0.004$] with near significant chronotype effect [LC>EC; $F(1,176)=3.21$, $p=0.08$]. Cortisol levels were higher in morning compared with afternoon [$F(1,154)=68.51$, $p<0.001$] and higher before exams compared with regular days [$F(1,154)=9.13$, $p=0.003$] without chronotype effect [$F(1,154)=1.15$, $p=0.28$]. However, post-hoc analysis shows that the amplitude of the cortisol rhythm before morning exam was smaller in LC compared with EC [$t(43)=2.07$, $p=0.044$], suggesting a blunting of the cortisol stress response in the morning.
Discussion: The blunting of the cortisol stress response before exams in LC group is a critical finding as such blunting was demonstrated in several psychiatric disorders. These findings may support the role of stress, cortisol and HPA as possible mediators between circadian disturbances and the large range of neuropsychiatric diseases.

EFFECT OF MASSAGE THERAPY ON ANXIETY FOLLOWING PRETERM BIRTH: BEHAVIORAL AND BIOLOGICAL IMPLICATIONS UTILIZING A NOVEL MICE MODEL

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Preterm birth affects 10.6% of all live births worldwide and leads to a variety of developmental impairments including physical development, cognitive abilities, and vulnerability to affective disorders. Touch-based interventions such as massage therapy in the first post-birth days were found to assist neural and behavioral development following premature birth. One of the main hypotheses is Oxytocin hormone is responsible for these positive effects. Yet, the brain mechanism underpinning the effects of massage therapy is not fully understood. In the current study, we will use a preterm birth mice model for examining massage-like stroking therapy and its implications following preterm birth.

Method: Pregnant female mice were injected with RU486 yielding successful parturitions on day 18 after conception which led to premature birth. For the control group, we injected Saline on the same day which led to normal parturitions on day 20 after conception. Half of the pups that were born were daily massaged from postnatal day 2 to 14. All pups passed various tests both in infancy and adulthood. Moreover, blood samples and brain tissues were taken and examined by qPCR and ELISA.

Results: In infancy and adulthood, PTB mice showed more anxiety-like behaviors, in addition, both PTB and control group were massaged threatened in infancy showed less anxiety-like behaviors. In adulthood, Oxytocin Hormone (OXT) levels in the blood were lower in PTB groups. Moreover, OXT and XTR levels were lower in the Hypothalamus for PTB groups.

Conclusion: As in humans, we observed some developmental impairments in PTB including lower birth weight, inferior motor skills, and a tendency to anxiety-like behaviors. Massage treatment given in infancy influenced and moderated these anxiety-like behaviors. Our study contributes in some way to the understanding of the underly mechanism of anxiety in PTB mice. Yet, the function of massage therapy remains unknown.

PHARMACOLOGICAL CHARACTERIZATION OF THE HEAD TWITCH RESPONSE INDUCED BY 5-MEO-DMT AND ITS EFFECT ON SYNAPTIC PLASTICITY

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Background: There is increasing interest in the therapeutic potential of psychedelics in psychiatric disorders. Like other serotonergic psychedelics, 5-MeO-DMT is thought to act via the 5-HT2A receptor to which it binds with high affinity. In rodents, 5-MeO-DMT induces a characteristic head twitch response (HTR) which is highly correlated with the psychedelic trip in humans in terms of intensity. Using 5-MeO-DMT, we sought to determine a dose related HTR response, modulation of HTR by a 5-HT2A antagonist and a 5-HT1A agonist, and the effect of different 5-MeO-DMT doses on synaptic plasticity as reflected by synaptic protein levels in 4 brain regions.
Methods: Male C57BL/6J mice (11 weeks, ~30g) were administered 5-MeO-DMT (supplied by Nextar) by intraperitoneal (i.p.) injection immediately before the assessment of HTR, at doses of 5-40 mg/kg alone, or at a dose of 10 mg/kg i.p. preceded by the 5-HT2A antagonist, M107900 (0.5 mg/kg) or the 5-HT1A agonist, 8OH-DPAT (1, 2 mg/kg). HTR was measured for 20 minutes in a custom-built magnetometer using mini magnets tagged to the mouse ears. Mice were sacrificed 12 days post injection and western blot was performed on the frontal cortex, amygdala, hippocampus, and striatum for the synaptic proteins PSD-95, GAP43, synaptophysin, SV2A.
Results: 5-MeO-DMT induced a dose-dependent increase in the frequency of HTR over 20 minutes. The 5-HT2A/5-HT1A modulators significantly attenuated HTR. 5-MeO-DMT 40 mg/kg significantly increased GAP43 and PSD95 in the frontal cortex and striatum, and SV2A in the amygdala 12 days post injection.
Conclusions: Using magnetometer-based automated evaluation of HTR in C57BL/6J mice, we have shown a clear dose response relationship for 5-MeO-DMT, which was modulated by a 5-HT2A antagonist and a 5-HT1A agonist. The increase in synaptic proteins we observed reflects enhanced synaptic plasticity and supports the potential therapeutic use of 5-MeO-DMT in psychiatric disorders.

PSYCHIATRISTS' ATTITUDES REGARDING TELEPSYCHIATRY, AND THE ASSOCIATION WITH PROFESSIONAL BURNOUT DURING THE COVID-19 PANDEMIC

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Introduction: The COVID-19 pandemic accelerated the implementation of Telemedicine. Telemedicine is particularly relevant to psychiatry as interventions are usually done without physical examinations. Research on clinicians' satisfaction and self-experience using telepsychiatry is limited. Professional burnout is a significant problem in the field of mental health. There is likely to be a complex link between professional burnout and telepsychiatry use, but this relationship has yet to be investigated.

Study aims:

1. Determine the levels of assimilation of telepsychiatry in Israel.
2. Explore the attitudes of adult, and child and adolescent psychiatrists toward the implementation and use of telepsychiatry during the COVID-19 pandemic.
3. Determine whether burnout levels among psychiatrists are associated with telepsychiatry use.

Methods: An online nationwide survey was sent to adult, and child and adolescent psychiatrists experts, and residents in Israel. The survey included demographic and professional data, a questionnaire regarding the levels of use and attitudes toward telepsychiatry, and a Burnout questionnaire. We received 316 responses.

Main findings:

1. The level of assimilation of telepsychiatry is relatively high, only about 30% of the respondents did not use it at all. A positive relationship was found between age and male gender to the degree of assimilation.
2. The level of satisfaction with the technology is high, with a positive relationship to age, as reflected in the differences between experts and residents. No relationship was found between geographic area and the degree of satisfaction.
3. High levels of professional burnout were found among participants. Female sex and being a resident were associated with higher burnout levels. A negative relationship was found between the level of assimilation of telepsychiatry and the levels of professional burnout. And so is between age and seniority in psychiatry and the level of burnout. A specialty area of adult psychiatry was associated with higher emotional exhaustion.

POTENTIAL BENEFITS OF CONCURRENT PSILOCYBIN AND CLOZAPINE IN PSYCHIATRIC DISORDERS

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Background: Psilocybin (PSIL) enhances neuroplasticity; therefore, it has therapeutic potential in the treatment of psychiatric disorders including schizophrenia. However, PSIL also induces transient psychotic-like side effects. We hypothesize that using PSIL in conjunction with clozapine (CLZ) will enhance the therapeutic effects of both agents while avoiding the psychotic-like side effects of PSIL.
Methods: Male C57Bl/6j mice were used in all experiments. PSIL (98.75% purity, 4.4 mg/kg) was provided by Usona Institute. The acute MK-801-induced hyperactivity model for schizophrenia (0.5 mg/kg i.p) was used. The open field test (OFT) was conducted 1 hour after administration of treatment (1mg/kg i.p CLZ with or without 4.4mg/kg i.p of PSIL) 30 min after MK-801 injection. OFT was conducted using the Noldus Ethovision system. Head Twitch Response (HTR), an accepted measure of psychotic-like effects of psychedelic agents, was evaluated immediately after administration of treatment (without MK-801) and HTR measured for 30 minutes in a magnetometer-based system using ear clip magnets. Two-way ANOVA was used for HTR and unpaired t-test for OFT analyses.
Results: HTR was reduced in a dose-dependent manner by CLZ. At a dose of 1mg/kg, HTR was significantly reduced; at a dose of 2mg/kg HTR was completely abolished. The reduction was significant for total HTR ($P=0.0001$, for CLZ 1mg/kg ; $P<0.0001$, for CLZ 2mg/kg) as well as HTR over time ($P<0.0001$ for both doses). CLZ alone and in combination with PSIL significantly reduced MK-801-induced hyperlocomotion activity as reflected in a reduction in distance traveled ($P=0.0004$ for CLZ and $P=0.0023$ CLZ&PSIL).
Conclusions: Our findings support the concept that psilocybin used in conjunction with clozapine results in therapeutic effects without psychotic-like side effects. Effects on negative-like features remain to be examined and are currently under study. Our findings suggest a role for the PSIL-CLZ combination in the treatment of psychiatric disorders.

MULTIMODAL ASSESSMENT OF CHANGES IN PAIN SENSITIVITY FOLLOWING SINGLE-SESSION COGNITIVE-EMOTIONAL TRAININGS

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Background: Cognitive-emotional trainings (CETs) for pain are suggested as promising intervention methods targeting core mechanisms related to pain processing and modulation. However, these trainings show high inconsistency in their ability to modify pain sensitivity, caused in part by varied research methodologies, diverse use of outcome measures, and pre-training individual differences in pain perception. Thus, our research aim is to evaluate the ability to modulate experimental pain in healthy individuals by using two modified single-session trainings using enhanced multimodality pain assessment.

Methods: Participants reported their pain catastrophizing and stress pre-training using computerized questionnaires and underwent a baseline pain assessment using quantitative sensory testing (QST). QST is a multimodality approach that includes ratings of suprathreshold heat pain stimuli, evaluation of pressure pain threshold as well as cold-water pain threshold and cold-water pain tolerance using the cold pressor test (CPT). Afterward, participants randomly completed either pain acceptance or pain attention bias modification (P-ABM) active trainings or their matching control conditions and were assessed again using the QST.

Results: Preliminary findings from 33 participants demonstrate they experienced a reduction in sensitivity to suprathreshold pain stimuli following active acceptance and P-ABM trainings, compared to the control (sham) conditions. Further, only participants in the active acceptance training reported an increase in pain threshold and pain tolerance in the CPT. No change was observed in the pressure pain threshold in any of the training groups.

Conclusions: Our preliminary results support the claim that CETs can reduce experimental pain sensitivity and increase pain tolerance. Moreover, our results emphasize the importance of multimodality pain assessment for evaluating pain sensitivity modification following pain management interventions, as the trainings led to changes in different pain sensitivity measures. Understanding the specific changes in pain sensitivity caused by each training is important in the efforts to establish CETs as therapeutic interventions for pain.

SYMPTOMS OF ATTENTION-DEFICIT\HYPERACTIVITY DISORDER ARE RELATED TO SUB-OPTIMAL AND INCONSISTENT TEMPORAL DECISION MAKING

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Attention-Deficit/Hyperactivity Disorder (ADHD) has been linked to steeper delay discounting. This study examines a different interpretation according to which ADHD is linked to sub-optimal temporal decision-making and suggests inconsistency as a potential underlying mechanism. In two experiments, MTurk workers completed a self-report questionnaire on symptoms of ADHD and a temporal decision-making task consisting of choices between smaller–immediate and larger–delayed options. The delayed option was better in some items, whereas the immediate option was better in others. We measured the rate of choices of the delayed option and the consistency of choices. The results of both studies show that high symptoms of ADHD were linked to fewer choices of the delayed option when it was better and more choices of the delayed option when it was not better. In addition, high ADHD was characterized by higher inconsistency in both conditions. The findings suggest that ADHD is linked to sub-optimal temporal decision-making rather than steeper delay discounting and provide further support to the phenomenon of inconsistency in ADHD.

ARE OBSESSIVE-COMPULSIVE SYMPTOMS STABLE OVER TIME? A LATENT TRANSITION ANALYSIS IN A YOUTH SAMPLE

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Objective: In this research, our aim was to distinguish between different obsessive-compulsive patterns at youth. This allows to cheque the stability of these different pattern trajectories over time and the association between these patterns to psychological distress.

Method: The study was based on the longitudinal Raine Study, utilizing follow-up visits at six time points (age 2,5,8,10,13,16). CBCL-OCS scores from 874 participants were used for latent transition analysis (LTA).

LTA was used to assign response patterns of all OCS items to estimate latent classes, their stability and transition probabilities over time. Model fit was decided considering BIC and AIC. Then, Multinomial logistic regression was performed, to investigate the association between latent class and clinical variables.

Results: LTA: Overall, the participants were classified into four subtypes: 15.7% into a stable no symptom class (class 1), 79.7% unstable minimal symptom class (class 2), 3% stable symptomatic class (class 3), and 1.6% unstable severe symptom class (class 4). Viewing classes prevalence over time indicated that only classes 1 and 3 increase proportionally over time.

Multinomial logistic regression: Compared to class 1, participants in class 2 had a significantly higher chance to suffer from stress, while participants in classes 3 and 4 had a significantly higher chance to suffer from depression, anxiety, and stress. In addition, compared to class 1, only participants in class 3 had a significantly higher chance to have depression and a difficult temperament.

Significance: This study differentiates between patterns of obsessive-compulsive symptoms at youth according to their latent class characteristics and views their stability and prevalence across time. Moreover, it allows us to understand the associations between these patterns to clinical situations.

We hope this creates a step forward in the ability to identify patterns in childhood development that might be related to clinical situations, enabling treatment at an earlier stage.

OBESITY AND POSTTRAUMATIC STRESS DISORDER – NOT A LIGHTWEIGHT MATTER

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According to the WHO, obesity is one of the most common noncommunicable diseases in the world. In addition to its role in energy storage, adipose tissue secretes hormones and signalling molecules (i.e., adipokines), which can easily cross the blood-brain barrier, and affect metabolism, inflammation, and plasticity processes. Still, most studies that have focused on the effect of stress were mostly conducted using healthy animals displaying normal body weight and fed with a regular diet. Therefore, information is lacking on the effects of stress in animal models under other types of diets, namely high-fat diet (HFD). The objective of th4is study was to determine whether an obesogenic Western-like HFD predisposes rats to stress response and post-traumatic stress responsivity.

Adult rats were fed ad-libitum for ten weeks with either the experimental high-fat diet (HFD) (41.4% kcal from fat) or the control (normal) diet (ND) (16.5% kcal from fat). Thereafter, rats from each group were exposed to predator scent stress (PSS) or sham-PSS for 15 min. Behavioral parameters were assessed using the elevated plus-maze and acoustic startle response after seven days, and freezing response to a trauma reminder on Day eight. Preset cut-off criteria classified exposed animals according to their individual behavioral responses. Brains were harvested for morphological (Golgi-cox) and molecular (Immunohistochemistry) analysis.

Our results revealed that HFD regimen and PSS exposure significantly amplified anxiety-like behaviors compared to ND-fed rats. Relative prevalence rates of behavioral response demonstrated significant differences in individuals displaying PTSD-phenotype among groups with almost twice the extreme disruptive behavior (EBR) for HFD than ND-fed rats. Interestingly, levels of Neuropeptide-Y were upregulated in the PSS-exposed HFD rats compared to ND rats, while the expression of its anxiolytic receptor 1, remained low. Alongside the worldwide medical problem of obesity, we found that HFD-induced obesity promotes PTSD-vulnerable phenotype in response to stress.

SOUNDS OF DANGER AND POST-TRAUMATIC STRESS RESPONSES IN CAPTIVE-BRED WILD RODENTS: ECOLOGICAL VALIDITY OF A TRANSLATIONAL MODEL OF POST-TRAUMATIC STRESS DISORDER

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In the wild, animals face a highly variable world, full of competitors and predators. Most predator attacks are unsuccessful, and the prey survives. However, the non-lethal effects of predators on prey behavioral responses, have not yet been discussed. Most experiments on animal models of behavioral stress responses or post-traumatic stress disorder (PTSD) have been carried out using commercial strains of rats and mice. A fundamental question is whether laboratory rodents appropriately express the behavioral responses of wild species in their natural environment; in other words, whether behavioral responses to stress observed in the laboratory can be generalized to natural behavior.

To further elucidate the relative contributions of the ecological and environmental influences, this study investigated the behavioral, physiological and morphological effects of auditory predator cues (owl territorial calls) in males and females of three wild rodent species in a laboratory set-up: the precocial spiny mouse, *Acomys cahirinus*; *Gerbillus henleyi*; and *Gerbillus gerbillus.* Gerbils are particularly interesting for the study of PTSD as these outbred models develop metabolic, physiological, and endocrine changes similar to those occurring in humans.

We found that species did not differ in their overall responses to imposed psychological stress and no significant differences were found in the prevalence of PTSD phenotype among species or between sexes. We also found that the PTSD phenotype individuals were typified by a blunted cortisol response to the stressor, which was significantly different from those observed in less or non-affected groups. Orexin-A, responsible for orchestrating various survival behaviors, was downregulated and dendritic complexity along the DG neurons was impaired in animals exhibiting PTSD phenotype.

Our results indicate that predator cues, elicited not only “fight or flight” responses but caused PTSD-like behavior and could cause, in some individuals, long-lasting physiological and morphological responses that parallel those seen in laboratory rodents or traumatized people

EFFECTS OF SITAGLIPTIN, A DIPEPTIDYL PEPTIDASE-IV (DPP-IV) INHIBITOR, ON BIO-BEHAVIORAL AND COGNITIVE RESPONSES IN THE PREDATOR SCENT STRESS MODEL OF POST-TRAUMATIC STRESS DISORDER

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Glucagon-like peptide-1 (GLP-1) is derived from both the enteroendocrine L-cells and preproglucagon-expressing neurons in the nucleus tractus solitarius of the brain stem. GLP-1-producing neurons project to multiple brain areas, including many that are critical to stress responses. GLP-1 protects neurons from oxidative stress, enhances neurogenesis, and reduces apoptosis and chronic inflammation. Endogenous GLP-1 derived from the gut is rapidly cleaved by dipeptidyl peptidase-IV (DPP-IV), with its half-life being less than two minutes. In addition to decreasing the degradation of GLP-1, DPP-IV inhibitors prevent the degradation of a number of vasoactive peptides, including brain neuropeptide Y (NPY). Previously, we reported that central NPY microinjection following stress can prevent the development of PTSD-like behaviors. Therefore, the therapeutic value of DPP-IV inhibitor, using Sitagliptin, in the aftermath of a traumatic experience is uncertain.

Animals exposed to predator scent stress received a single bolus of DPP-IV or vehicle 1 h post-exposure or given repeatedly (3 days). Outcomes were assessed using the elevated plus-maze and acoustic startle response at 7 days and freezing response to a trauma reminder on Day 8. Surprisingly, we did not observe the expected reduction in anxiety-like behavior in DPP-IV-treated rats. No significant effect on prevalence rates of PTSD-phenotype was observed for either dose of DPP-IV as compared to vehicle.

A possible explanation for the unexpected results is the reduced NPY-Y1 receptor responsiveness to its ligand. There may also be region-specific or pathway-specific differences in the effects of NPY overexpression on receptors since the expression level of the different types of NPY receptors is not homogenous throughout the brain. Moreover, the overabundance of NPY could lead to desensitization of NPY receptors, which is common for GPCRs in the presence of abundant ligands. This can be caused by reduced receptor surface expression in the neuron, and/or a decrease in receptor signaling efficiency.

CHARACTERISTICS OF MMT PATIENTS WITH HYPERTENTION

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Background: As methadone maintenance treatment is a chronic one, many of the patients in our clinic grew older, and we assumed the incidence of hypertension among them might increase.

Aims: to evaluate prevalence of hypertension (HTN) in a cross-sectional design study, among all current MMT patients, and characterize risk factors.

Methods: Two separate (one week apart) measures of blood pressure were taken in the morning between August 2022 and September 2022, among all current MMT patients. Drug in urine, socioeconomic and addiction history characteristics were taken from patients' chart.

Results: Of 291 patients, 98 (33.7%) were found with HTN (Systolic BP ≥140 mmHg twice). The HTN and non-HTN groups did not differ in mean age (57.2±9.6 vs. 55.0±9.7, p=0.08) and duration in MMT (11.4±8.6 vs. 9.8±8.3, p=0.1), although age linearly correlated with duration in MMT (R=0.3, p<0.001) and with systolic blood pressure (R=0.27, p<0.001). The groups also did not differ by gender (male proportion 81.6% vs. 76.2%, p=0.4) and other socioeconomic and addiction history characteristics. However, the HTN group had higher BMI (28.1±5.4 vs. 25.5±5.2, p<0.001), and the HTN group had higher BMI (28.1±5.4 vs. 25.5±5.2, p<0.001), and had lower proportion of patients with urine positive to benzodiazepine (18.4% vs. 33.2%, p=0.009), cocaine (11.2% vs. 25.9%, p=0.004), and opioids (3.1% vs. 17.6%, p<0.001) with no difference in cannabis (13.3% vs. 14.5%, p=0.9).

Conclusion: We now expand our previous finding of weight gain among patients who succeed drug abstinence, to blood pressure elevation. Weight gain is a known risk factor for hypertension. To prevent hypertension, a serious life-threatening condition, medication is needed accompanied by a weight loss intervention.

PREDICTORS FOR OUTCOME IN METHADONE MAINTENANCE TREATMENT - A 29 YEARS OF EXPERIENCE

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Aims: To identify predictors for cumulative retention among a cohort of methadone maintenance treatment (MMT) patients duration in MMT of first admission (between June 1993 - June 2022) and up to December 2022 was studied in a cohort of 1082 patients.

Results: longer retention predictors using multivariate cox model were older (30+) age at admission, no other substance except opioids on admission, being immigrant from Russia, self-admitted (and not referred by medical or other facilities) and having both Axis I&II or none psychiatric diagnosis (compared to Axis II only, or I only). In a model that included a subgroup of this cohort that had genetic data of selected variants in the delta opioid receptor *OPRD1* gene (n = 488), a longer cumulative retention was found for SNP rs204076 under the dominant model. Patients with the TT or AT genotype (n = 251) stayed longer than those with the AA genotype (n = 237) (11.2 years, 95% CI 9.8-12.7 vs. 8.8 years, 95% CI 7.7-10.0, chi-square 4.4, p = 0.04). Including the TT/AT genotypes group in the Cox model, the TT/AT group was found as an independent predictor of longer retention, together with no other substance except opioids on admission, and having both Axis I&II or none psychiatric diagnosis (compared to Axis II only, or I only).

Conclusions: both genetic and environment factors predict treatment outcome of opioid users. The presence of the *OPRD1* SNP rs204076 variant T allele, which associated with lower expression of the delta opioid receptor in the cortex, predicts longer retention time among opioid users in MMT, in addition to younger admission age, no other substance abuse except opioids on admission, and no axis II only or I only psychiatric diagnosis.

INDIVIDUAL BEHAVIORAL PROFILING AS A TRANSLATIONAL APPROACH TO ASSESS TREATMENT EFFICACY IN AN ANIMAL MODEL OF PTSD

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At present, the research of psychiatric pharmacological treatments in animal models mainly utilizes the comparison of group averages in order to investigate treatment efficacy. Clinically, these treatments usually result in partial success rates. Specifically, the first line pharmacological treatments in PTSD patients are serotonin reuptake inhibitors (SSRIs) and then tricyclic antidepressant (TCAs). Both pharmacological treatments lead to full recovery in less than 30% of PTSD patients, whereas when considering sex differences, men are about as twice more responsive to TCAs than SSRIs. To this day there is a profound lack of knowledge regarding the neural mechanisms that underlie recovery by these pharmacological agents.

We applied a behavioural profiling analysis in an animal model of PTSD with male rats. We differentiated between trauma-affected individuals and unaffected individuals, thereafter treated trauma affected individuals for one month with either SSRIs or TCAs. We than differentiated between the treatment responders and the non-responders based on their behavioural profiling post treatment. Further, we conducted local field electrophysiological recordings from the dorsal dentate gyrus to examine changes in local circuits activity and long-term potentiation (LTP).

Our results revealed responsiveness rates of about 35% to the SSRIs treatment and 60% to the TCAs treatment, alike statistical data from men with PTSD. Further, the electrophysiological recordings revealed significant differences in local circuits and LTP between the responders and non-responders to the SSRIs treatment, but not between responders and non-responders to the TCAs treatment. These findings suggest that a shift in excitatory-inhibitory balance in the hippocampus is likely associated with responsiveness to SSRIs, but not to TCAs. Together, our results suggest a proof of concept for the strong translational power of our behavioural profiling approach for investigating psychiatric pharmacological treatment efficacy.

SUBCORTICAL STRUCTURES AND PSYCHOPATHOLOGY IN CHILDREN, A LARGE POPULATION STUDY

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The subcortical structures are a group of diverse neural formations deep within the brain. This structures act as information hubs of the nervous system and modulate information passing to the different areas of the brain. There are known associations between the subcortical structures and psychiatric disorders in adult populations, less is known about this association in children. In this poster, I will show how we can take advantage of large population studies, as we examine the associations between subcortical volumes and psychiatric disorders in children. The study sample include 11,875 youth from 21 sites from age 9 to 10 years collected through the Adolescent Brain Cognitive Development (ABCD) project. Data includes extracted MRI volumes of 14 regions of interest (7 bilateral subcortical regions: accumbens area, amygdala, caudate, hippocampus, putamen, pallidum, thalamus). All participants were interviewed with KSADS for the diagnosis of psychiatric disorders. The prevalence of psychiatric disorders in this community sample was depressive disorder 5.03%, ADHD 3.53%, anxiety disorder 3.27%, OCD 7.7% and eating disorders 0.1% (Klein, 2011; Cordova, 2022; Potter, 2022). Associations between brain structures and psychiatric disorders in such a big sample can help us to better understand the psychopathology of this disorders and lead to better prevention and treatments in the future.

A FOLLOWING WAVE PATTERN OF SUICIDE RELATED PEDIATRIC ER AD-MISSIONS IN THE TIME OF COVID-19 PANDEMIC

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The COVID-19 pandemic and response, which included physical distancing and stay-at-home orders, disrupted the daily life of children and adolescents, isolating them from their peers, school, and other meaningful contacts. The present study aims to add to the accumulating evidence on the impact of the pandemic on child and adolescent suicidal behavior. Data from Schneider Children Medical Center of Israel pediatric emergency room admissions for psychiatric consultation for suicidal risk assessment between January 1st, 2020, and April 16th, 2022, were extracted. We applied Time Lagged Cross Correlation (TLCC) analysis and Granger Causality test to test the temporal relationships between the COVID-19 infection waves and the patterns of suicide-related emergency room admissions. The results revealed a significant lagged correlation between the national COVID-19 infection rate and emergency room admissions rate. The highest correlation was above 0.4 and was found in a lag of 80 to 100 days from the infection rate to ER admission rate. The findings show that the effect of public crises changes over time and may be lagged. This may have important implications for mental health services' readiness to serve growing numbers of children and adolescents at risk for suicide.

INVESTIGATION OF DAILY LIFE PARTICIPATION IN POST-TRAUMATIC STRESS DISORDER: CHARACTERISTICS AND AFFECTING FACTORS

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Introduction: Post-Traumatic Stress Disorder (PTSD) causes significant disability and burden due to, among other factors, interruption in a range of daily-life activities. To date little research has been done to delineate comprehensive patterns of daily-life participation among people with PTSD. Moreover, our understanding of factors affecting participation in PTSD is limited, given that relief in the PTSD symptoms does not guarantee returning to satisfying daily life activities.
Objectives: Investigate objective and subjective participation dimensions among individuals with PTSD in comparison to healthy controls; and explore the impact of personal and illness-related factors, body functions and environment on the participation.
Methods: Thirty-one individuals with PTSD (age: M=34.3, SD =9.2; women: 24, 77.4%) and matching by age and gender healthy controls participated in this cross-sectional study. The participants completed standard assessments for PTSD symptoms severity, general cognitive profile, executive functions (EF), sensory processing, self-efficacy, capacity to perform everyday activities, environmental properties, and objective and subjective dimensions of participation in daily life.
Results: Lower diversity ($t(58)=-4.73$, $P<0.01$) and frequency ($t(58)=-2.42$, $P=0.018$) of participation was found in PTSD, but not enjoyment and satisfaction ($-7.47<t(58)<-1.61$, $p>0.05$). Diversity, frequency and experience of meaning were inferior in those who reported on avoidance from sensory stimuli (71%; $2.5<t<2.9$, $p<.05$). The diversity was correlated with self-reported EF ($r=0.465$, $p<.05$), and environment properties ($r=0.5$, $p<.01$). The frequency was associated with self-reported EF ($r=0.45$, $p<.05$). PTSD symptoms severity was not correlated with the participation ($-0.35<r<-0.01$, $p<.05$).
Conclusions: Restriction in objective dimensions of participation in PTSD raises a major concern given its profound impact on well-being and burden. The study reveals unique patterns of association between the participation indices and personal and illness related factors in PTSD, rising an urgent call for further research to expand our knowledge with the ultimate goal of contributing to well-being and health of individuals with PTSD.

TAKING ADVANTAGE OF BIG DATA: OPPORTUNITIES AND CHALLENGES

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Serur and Segal will present results for the Adolescent Brain Cognitive Development (ABCD) study that includes 11,875 youth from 21 sites from ages 9 to 10 years. Serur will focus on MRI volumes of 14 regions of interest (7 bilateral subcortical regions: accumbens area, amygdala, caudate, hippocampus, putamen, pallidum, thalamus). The prevalence of psychiatric disorders in this sample was depressive disorder 5.03%, ADHD 3.53%, anxiety disorder 3.27%, OCD 7.7% and eating disorders 0.1%. Segal will focus on integrating polygenic risk scores for ADHD together with high-resolution structural MRI data to predict individual cognitive endophenotypes of ADHD as well as individual ADHD symptoms, and present preliminary results of our analyses. Finally, Elkon will discuss the genetic basis of autism spectrum disorder (ASD). It is estimated that, overall, rare de novo and transmitted mutations (including single-nucleotide, indels and larger structural variants) in protein-coding sequences account for 20%-30% of ASD cases. Accordingly, the vast majority of mutations occur in intronic or intergenic non-coding sequences. However, our ability to interpret the functional impact of noncoding mutations is rudimentary. Our research explores potential contributions of de novo mutations (DNMs) in regulatory elements that control gene expression (promoter regions and distal enhancers). Using a large whole-genome sequencing (WGS) dataset from the Simons Simplex Collection (SSC), with 1,790 families in which the proband, both parents and an unaffected sibling were sequenced, we systematically search for regulatory elements that are enriched for probands' DNMs compared to the matched siblings. We find such enrichments in promoter regions of (a) genes that are specifically expressed in the brain and (b) highly constrained genes that are significantly depleted of loss-of-function mutations (LoF intolerant genes). Functional characterization of the affected genes indicates that coding and noncoding DNMs that contribute to ASD converge into common biological processes

DEFERIPRONE-MEDIATED REVERSAL OF INDUCED SCHIZOPHRENIA-LIKE PHENOTYPES IN MICE

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Schizophrenia (Scz) is a devastating brain disorder with major public health implications. However, current medications treat only one component of the disorder (psychosis), while leaving the debilitating negative and cognitive symptoms largely unaddressed. As treatment options are limited primarily because biological mechanisms underlying the disorder are poorly understood, testing treatments based on novel mechanistic insights is urgently needed.

The hypothesis that a disturbance of brain iron metabolism is involved Scz pathophysiology was mentioned in the 1990s, but has been largely overlooked since, despite a long-held recognition that iron homeostasis in the brain is critical. In our research, we use deferiprone, an iron-chelating drug used to treat iron-overload disorders, as an alternative form of treatment in our SCZ mouse models.

In this poster, we will display our behavioral findings regarding the deferiprone rescue of SCZ-like phenotypes induced by acute psychomimetic drugs such as amphetamine and ketamine in large mouse cohorts. Hyperlocomotion in the open field test (OFT) is a primary phenotype indicative of psychosis in animal models. While both amphetamine and ketamine consistently induce hyperlocomotion, mice that were treated with deferiprone prior to receiving amphetamine or ketamine maintained locomotor velocity comparable to control mice. Additional SCZ-like phenotypes that were rescued by deferiprone treatment include thigmotaxis and hyper-rotating behavior in the OFT, impaired sensory gating in the pre-pulse inhabitation paradigm, and head-twitch response (HTR)- a unique tick-like behavior stimulated by various psychedelic compounds.

EMOTION REGULATORY SELECTION FLEXIBILITY ROADMAP FROM BASIC TO TRANSLATIONAL RESEARCH

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Flexibly selecting between available regulatory strategies in a manner that is sensitive to differing situational demands, is key to well-being and absent in several psychopathologies. In this talk I describe basic science work mapping the determinants and building blocks of regulatory selection flexibility. I then use these findings to inform trauma and mood related pathologies, by identifying regulatory selection flexibility as a target mechanism that can be improved, providing opportunities for tailored interventions with individuals with psychopathologies.

REDUCED EMOTION REGULATORY SELECTION FLEXIBILITY IN POST-TRAUMATIC STRESS DISORDER: POTENTIAL TARGET MECHANISM IN PTSD

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Contemporary views of emotion dysregulation in post-traumatic stress disorder (PTSD) highlight reduced ability to flexibly select regulatory strategies according to differing situational demands. However, empirical evidence of reduced regulatory selection flexibility in PTSD is lacking. Multiple studies show that healthy individuals demonstrate regulatory selection flexibility manifested in selecting attentional disengagement regulatory strategies (e.g. distraction) in high-intensity emotional contexts and selecting engagement meaning change strategies (e.g. reappraisal) in low-intensity contexts. I present two studies in two different PTSD populations comparing student participants with high (*N* = 22) post-traumatic symptoms (PTS, meeting the clinical cutoff for PTSD) and participants with low (*N* = 22) post-traumatic symptoms and as second study that included PTSD diagnosed women (*N* = 31) due to childhood sexual abuse and matched non-clinical women (*N* = 31). In both studies, participants completed a well-established regulatory selection flexibility performance-based paradigm that involves selecting between distraction and reappraisal to regulate negative emotional words of low and high intensity. Results provide converging evidence for reduced emotion regulatory selection flexibility in two different PTSD populations, suggesting this impairment may constitute an important underlying mechanism in PTSD. Accordingly, improving regulatory selection flexibility could be translated into novel interventions in effort to improve regulatory selection.

ENHANCING EMOTION REGULATORY SELECTION FLEXIBILITY IN HEALTHY INDIVIDUALS: TARGET MECHANISM ENGAGEMENT

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Regulatory selection flexibility, has been conceptually associated with mental health but has not been a target for interventions. Addressing this gap, the present study aimed to improve regulatory selection flexibility among healthy individuals through an innovative intervention and to test its association to mental health. In a novel three-session intervention, participants (N=62) were randomly allocated to an active or control arm. In the intervention group participants were trained to improve regulatory selection flexibility through a computerized training in which they were exposed to emotional stimuli and were asked to select a regulatory strategy in a flexible manner. The active control group was similar in nature to the intervention group (number and length of sessions, content about emotion regulation, homework etc.) but participants were not taught how to select flexibly between different emotion regulation strategies. Changes in regulatory selection flexibility were assessed using a well-established regulatory selection flexibility performance-based paradigm pre-and-post intervention. Relative to the active control group, the intervention group showed improved regulatory selection flexibility and well-being following the intervention. The present study provides the first evidence for a novel intervention that improves regulatory selection flexibility and has a positive effect on mental health.

THE ROLE OF BODY-BASED SIGNALS IN EMOTION REGULATION SELECTION AND THE ABILITY OF MINDFULNESS TO MODULATE IT

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One central aspect of any emotional context is the physiological condition of the body, which is in tight reciprocal relationship with the emotional experience. Bodily signals are believed to provide important contextual information that can influence regulatory processes. Indeed, body-based signals have been demonstrated to affect emotion reactivity and emotion regulation processes. However, their role in regulatory selection flexibility, the ability to beneficially choose a regulation strategy with respect to a given context has not been studied. In a series of studies conducted in our lab, we were able to show the involvement of a wide range of bodily-related signals, from neuro-physiological measures of heart-brain interactions (heart-beat evoked potentials) to measures of the autonomic nervous system and facial electromyography in the flexible selection between regulatory strategies. We also found that this body-regulatory selection relation can be enhanced via a body-based intervention such as mindfulness, which in turn affects well-being. The findings will be discussed in the context of a wellbeing-intervention model developed in our lab.

NEURAL CORRELATES OF AVOIDANCE LEARNING AND THREAT EXTINCTION

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Threat avoidance is necessary for survival, yet excessive and persistent avoidance in the absence of real danger can become maladaptive. Extinguishing avoidance is difficult because it prevents individuals from confronting excessive threat beliefs, thereby maintaining fear and avoidance cycle. The aim of the proposed study is to examine the behavioral, cognitive, and neural correlates underlying avoidance learning and threat extinction. Specifically, individual differences in intolerance of uncertainty (IU) and trait anxiety (TA) will be examined as vulnerability factors for maladaptive avoidance learning.

The paradigm will include four phases. First, in differential *threat acquisition*, one conditioned stimulus (CS+) will be repeatedlypaired with an aversive sound (unconditioned stimulus; US), while another stimulus (CS-) will serve as a safety cue. Second, during *avoidance learning*, participants could avoid the aversive sound by pressing the avoidance button, which will prevent the upcoming US in 80% of trials. Partial reinforcement allows us to examine the role of prediction-error, the difference between a received and an expected outcome, in avoidance learning. Third, Pavlovian and operant learning approaches to *extinction* will be compared. In the Pavlovian extinction condition, the avoidance button will be removed. In the operant extinction condition, participants could choose to avoid the US and receive low reward or not to avoid and receive high reward. In both extinction conditions no USs will be presented. Finally, to examine the recovery of avoidance after extinction, the avoidance button will reappear during *avoidance test*. During all task phases, we will measure avoidance response, self-reported fear and relief and two EEG components: Late Positive Potentials (LPP), measuring emotional valence, and feedback-related negativity (FRN), measuring prediction-error.

We hypothesize that greater avoidance responses and fear ratings will be associated with high IU and TA. The role of LPP, FRN and relief ratings in avoidance learning and extinction will be explored.

THE EFFECTS OF CHILDHOOD ADVERSITY ON ACUTE STRESS RESPONSE (ASR) AND POSTTRAUMATIC STRESS DISORDER (PTSD) MEDIATED BY CORTISOL AND OREXIN

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A traumatic event is one in which a person senses that they or others are in mortal danger or may be significantly harmed. After undergoing a traumatic event, most people experience Acute StressResponse / Disorder (ASR / D) and some even develop Post-Traumatic Stress Disorder (PTSD). The current study seeks to assess the effects and relationship between exposure to early traumatic events and ASD/R after exposure to a traumatic event in the present. We further seek to examine whether this relationship is mediated by biological indexes such as cortisol and orexin levels measured shortly after the traumatic event. To that end, we clinically and biologically monitor people who arrive at an emergency department (ED) within six hours ("golden hour") from the moment they have been exposed to a traumatic event and exhibit ASR symptoms. Upon their arrival at the ED physiological measurements such as blood pressure and heart rate will be collected along with blood samples that will be tested for cortisol and orexin levels. In a follow-up session, we inquire as to which of the subjects has previously been exposed to a traumatic event. From the data collected so far, no significant relationship emerges between the various indices mentioned. However, a possibility has been raised that an experience of an early traumatic event may be a protective factor against the development of PTSD. It seems possible that early trauma may affect PTSD not just as a risk factor, but maybe, in some situations, as a protective factor as well. These results make us wonder if experiencing trauma early on may help us accept better later negative experiences and avoid their impact.

QUALITY OVER QUANTITY: THE POSITIVE AND LONG-TERM EFFECT OF SOCIAL RELATIONSHIPS ON WELLBEING ANXIETY AND HEALTH DURING COVID-19

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As Covid-19 spread across the world at a frightening rate, it caused a tremendous impact on every aspect of life. The situation affected the public profoundly and increased anxiety, stress, and loneliness. Studies conducted worldwide and in Israel focused mainly on psychological distress during the acute period of Covid-19. Still, very few examined the long-term effects of the first lockdown on mental health a year later.

The present study aims to understand the factors affecting wellbeing during the first Covid-19 lockdown in Israel and a year later. We uniquely measured the effect of social relationship quality on the wellbeing of an Israeli study sample with a total of 206 subjects, 84% female, and a mean age of 31.5. At the first Covid-19 lockdown, subjects responded to a validated questionnaire assessing their emotional state and wellbeing. Subsequently, daily surveys were administered using the Beiwe smartphone app for 43 days, measuring anxiety, social environment, and more. A year later, the initial questionnaires were repeated.

Our main finding is the detrimental effect of anxiety, which majorly impacted wellbeing during the first lockdown and predicts a deterioration in health and wellbeing a year later. Positive social relationships predicted improvement in wellbeing during the first lockdown and mitigated the negative effect of anxiety, positively affecting health and wellbeing a year later. Loneliness had the opposite effect. Other factors like romantic relations, meditation, and physical activity were strongly and positively associated with wellbeing during the first lockdown.

In conclusion, our findings emphasize the crucial role of the social environment on wellbeing, mental and physical health, especially at uncertain and distressing times, and how it mitigates the negative effect of anxiety. These findings help us understand the factors affecting wellbeing during distress and isolation and offer ways to reduce the deleterious effects.

DEATH EXPERIENCES DURING AYAHUASCA CEREMONIES DECREASE SELF-PRIORITIZATION AND ENHANCE ENVIRONMENTAL CONCERN

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Research on the long-term effects of psychedelic drugs has drastically increased in recent years. Despite a wide agreement regarding the pivotal mechanistic role of the subjective experiences that unfold during acute psychedelic intake, very little has been done in the direction of better characterizing such experiences and determining their predictors and long-term outcomes. The present research, as part of a larger neurophenomenological effort examining psychedelic-induced 'death' experiences, spotlights – for the first time in the literature – the characteristics and outcomes of the lifetime prevalence of acute experiences related to one's death during ayahuasca ceremonies. Our findings indicate that these experiences occur in about two-thirds of experienced ayahuasca ceremony participants, are typically strong and transformative, and that their frequency is not predicted by overall lifetime ceremony participation, demographics and personality. Importantly, these experiences are not associated with psychopathology including state and trait anxiety, death anxiety, depression, and depersonalization. Rather, our findings show that death experiences are related to a sense of having transcended death and predict a decrease in a behavioral measure of self-prioritization. Finally, we show that having undergone death experiences enhances concern for the environment. Overall, our preliminary findings highlight the safety and efficacy of death experiences during ayahuasca ceremonies, corroborate the previously hypothesized link between self and death processing, and support the latter as a putative mechanism of action for psychedelics' long-term salutatory effects. Ongoing studies from our lab aim at validating these initial results in a larger-scale survey, gaining a firmer understanding of these experiences by way of phenomenological interviews, as well as mapping their underlying neural mechanisms.

A CHANGE OF MIND: SECONDARY PREVENTION OF POST-TRAUMATIC STRESS DISORDER WITH MDMA IN AN ANIMAL MODEL

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MDMA (3,4-methylenedioxymethamphetamine), a synthetic amphetamine derivative paired with psychotherapy sessions, has demonstrated long-lasting improvements in symptoms of post-traumatic stress disorder (PTSD).

However, the effects of MDMA as a post-stressor intervention have not been tested before. This research examines, in an established animal model of PTSD, whether MDMA in the aftermath of a stressogenic experience can alleviate or altogether prevent PTSD-related symptoms.

Rats exposed to predator scent stress (PSS) or sham-PSS were treated 30 minutes later with 2.5, 5, 10 mg/kg MDMA or saline. One hour after the treatment, urine samples were taken, and brains were dissected to evaluate levels of hippocampal norepinephrine transporter and glucocorticoid receptors. PSS-exposed rats (n=10) were sacrificed for molecular analysis.

Behavior responses were assessed in the elevated plus maze and acoustic startle response 7 days after the initial exposure, and freezing response upon exposure to a trauma-related cue was assessed on day 8.

MDMA (10 mg/kg) administered immediately after PSS significantly reduced anxiety-like behavior 7 days later and improved resilience to a trauma cue, compared with 2.5, 5 mg/kg MDMA or saline.

Urine corticosterone levels and norepinephrine in the hippocampus significantly increased in exposed rats treated with MDMA (10 mg/kg) compared with other conditions. Urine levels of norepinephrine increase with dosage, and norepinephrine transporter levels in the hippocampus are significantly higher for all exposed groups compared to sham-PSS saline-treated rats.

The ratio of norepinephrine transporter and glucocorticoid receptors has an important role in consolidation processes. This ratio is low in the exposed 10 mg/kg MDMA-treated rats compared with other exposed rats and similar to the value of the control sham-PSS saline-treated rats. This suggests that a single high dose of MDMA, immediately after exposure to PSS, might have disrupted the consolidation of the traumatic memory to long-term memory and thus have reduced the PTSD-like behavioral responses.

MULTI-OMICS REVEALS CANDIDATE BIOMARKERS FOR SSRI RESPONSE IN DEPRESSED AND ANXIOUS CHILDREN AND ADOLESCENTS

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Objectives: While selective serotonin reuptake inhibitors (SSRIs) are the most commonly used class of antidepressants in youth, clinicians face several challenges when considering treatment for young patients with depression and/or anxiety. Markers for predicting treatment outcome are still lacking. The interplay of clinical, genetic, epigenetic, and metabolic factors, and their predictive power on treatment outcome in the young population should be studied in order to better pre-identify patients for non-response to serotonin selective reuptake inhibitors.
Experimental Procedures: Children and adolescents with depressive and/or anxiety disorders were enrolled and treated with SSRI. Extensive clinical assessment using several validated questionnaires and blood was collected at baseline (pre-treatment). Five data domains were produced for each patient: phenotype data and multi-omics (SNP array, microRNA profile, methylation analysis, and metabolomics). Treatment response was defined according to the clinical global impression severity – improvement (CGI-I) scale and evaluated after eight weeks of treatment.
Methods: Eachomics data (pre-treatment) was QCed and analyzed independently, by state-of-the-art statistical approaches, to reduce data dimensions and obtain candidate markers that can predict treatment response (at week 8). The predictive power of each set of markers was assessed. A polygenic risk score model was constructed to represent genetic propensity to SSRI response. Finally, all markers were integrated into a multi-omics prediction model using machine learning.
Results: ATotal of 40predictive biomarkers were subjected to feature selection and predictive modeling, resulting in a non-linear classification model with 12 multi-omics features. Multi-omics model reached a ROC AUC of 0.93 (sensitivity of 0.79, specificity 0.91, NPV 0.89 and 0.83 PPV).
Conclusion: Our results support a decisive role for machine learning in multi-omics studies of antidepressant treatment. Especially, predictors related to epigenetics moderate treatment success. However, prospective application of prediction models will be necessary to prove their clinical value.

THE PRICE OF INTERNSHIP THROUGH COVID-19: 1ST YEAR PHYSICIANS REPORT SUBSTANTIAL MENTAL HEALTH SYMPTOMS DURING THE PANDEMIC

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Objectives: To examine the prevalence of mental health symptoms among medical interns working for the first time as physicians in a large tertiary hospital in Israel during the 1st COVID year.

Methods: All interns who worked for at least 2 months during the 1st COVID year (March 2020-February 2021) at the Tel-Aviv Sourasky Medical Center (TASMC), a large tertiary general hospital in Israel were approached simultaneously during April-May 2021 and were requested to fill in an online survey. In each questionnaire, the interns were asked to refer to the worst time they endured the symptoms described. Included were all medical. Depression and anxiety symptoms, post-traumatic stress symptoms and Burnout measures were evaluated using validated questionnaires. Depressive/anxiety symptoms were defined as primary end measures. We assessed the association between depression and anxiety symptoms, and demographic, post-traumatic and burnout measures.

Results: 145 out of 188 interns completed the study (77% overall response rate). The mean age was 30.36±2.97. Almost half the interns (47%) reported depression/anxiety symptoms. The high depression/anxiety group was characterized by a lower mean age (29.87±2.93 vs. 30.92±2.91, $p=0.041$), higher post-traumatic symptoms (15.62±13.32 vs. 3.63±5.59, $p<0.0001$) and higher scores in 2/3 burnout subscales - emotional exhaustion (5.09±1.29 vs. 3.61±1.38, $p=0.000001$) and depersonalization (3.83±1.71 vs. 2.94±1.46, $p=0.002$). 11.4% of interns in the full sample reported they used cannabis or alcohol as "self-medication".

Conclusions: medical interns serving for their first year as physicians during the COVID pandemic, developed mental symptoms in alarming numbers. The findings point to a crucial need to implement active interventions to protect these doctors, so that they can safely embark on their medical careers, specifically in times of global health crises.

AGE RELATED DUAL EFFECT OF ULTRA-LOW DOSE THC ON LONG-TERM MEMORY

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Δ9-tetrahydrocannabinol (THC) is emerging as a promising therapeutic agent. While cannabis has its negative effects, including anxiety and cognitive functions, In a recent study, we found that a single injection of an ultra-low dose of THC (ULD-THC; 0.002mg/kg) significantly improved cognition in 24 month old mice, and had a negative effect on young mice. In order to better understand the age dependent dual effect of ULD-THC, this study aims to characterize the cognitive response to ULD-THC at several time-points, and its underlying biological mechanism. This could help in understanding when the therapeutic effects of THC can be helpful and when it can be harmful. ICR female mice (20 mice per group) were given a single dose of ULD-THC (0.002mg/kg) or vehicle i.p. and examined for short and long-term memory, spatial memory and strategy shifting at 3 different time points: early adulthood (6 months), late adulthood (12 months) and old age (18 months). After which, Hippocampus and Preforntsal tissues were collected and will be examined for the expression of various genes (using qPCR) and proteins (using western blot) involved in the neurotrophic and serotonergic system. Our results indicate that the shifting point between the harmful and beneficial effect of ULD-THC is around 12 months. Healthy Mice receiving ULD-THC at 6 months showed cognitive decline after the ULD-THC treatment, while mice at the age of 18 months with age-related cognitive decline benefited from the treatment. To conclude, ULD-THC may be used in the future as a medicine for neurodegenerative diseases associated with old age, but with caution as we saw that it can cause cognitive damage at a young age. We discovered that the critical age for reversing the cognitive response to THC is 12-month-old mice. More research is needed to understand the mechanism underlying this phenomenon.

INVOLVEMENT OF THE GUT MICROBIOTA IN THE PROGRESS OF PTSD AND TREATMENT

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Post-traumatic stress disorder (PTSD) is a chronic and debilitating anxiety disorder that may develop in about 20% of survivors of a life-threatening traumatic event.

In this research, we used a unique animal model established in our laboratory. This model is based on a novel approach that identifies and separates animals that, after exposure to the trauma, will develop symptoms that mimic PTSD.

In order to identify rats that mimic symptoms of PTSD, we analyzed the rats behavior following exposure to trauma, and according to the results we divided them into two groups: Susceptible ('PTSD-like') and resilient ('non-PTSD-like). Naïve rats are used as a control. Eventually 20% of the rats exposed to trauma are determined as 'PTSD-like'.

To explore the possibility that the gut microbiome influences the development of PTSD, we performed fecal microbiome transplantation (FMT) from resilient to susceptible and vice versa. Upon exploring the resilient and susceptible rats, we found that resilient rats did not respond to the FMT, while susceptible rats became more resilient to the trauma.

Following the success of the FMT, we investigated the gut microbiome composition by collecting stool samples in three stages of the model- baseline (prior to the exposure), Exposure (the traumatic event), RE-2 (second reminder to the traumatic event). The stool samples were sent for analysis in the US by Zymo company, and results were further analyzed by professor Yoram Louzuon and his lab.

To conclude, we hypothesize that microbiome-based treatment could be a novel approach to treating PTSD.

EVIDENCE FOR INTACT INTEGRATION OF REINFORCEMENT-RELATED CUES MAJOR DEPRESSIVE DISORDER

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Multiple reward-related processes appear to be altered in Major Depressive Disorder (MDD), including impairment in the ability to integrate reinforcement history to adjust future behavior. While most studies focused mainly on responding to tangible outcomes (`rewards' like food or monetary gain), behavioral findings from our lab have corroborated the existence of Reinforcement from Sensorimotor Predictability (a 'valence-free' reinforcer; RSP) show that both the general population and individuals suffering from MDD show the effects of RSP on the lower levels of action selection (motor programming). The present study builds on those findings to investigate whether MDD sufferers have difficulties encoding probabilistic reinforcement-related cues in general or whether this applies only to the encoding of tangible rewards. Clinically depressed individuals (N=82), as well as healthy controls (N=75), were instructed to voluntarily, yet randomly, press one of four keys on a keyboard, given an imperative cue. Each key was associated with a different probability of producing feedback. The type of feedback was manipulated between subjects as indicating (a) a significant monetary outcome; (b) a negligible monetary outcome; (c) RSP feedback. The fourth group received no perceptual feedback. Interim results indicate that MDD is not associated with a global impairment in reinforcement-related cue integration and suggest that previously documented issues with reward integration are caused by upstream reward-related processes. Interestingly, individuals suffering from MDD were seemingly more sensitive to rewards than the HC n and maintained their response bias throughout the experiment (despite being reminded about the requirement for randomness), while HC avoided such biases in adherence to the task instructions.

INNOVATIVE TREATMENT FOR DEPRESSION USING PSYCHEDELIC-LIKE SUBSTANCES

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Background: Ketamine was suggested as a treatment for depression albeit with an acute effect. 2-Fluorodeschloroketamine (2-FDCK) is a psychoactive-like compound, which has close structural homology with Ketamine. The pharmacological characteristic of 2-FDCK were suggested that the effects of 2-FDCK may last longer than those of ketamine. Hence, we desired to explore the possibility of the anti-depressant effect on the long-term.

Methods: Utilizing the Forced Swim Test (FST) model, we evaluated the anti-depression-like effect of 2-FDCK on the Flinders Sensitive Line (FSL) rat model. Measuring the immobility of the rats (defined as a suspension of swimming), as a test to evaluate the motivation, is one of the main characteristics of depressive-like behavior. 2-FDCK and Ketamine (10 mg/kg) or a vehicle were injected intra-peritoneally into FSLs. Additionally, using the Open field Test (OFT), to rule out an effect of 2-FDCK on the motor locomotion.

Results: 2-FDCK, showed a significant anti-depressant efficacy in on FSL male and female rats model, superior to Ketamine. A K-cluster analysis in male enabled the separation of two different sub-groups with statistical significance in a non-biased manner with high integrity, 40% of total 2-FDCK treated rats showed no significant response, and 60% with substantial attenuation of motivation in the swim test. In female we show a strong effect of the substance, that improve the motivation of the rats without subgroups segregation.

Conclusion: We suggest that our preliminary results confirmed 2-FDCK has a potential novel antidepressant like-effect superior to Ketamine. The results show an apparent all-or-non effect in male rats.

CORTISOL SYNCHRONY PATTERNS IN PSYCHOTHERAPY FOR MAJOR DEPRESSIVE DISORDER

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Introduction: Accumulating research emphasizes the role of cortisol synchrony in interpersonal interactions. While the role of cortisol in psychotherapy is already being investigated, no studies attempted to explore cortisol synchrony and its effect on treatment progress and outcome. In this study, we sought to explore (a) the existence of distinct patterns of cortisol synchrony patients and therapist dyads throughout treatment, and (b) characterize the patterns and test their associations with pre-treatment patients' characteristics, treatment progress, and treatment outcome measures.

Method: Fifty patients, and their therapists, participated in 16 weeks of short-term psychodynamic treatment for major depressive disorder. Salivary cortisol samples were collected from patients and therapists before and after each session, at 4-time points (weeks 4, 8, 12, and 16). Samples were collected 30 minutes before therapy and immediately after. In addition, patients filled out self-report questionnaires at baseline, treatment sessions were coded on the rupture-resolution rating system, and Hamilton rating scale for depression (HRSD) scores were used as the treatment outcome measure.

Results: (a) Three patterns of synchrony have been identified: Synchronized, Unsynchronized, and Unresponsive therapist. (b) Different patterns of pre-treatment, treatment progress and outcome have been identified for each pattern. Specifically, compared to the unsynchronized and Unresponsive categories, patients in the synchronized category were significantly more anxious and dominant in their relationships and were more prone to ruptures; received fewer repairs throughout treatment. In addition, patients in the Unsynchronized category changed the least in HRSD scores by the end of treatment.

Discussion: Results are in line with existing literature on the possibly aversive role of cortisol synchrony in interpersonal interactions and form important hypotheses for future research.

PSYCHOEDUCATIONAL "SKILLS AND RESILIENCE" GROUP FOR THE PERINATAL POPULATION STRUGGLING WITH SYMPTOMS RELATED TO PAST EXPERIENCED TRAUMA

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A growing body of research suggests that childhood maltreatment influences parenting attitudes and behaviour later in life. For example, during childhood and adolescence, physical or emotional abuse has been linked to heightened self-criticism, lower self-esteem and confidence, social withdrawal and more. Maternal psychopathology, symptoms of complex PTSD, anxiety and depression during the perinatal period may interfere with a mother's capacity to parent, thereby affecting subsequent bonding and attachment. Mitigating this risk through therapeutic approaches can better the mother-child bond.

In my proposed presentation, I will discuss a virtual clinical intervention designed to help patients learn to be more effective in caring for themselves and responding to intense emotions during the perinatal period.

Using my experience in treating trauma in individual and group settings, we developed a virtual eight-week psychoeducational group for the perinatal population. We utilized different tools from DBT, Behavioral Activation, Mindfulness and self-compassion therapies, the Internal Family System, and Janina Fisher's psychoeducational technics from "transforming the living legacy of trauma.".

Treating trauma symptoms in a perinatal period needs to be very delicate and sensitive to this particular time frame in the patient life. Thus, adjustments must be made to the more known approaches in trauma therapy programs.

This group is based on the weekly meeting program model. Each week, there is a brief sharing time at the start of the meeting, interactive learning of specific topics and weekly assignments. The goal is to create a foundation of resilience and build skills like grounding, mindfulness, recognizing the voice of self-critic, boundaries and interpersonal skills, which are all very relevant in the perinatal period.

The group was developed as my end-of-fellowship project. This clinical intervention continues to be offered to patients from the Perinatal Mental Health Program at Mount Sinai Hospital in Toronto as an add-on to psychiatric care.

1 - CASE REPORT OF HYPNOTHERAPY OF A PATIENT WITH FUNCTIONAL MOTOR DISORDER (FMD) PRESENTING WITH TREMOR

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Introduction: This talk will present a patient suffering from FMD, manifested by a severely debilitating tremor limited to the left hand. While presenting the case, the FMD disorder will be described from a clinical and diagnostic point of view, addressing the neurobiological mechanisms of this disorder and hypnotherapy.

The case report: The patient, 23 years old, generally healthy, and with no psychiatric history, developed a conversion tremor (FMD) after firing a gun at a shooting range during her military service. Over the course of about four years, her condition deteriorated and she underwent an extensive investigation without a definite diagnosis. Finally, she was diagnosed with FMD and was referred for treatment. The course of treatment will be described, illustrating the various stages in therapy through video clips. The treatment lasted about four months and included 14 therapeutic sessions including psycho-education and specific hypnotic techniques. Following therapy, the patient reached full remission.

Discussion: We hypothesize that in this case, the mutative factor of the hypnotherapy was through "strengthening" the connectivity of brain networks related to the sense of agency in general and through a network involving the TPJ area in particular.

ENHANCING INTER-BRAIN COUPLING WITH DYADIC NEUROFEEDBACK

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Accumulating evidence from hyperscanning (scanning two participants simultaneously) fNIRS studies shows that brain regions of interacting individuals may become coupled during social interactions, which indicates that brain-to-brain coupling may relate to various forms of human connection. Yet it is unclear whether neural coupling and human connection are causally linked. Here we aim to develop a novel dyadic-neurofeedback technology that allows drawing causal inferences between inter-brain plasticity and connectedness. The technology will give two interacting participants feedback on the extent to which their brains are coupled in real-time and allow them to attempt to change this coupling. We take advantage of the high temporal resolution of state-of-the-art dual-functional Near-Infrared Spectroscopy (fNIRS) setup and examine the malleability of inter-brain coupling between the inferior frontal gyrus (IFG) of dyads with real-time dyadic neurofeedback, consequently we measure to what extent their behavioral connectedness has changed. The results of the pilot study indicate that training with upregulation of inter-brain coupling is associated with higher ratings of state connectedness. This provides initial evidence for the potential behavioural consequences of dyadic neurofeedback training, indicating that increased inter-brain coupling may translate into behavioural gains. In the next stage we plan to examine the gains in different behavioral domains (e.g empathy), and if those gains can be generalized during interactions outside the current dyadic setting.

SENSE OF COHERENCE MODERATES THE LINK BETWEEN ADHD SYMPTOMS AND FUNCTIONAL IMPAIRMENT

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Background: ADHD is linked to functional impairment in various domains. However, research on protective factors that mitigate this link is still lacking. The Salutogenic Model of Health offers the "Sense of Coherence" (SOC), establishing that individuals who see their lives as logical, meaningful, and manageable are more resistant to various risk factors. The present study examined whether SOC may protect against ADHD-related antisocial behavior, substance abuse, emotional distress, and (lack of) happiness.

Methods and Results: In the first study, 2025 adults completed scales assessing ADHD symptoms, antisocial behavior, and sociodemographic factors including age, gender, urbanity, place of birth, socioeconomic status, family status, and religiosity. ADHD symptoms predicted antisocial behavior more than all of the sociodemographic variables combined.

In the second study, 3180 participants aged 15–50 completed scales assessing ADHD symptoms, various types of antisocial behaviors, and SOC. Structural equation modeling revealed an interaction between ADHD symptoms and SOC in predicting each type of antisocial behavior. The link between ADHD symptoms and antisocial behavior was significantly weaker for high than low SOC participants, regardless of age group. A set of subsequent analyses focused on 468 participants who reported being diagnosed with ADHD. It was found that those who reported a higher SOC also reported lower functional impairments in anti-social behavior, substance abuse, emotional distress, and lack of happiness.

Conclusions: These studies found that people with high SOC are protected against ADHD-related various functional impairments, justifying further prospective and intervention studies.

N-OLEOYL GLYCINE AND N-OLEOYL ALANINE ATTENUATE ALCOHOL SELF-ADMINISTRATION AND PREFERENCE IN MICE

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The endocannabinoid system (ECS) plays a key modulatory role during synaptic plasticity and homeostatic processes in the brain, and has an important role in the neurobiological processes underlying drug addiction. We have previously shown that elevated ECS response to psychostimulant (cocaine) is involved in regulating the development and expression of cocaine conditioned reward and cocaine sensitization. Here, we set to determine the involvement of ECS in alcohol addiction. We first measured the levels of eCBs in different brain areas of the reward system following chronic alcohol self-administration using liquid chromatography-mass spectrometry (LCMS). We found that following chronic intermittent alcohol consumption, the levels of N-oleoyl glycine (OlGly) was significantly elevated in the prefrontal cortex (PFC), and N-oleoyl alanine (OlAla) was significantly elevated in the PFC, nucleus accumbens (NAc) and ventral tegmental area (VTA) in a region-specific manner. We next tested whether exogenous administration of OlGly or OlAla will attenuate alcohol consumption and preference. We found that IP administration of OlGly or OlAla (60mg/kg) during intermittent alcohol consumption significantly reduced alcohol intake and preference. These findings suggest that the ECS negatively regulates alcohol consumption and boosting selective endocannabinoids exogenously have beneficial effects against alcohol consumption and hopefully in preventing relapse.

INVESTIGATING NONVERBAL SYNCHRONY AS A MECHANISM UNDERLYING POOR PROGNOSIS OF DEPRESSION IN PATIENTS WITH A COMORBID BORDERLINE PERSONALITY DISORDER

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Aim: Patients who suffer from borderline personality disorder (BPD) and major depressive disorder (MDD) benefit less from psychotherapy, as opposed to patients with MDD without BPD. This is the most common comorbidity in BPD, with rates of comorbidity ranging between 53% to 83%. This population suffers from a poorer prognosis of treatment success for MDD and a more severe clinical presentation of depression. The aim of the current study is to investigate the underlying mechanisms that lead to change in psychotherapy, that differ in this clinical population and in turn shed light on their poorer prognosis. The current study focuses on the mechanism of nonverbal synchrony between the patient and therapist.

Method: Eighty-seven patients recruited to a randomized controlled trial received 16 50-min sessions of either supportive-expressive or supportive psychotherapy. All sessions were video-taped and analyzed for nonverbal synchrony using Motion Energy Analysis (MEA). BPD was assessed using the Structured Interview for DSM-VI Personality (SIDP-VI) prior to beginning of treatment. Treatment outcome was measured using a one-item measure of session effectiveness reported by the patient after each session. Analysis was conducted using PROC MIXED with SAS software.

Results: In the first session, nonverbal synchrony was significantly lower in patients with MDD and BPD as compared to patients with MDD without BPD. However, patients with MDD and BPD synchronized more over time and "caught up" to patients with MDD without BPD. In turn, higher nonverbal synchrony predicted more effective sessions, as reported by the patients.

Discussion: The current study holds the potential to shed light on the processes that lead to successful or unsuccessful treatment for MDD in patients with BPD. Broadening our understanding of these mechanisms has potential clinical implications allowing us to better tailor treatments to the specific needs of this clinical population.

THE PSYCHEDELIC PSILOCYBIN INDUCES SHORT TERM ANXIETY THROUGH A DIFFERENT MOLECULAR PATHWAY FROM THE PSYCHEDELIC RESPONSE

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Psilocybin has emerged as a major research interest due to its potential as a treatment for several neuropsychological disorders, in particular anxiety and depression. Psilocybin is known to induce psychedelic and hallucinogenic effects which is mediated by its metabolite psilocin, a non-selective serotonin 5-HT2A receptor agonist, which through modulation of the serotonergic (5-HT) systems leads to regulation of excitatory neurotransmission and gene transcription in the brain. However, there is little knowledge regarding the brain regions, cell types, genes and mechanisms through which psilocybin may affect depression and anxiety related behaviors. The purpose of our study is to investigate how psilocybin affects anxiety and depressive-related behaviors, and how neuronal activity and molecular pathways change in association with behavioral changes. We found that Psilocybin induced an acute increase in anxiety-related behavior in multiple behavioral paradigms in mice. Immunohistochemistry analysis revealed that psilocybin induces a specific activation of neurons in the amygdala. In addition, we found that pharmacological blocking of 5-HT2A receptor attenuates psilocybin-induced head twitch response, a mouse correlate of psychedelic response, but did not rescue psilocybin effect on anxiety-related behavior. We have further performed phosphoprotein analysis in the amygdala to discover signal transduction pathways that are activated by psilocybin either in the presence or absence of the 5-HT2A receptor antagonist. Our data suggests that Psilocybin induces changes in anxiety-related behaviors through a molecular pathway which is distinct from the 5-HT2A psychedelic inducing pathway. These results give important insights into how psilocybin may induce short-term anxiety-causing effects.

SET SHIFTING AS A POTENTIAL MAINTENANCE MECHANISM OF ANOREXIA NERVOSA

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Anorexia nervosa (AN) is characterized by a severe food intake restriction leading to significant weight loss. It has been suggested that abnormalities in cognitive functioning during adolescence may account for various clinical phenotypes in AN. Specifically, rigid thinking among adolescents with AN was proposed to reflect inefficient set-shifting abilities (i.e., the cognitive ability to shift back and forth between multiple tasks and mental sets). However, studies that assessed set-shifting among adolescents with AN commonly report inconsistent findings. This study examined the causal influence of affective state and exposure to various food types on set-shifting among adolescents with AN. If set shifting abnormalities act to maintain disordered eating, it should interact with triggers for disordered eating behaviors such as food exposure and negative affect. Twenty-six adolescents with AN and 42 healthy adolescents with no eating pathology completed an emotion-food task-switching paradigm in which they were presented with food images inside a colored frame. They were requested to classify the food's flavor or the frame's color. Participants were exposed to a negative or neutral image in each trial to manipulate an affective state. The results demonstrated greater difficulty disengaging from the food among adolescents with AN compared to healthy individuals. However, this occurred only after exposure to negative images. The results support the causal influence of negative emotionality on cognitive rigidity around food among adolescents with AN. The findings further emphasize that situational factors such as affective state and exposure to foods play an essential role in modulating cognitive rigidity in adolescents with AN.

INDIVIDUAL VARIATION IN POSTTRAUMATIC STRESS DISORDER SYMPTOMOLOGY AS DEPICTED BY APPROACH-AVOIDANCE CONFLICT

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Post-Traumatic Stress Disorder (PTSD) is a disorder developed following exposure to a traumatic experience/s, while the majority of people will not develop PTSD, those who experience exacerbated symptoms also show heterogeneity in their duration and severity, implying different dynamics of PTSD development. These dynamics can be seen as four distinct trajectories (i.e., chronic, recovery) following the traumatic event; suggesting high importance to the individual response following such event/s. These trajectories have been examined in order to delineate the underlying neurobehavioral processes that account for PTSD development. Two dominant processes examined are reward processing and response to negative stimuli, which are related to PTSD key symptoms, anhedonia, and heigh avoidance tendencies (correspondingly). These processes may be accounted for an imbalance between Approach and Avoidance tendencies (i.e., Approach-Avoidance Conflict, AAC) in PTSD. The goals of this research are to delineate the dynamic pathway of PTSD clinical symptoms among trauma survivors ~36 months after the traumatic exposure, in order to understand the psychopathology behavior more than a year after the traumatic exposure. Secondly, we aim to investigate the association between neurobehavioral AAC and PTSD clinical symptoms (~36 months after the trauma event), in order to understand the role of the imbalance between approach-avoidance in PTSD. This study probed clinical, and fMRI assessments of 80 traumatic survivors 1, 6, 14, and ~36 months following admission to the Emergency Department. Preliminary findings demonstrated PTSD symptom trajectories, ranging from full remission to a lifelong debilitating disorder ~36 months following the traumatic event exposure. Moreover, we demonstrate a novel association between neurobehavioral AAC and PTSD clinical symptoms ~36 months following trauma exposure.

NEONATAL KETAMINE MODEL OF SCHIZOPHRENIA – COGNITIVE DEFICITS, AFFECTIVE AND SOCIAL ABNORMALITIES

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Schizophrenia is a widespread psychiatric disorder that affects 0.5-1.0 percent of the world's population and induces significant, long-term disability that exacts high personal and societal cost. Negative symptoms, which respond poorly to available antipsychotic drugs, are the primary cause of this disability. Preclinical translational models of schizophrenia are powerful tools in the development of novel and effective treatments for the disease. The present study tested the effect of neonatal ketamine treatment on cognitive, affective, and social phenotypes of the adult mice.

ICR male mice were treated with either saline (n=16) or 40mg/kg ketamine (n=15) on PNDs 6-9, 12-13. Behavioral phenotyping started when mice were 3-month-old, and was consisted of cognitive (Y-maze, radial arm water-maze, fear conditioning), social (social exploration, social interaction in pairs, tube dominance test, male sexual behavior), and affective (forced-swim test, open field, elevated plus maze) tests. In addition, response to acute ketamine and amphetamine injection were tested.

Ketamine-treated mice displayed cognitive impairments compared with saline-treated mice, demonstrated in the Y-maze test of working memory ($t[29]=2.105$, $p=0.0441$) and in the RAWM test of spatial navigation ($F[1,28]=6.727$, $p=0.0149$); lower social dominance ($t[25]=2.085$, $p=0.0471$), and lower interest in hedonic social behaviors demonstrated in the social exploration ($t[20]=2.235$, $p=0.037$) and male sexual behavior ($t[29]=3.209$, $p=0.0033$) tests; and higher anxiety, demonstrated both in higher permeance of the wall area in the open field ($t[29]=2.476$, $p=0.0194$), and higher freezing rate in a novel context in the fear conditioning test ($t[29]=2.075$, $p=0.0469$). interestingly, ketamine-treated mice displayed lower response to acute amphetamine ($F[1,28]=7.396$, $P=0.0409$).

Taken together, these results indicate that neonate ketamine treatment induces long-lasting deficits and may serve as a powerful tool in the development of novel treatments to schizophrenia and psychosis.

THE COLLAPSE OF MORTALITY DEFENSES IN TIMES OF COVID-19 AND THEIR EFFECT OF ENVIRONMENTAL ATTITUDES

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We have recently demonstrated that death-denial involves self-specific prediction-based neurocognitive mechanisms attributing death to the other, but not to oneself, thus shielding the self from existential threat. The Covid-19 epidemic presented unique circumstances for examining the impact of constant and persistent personally-relevant death reminders and true existential terror on death processing in general, and these brain-based denial mechanisms in particular. Additionally, we aimed at assessing their impact on environmental concern, a link which has been previously hypothesized but not yet empirically demonstrated. Fifty healthy participants were invited during Covid-19 throughout a six-month period. They underwent a previously validated magnetoencephalography visual mismatch response paradigm indexing death denial, a host of explicit and implicit behavioral and self-report measures gauging different aspects of death processing, as well as an environment attitudes survey. The results suggest that the brain's defenses against mortality may have collapsed Covid-19, but may be gradually re-emerging as time passes from the plague's onset. Furthermore, temporal correlations were found with multiple behavioral and self-report measures demonstrating that Covid-19 impacted death processing on multiple levels of the cognitive hierarchy. Finally, we demonstrate that how death is processed, and in particular the implicit and neural measures of death denial, strongly predict diminished environmental concern. These findings highlight the malleability of the brain's response to existential threat under extreme real-life conditions and demonstrate their impact on concern towards the environment.

ADHD AND RISKY BEHAVIOR AMONG SPECIAL- AND REGULAR-ECUATION STUDENTS IN EAST JERUSALEM

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Studies have shown that adolescents with ADHD are likely to engage in risky behaviors such as smoking, substance abuse, dangerous driving, and unprotected sex. The East Jerusalem education system is characterized by large gaps relative to the west of the city, density and shortages, and higher dropout rates; therefore, its students may be at increased risk for involvement in risk behavior. In a series of two studies, the extent of engagement in risky behavior and its characteristics among Palestinian Arab high-school students from East Jerusalem were examined.

One-hundred sixty-nine students from grades 7-14 at three special education schools participated in the first study, and 1046 students from grades 7-12 at six regular-education schools participated in the second study. Questionnaires were used to examine ADHD symptoms, engagement in various risk behaviors, and descriptive and injuctive norms regardinf these behaviors.

Results showed that in both sampls risky behavior was predicted by male gender, older age, ADHD symptoms, and descriptive and injunctive norms. ADHD symptoms correlated with higher perceived risky behavior-related descriptive and injunctive norms.

This study demonstrates the link between ADHD and risky behavior among a youth population that has not yet been studied. Understanding the links between risky behavior and ADHD is essential for developing intervention models for adolescents. Such models can contribute to reducing gaps in education and welfare systems throughout East Jerusalem.

MEAI - A PSYCHEDELIC DRUG AS A POTENTIAL TREATMENT OF COCAINE ADDICTION

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5-Methoxy-2-aminoindane (MEAI) is a psychoactive compound which has been used recreationally by many people, who report a mild euphoric, alcohol-like experience. MEAI is believed to impart a feeling of satiety or contentedness and regulate or even discourage binge drinking. We wanted to test if it could be a possible non-rewarding, therapeutic treatment for substance use disorder (SUD).

Utilizing the Conditioned Place Preference (CPP) model, we evaluated MEAI's non-rewarding effects on rats and determined whether MEAI can be an effective treatment for cocaine preference in rats. Rats learned to associate between reward and an environmental cue. Baseline was conducted to determine rat's natural preference in a striped and smooth compartment in a closed arena. During the training period, the animal was placed twice a day into the different compartments after being injected (i.p) with saline and the test article. Finally, a test was conducted in the same conditions as the baseline. Using the sucrose (natural reward) and cocaine self-administration model, we explored the effect of MEAI on natural reward and on the substance-use-disorder rat model. Rats were put in in operant conditioning chambers for one hour a day and trained to self-administer cocaine/sucrose. Cocaine craving was determined by active lever presses.

A dose response test indicated a significant non-rewarding effect for 5mg/kg, therefore we decided to further test this dose's efficacy on cocaine preference. A K-cluster test revealed two different sub-groups with statistical significance in a non-biased manner with high integrity. One group (60% of the subjects) expressed a significant attenuation of craving albeit the rest 40% showed no significant effect on craving.

Due to this data, we postulate MEAI as a safe, non-rewarding compound, which is not likely to express addiction-like properties. Moreover, results indicate an all-or-non effect that may result from the suggestive-like nature of a psychedelic like substance.

DISSOCIATION AND SUICIDALITY IN EATING DISORDERS: MEDIATING AND MODERATING FACTORS

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Background: In patients with eating disorders (EDs), elevated dissociation may increase the risk of suicide. The aims of the present study were: 1) To examine the relationship between dissociative symptoms and suicidality in female adolescents with EDs, and 2) To assess potential factors that would intervene in these relationships including bodily related disturbances, depression, anxiety, severity of ED symptoms, body mass index (BMI), and type and duration of the ED.
Methods: The study included 172 inpatients: 65 with anorexia nervosa restricting type, 60 with anorexia nervosa binge/purge type, and 37 with bulimia nervosa. Participants were assessed using self-rating questionnaires for dissociation, suicidality, bodily related parameters, and severity of ED symptomatology, depression, and anxiety.
Results: We found that dissociation and suicidality were directly associated. In addition, depression and anxiety moderated the mediating role of body image parameters in the association between increased dissociation and increased suicidality. Thus, only in inpatients with high depression and anxiety, i.e., above the median range, body image disturbances were found to mediate the association between dissociation and suicidality. ED-related parameters did not moderate these relationships.
Conclusions: Our study demonstrates that in inpatients with EDs, increased dissociation may be significantly associated with increased suicidality, both directly and via the intervening influence of body image, depression, and anxiety.

DOES INTERPRETING THE WORLD AS MORE POSITIVE REDUCE SOCIAL ANXIETY? ECOLOGICAL VALIDATION OF COGNITIVE TRAINING FOR INTERPRETATION BIAS AMONG INDIVIDUALS WITH SOCIAL ANXIETY DISORDER

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One of the known difficulties in treating social anxiety disorder (SAD) is that treatment robustly affects self-report on feelings, but its influence of actual behavior in social situations is lower. Interpretation bias of social situations is considered as an important factor in SAD. Although previous studies support the efficacy of cognitive bias modification for interpretation bias (CBM-I) in modifying interpretations of ambiguous information and reducing social anxiety symptoms, the effects of CBM-I on *behavior* within a social situation have been scarcely explored. Therefore, the current study aims to examine the effect of CBM-I on behavior, assessed by measuring the motivation to be included in a social situation. Sixty participants meeting the criteria for SAD will be enrolled in a randomized trial comparing CBM-I with Dummy-CBM. In the interpretation training procedure, participants decide whether a word implying a threatening or benign meaning is related to an ambiguous social scenario. The participants in the CBM-I group are reinforced for interpreting ambiguous social scenarios in a benign manner. In the control group (i.e., Dummy-CBM), participants are reinforced for threatening and benign interpretations equally. To assess inclusion motivation, the training is followed by a social task, a version of the Cyberball paradigm that allows participants to actively influence their inclusion by waving a virtual hand. Participants also complete two tasks measuring interpretation bias using sentences describing ambiguous situations, as well as by interpreting emotional facial expressions.
Preliminary results (n=10) show that participants in the CBM-I group significantly interpret ambiguous situations and emotional facial expressions as being more positive and less negative compared to the control training. Furthermore, they reported feeling less ignored and more important and powerful during the social task. These preliminary findings suggest that cognitive training for interpretation have a potential to relieve SAD symptoms and enhance social motivation and behavior.

THE ROLE OF THE CENTRAL-AMYGDALA IN THREAT RESPONSE IN SEMI-NATURAL ENVIRONMENT

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Threat response is a complex sequence of behaviors that involves multiple brain regions. Following the threat-imminence continuum (TIC) theory, it has been proposed that the behaviors exhibited by rodents in response to different levels of threat are governed by different neuronal populations in the central amygdala (CeA). These neuronal populations include the CeA corticotropin-releasing factor (CeACRF) and CeA oxytocin-receptor (CeAOTR) expressing neurons. Current paradigms can show animals' reactions to a specific threat level but fall short of displaying the complete set of behaviors (risk assessment, avoidance, fight/jumping). To improve the ethological relevance of behavioral experiments, our lab has established an enriched semi-natural setup (Social Box) in which animals can be housed in groups for several days and are automatically tracked. Combining the Social Box with a novel device of our design - the Foraging Tower (FT) - we could observe different behaviors displayed by mice in an environment where the threat levels vary from low to high imminence. The FT successfully induces a threat response to predatory-like stimuli (12 kHz tones) versus non-threatening stimuli (5 kHz tones), evidenced by the presence or absence of flight behavior in conditioned mice while foraging for food. Using this setup, we will further correlate specific behavior exhibited by mice in the threat response continuum with neuronal substrates in the CeA.

ANKRD55 AS A NOVEL REGULATOR OF PTSD SUSCEPTIBILITY: ANATOMICAL AND GENE REGULATION CHARACTERIZATION

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Post-traumatic stress disorder (PTSD) is a debilitating mental illness that develops in approximately 10% of individuals following exposure to a traumatic event. The genetic mechanisms underlying individual differences in PTSD susceptibility are poorly understood and the treatment is limited. One candidate gene that might be involved in these mechanisms is *ANKRD55*, which was significantly linked to PTSD susceptibility in a genome-wide association study (GWAS). Nevertheless, not much is known about the role of *ANKRD55*, particularly with regards to brain expression and function in stress-related behaviors. Here, we characterized for the first time *Ankrd55* RNA brain expression and showed that *Ankrd55* is localized in both excitatory and inhibitory neurons. Additionally, we show that *Ankrd55* is differentially expressed in the amygdala in a sexually dimorphic manner in response to both traumatic and immunological stressors. Furthermore, having generated the first reported Ankrd55 conditional knockout (KO) mouse line, we show that *Ankrd55* KO exhibit anxiety-like phenotypes when using two different cell type specific KO in both CaMK2 and GAD2 positive neurons. By showing a link between *Ankrd55* and stress regulation and determining *Ankrd55* brain localization we can provide better understanding of the genetic and cellular mechanisms underlying stress related pathologies.

TARGETING LABILE BRAIN IRON IN PHARMACOLOGICAL MODELS OF PSYCHOSIS

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Schizophrenia is a mental illness affecting 1% of society and has both a social and economic burden on society. Yet, since the development of the Atypical antipsychotic drugs more than 3 decades ago there has been no breakthrough in the field. Treatments for this disorder help only with part of the positive symptoms, leaving negative and cognitive symptoms untreated, and up to 30% of patients show some to complete resistance to treatments. A main reason no breakthrough was made during these years is lack of understanding of brain mechanisms underlying the disorder. Following a recent study that indicated elevated brain iron levels in schizophrenia patients, the present study was designed to gain further understanding of these brain mechanisms by focusing on the hypothesis that labile iron levels in the brain are involved in the pathophysiology of schizophrenia, specifically in the enzyme reaction of monoamine synthesis. This hypothesis was first introduced over 25 years ago but has been largely overlooked until recently. In the present study, we administered a variety of psychotic inducing substances to mice to measure changes in iron levels: amphetamine (3mg/kg i.p., N=49), ketamine (50 mg/kg i.p., N=65), as well as deferiprone (100 mg/kg i.p., N=57), an FDA approved iron chelator, or saline. We then used an ICP-MS analysis to detect changes in iron levels in specimens from the PFC, basal ganglia, and Hippocampus. We did not find any significant change in iron levels in the PFC ($F(3,45)=4.16$, $P=0.0048$) and aim to further investigate this, as well as to test changes in the other ROIs. We hypothesize that iron might be targeted by deferiprone and therefore cannot bind to enzymes during protein synthesis, yet it does not leave the cell. Altogether, we hope that our findings will allow to use metal chelators as a treatment in the future.

CHILDHOOD TRAUMA INCREASES RISK FOR PERINATAL MOOD AND ANXIETY DISORDERS (PMAD) AND ALTERS DMN CONNECTIVITY, WHICH MAY BE A PATHWAY TO THE ONSET OF PMAD

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Introduction: Women with childhood trauma (CT) are at increased risk for Perinatal Mood and Anxiety Disorders (PMAD)[1]. One explanation is that CT changes psychological and neurobiological development and these changes constitute a vulnerability factor for psychopathology, especially during stressful times[2], like the perinatal period[3]. However, the pathways through which trauma affects PMAD are still unclear. The Default Mode Network (DMN) is affected by trauma and psychopathology[4] and has high neuroplasticity in the perinatal period[5]. Therefore, we postulate that CT disrupts DMN-neuroplasticity during pregnancy and childbirth, which may explain the vulnerability of women with CT to PMAD. We hypothesize that women with CT will: 1) be at greater risk of PMAD during the perinatal period, 2) have different DMN-neuroplasticity after pregnancy.

Methods: 104 women (*Mean age*=25.9,*SD*=4) filled out questionnaires about childhood trauma (CTQ), depression (PHQ-9) and anxiety (GAD-7) before pregnancy. After birth, they filled out PHQ-9 and GAD-7 again. Preliminary neurobiologicalanalysis included five subjects who went through a resting-state functional magnetic resonance (fMRI) scan. Individual DMN connectivity maps were created before pregnancy and after birth and then were compared.

Results: 18 women (17.3%) reported CT history.

Pre-pregnancy, there were no significant associations between CTQ and PHQ-9 (r=0.109,p>0.05) or GAD-7 scores (r=0.043,p>0.05).

Postpartum, there were significant associations between PHQ-9 and: CTQ score (r=0.543,p<0.05), emotional abuse subscale (r=0.562,p<0.05) and physical neglect subscale (r=0.508,p<0.05). There were no significant associations between CTQ and GAD-7 scores (r=0.213,p>0.05). Pre-pregnancy connectivity was higher only in the medial-prefrontal cortex (*Meanbeta*=0.44, *SD*=0.31), compared to post-partum (*Mean*=0.39,*SD*=0.13). All other ROIs showed higher post-partum connectivity.

Conclusions: Women with CT show greater risk to psychopathology in the perinatal period. The DMN changes during pregnancy. Since it is influenced by trauma and psychopathology, we believe that focusing on the changes in DMN connectivity could be a pathway to the onset of PMAD.

ANXIOLYTIC AND ANTIDEPRESSANTS' EFFECT OF CRATAEGUS PINNATIFIDA (SHAN ZHA): BIOCHEMICAL MECHANISMS

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Background: Depression and anxiety disorders are highly prevalent. Selective serotonin reuptake inhibitors (SSRIs) are the current first-line treatment for these disorders, but they have pronounced limitations and side effects. Therefore, there is a clear need to explore alternative treatments. Recently, various Chinese medicines have been tested as remedies for depression and anxiety - particularly we found that a novel herbal treatment consisting of four herbs; Shan-zha, Fu-xiao-mai, Baihe and Da-zao, has demonstrated efficacy in pre-clinical studies comparable to conventional pharmaceutical treatments without causing bothersome adverse effects.

Methods: we examined the antidepressant-like and anxiolytic-like activities of each individual herb composing the NHT on stressed mice exposed to unpredictable chronic mild stress. Then we explored the possible mechanisms of action of the herbs, specifically SERT and the 5-HT1A receptor, using functional assays in Xenopus oocytes expression system.

Results: Our results identify the Shan-zha herb as the most effective component of NHT. We show that Shan-zha works similarly as NHT and escitalopram, as it reduces both anxiety and depressive like-behaviors and elevates BDNF expression in the hippocampus and Pre-frontal cortex (PFC). Chronic treatment with Shan Zha did not alter serotonin transporter expression in the PFC, as opposed to escitalopram treatment. This finding was confirmed followed our electrophysiological results in oocytes since as opposed to escitalopram Shan-zha did not block SERT activity. However, it partially activated 5HT1A receptor. Further examination of stressed mice revealed that NHT and Shan-zha herb does not induce two of the common side effects normally induced by escitalopram, namely, sexual dysfunction and weight gain.

Conclusion: This research moves us toward finding a most-needed alternative to the conventional treatments offered today for treating mild to moderate depression and anxiety.

CANNABIDIOL MODULATES ALTERATIONS IN PFC MICRORNAS IN A RAT MODEL OF DEPRESSION

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Background: Recent findings suggest that cannabidiol (CBD) can potentially be used as an antidepressant agent. In this study, we examined the association between the antidepressant effects of CBD and alterations in brain microRNAs in the unpredictable chronic mild stress (UCMS) model for depression.

Methods: UCMS male rats were injected with vehicle or CBD (10 mg/kg) and tested for immobility time in the forced swim test. Alterations in miRNAs (miR16, miR124, miR135a) and genes that encode for the 5HT1a receptor and the serotonergic transporter SERT were examined.

Results: UCMS increased immobility time in a forced swim test (i.e., depressive-like behavior) and altered the expression of miRNAs and mRNAs in the ventromedial prefrontal cortex (vmPFC), raphe nucleus, and nucleus accumbens. Importantly, CBD restored UCMS-induced upregulation in miR-16 and miR-135 in the vmPFC as well as the increase in immobility time. CBD also restored the UCMS-induced decrease in htr1a, the gene that encodes for the serotonergic 5HT1a receptor; using a pharmacological approach, we found that the 5HT1a receptor antagonist WAY100135 blocked the antidepressant-like effect of CBD on immobility time.

Conclusion: Our findings suggest that CBD has antidepressant properties in a rat model for depression that are associated with alterations in miR-16 and miR-135 in the vmPFC and are mediated by the 5HT1a receptor.

PRENATAL STRESS INDUCED PERTURBATION IN NEURONAL CELL MIGRATION REVEALED BY UNBIASED RNA SEQUENCING

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Human epidemiology and preclinical studies have convincingly shown the long-lasting effect of early life stress on the development of individual differences in stress responsivity and subsequent psychopathologies later in life. The disparity between individual starts as early as *in-utero*, during the critical period of brain development. Robust evidence suggests that prenatal stress plays a significant role in the onset of severe and impairing psychiatric conditions, including major depressive disorder, schizophrenia, and stress-related disorders.

Transcriptional modifications are one of the main mechanisms known to mediate the effect of environmental challenges such as prenatal stress. These alterations can occur during the critical window of development and may translate to physiological and anatomical changes in neuronal activity and connectivity. Currently, most studies have focused on genes of interest, limiting our understanding to a small subset of related pathways. In our current study we aim to identify and characterize novel pathways effected by prenatal stress using unbiased sequencing methods, thus shed new light on the mechanisms perturbed by prenatal stress.

We utilize a mouse model to mimic the adverse effect of prenatal stress shown in humans. We induce psychogenic stress during gestation and monitor physiological measurements and the behavioral effect on the offspring. Mice exposed to prenatal stress were characterized by higher anxiety like behavior. Interestingly, this effect was more profound in males.

Using RNA sequencing we characterize molecular differences between prenatally stressed mice and control on postnatal day 1. We focused on the prefrontal cortex, a brain region that is strongly involved in emotional processing, and dysregulation in this brain region is frequently observed in psychiatric disorders. Our results suggest that prenatal stress may affects integral brain development through regulation of genes related to neuronal cell migration and extracellular matrix formation.

LATE POSITIVE POTENTIAL IS LESS SENSITIVE TO EXTINCTION AND MAY REFLECT SUSTAINED ATTENTION TOWARD A THREAT CUE AMONG BOTH YOUTH AND ADULTS

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Threat learning is a central mechanism underlying the development of anxiety disorders. Understanding its neural underpinnings, particularly from a developmental perspective, and their association with later anxiety symptomatology is imperative. The current study extends common self-reports and peripheral psychophysiological indices in threat learning research by measuring late positive potential (LPP), an event-related potential (ERP) component reflecting a response to emotionally significant stimuli.

Fifty-six adults (*M* = 24.57 years, *SD* = 3.51) and 57 adolescents (*M* = 15.12 years, *SD* = 1.68) completed a differential threat-learning paradigm with yellow and blue bells serving as the conditioned stimuli (CSs). The acquisition phase consisted of 3 blocks, each comprised of 10 CS+ and 10 CS- presentations. The CS+ was paired with an aversive sound, unconditional stimulus (UCS), with 60% reinforcement rate. Twenty-four hours later, participants returned for an extinction phase consisted of 6 blocks with 10 representations of each stimulus in every block, and no UCS. In addition to ERP/LPP, self-reported fear, threat-expectancy, skin conductance response (SCR) and electrocardiogram (ECG) were measured.

Preliminary results show that both adolescents and adults exhibit greater LPP towards the CS+ (*M* = 3.90, *SD* = .262) compared to the CS- (*M* =3.06, *SD* = .215), $F(1, 91) = 20.18$, $p < .000$, in both early and late phases of extinction. Furthermore, youth showed overall greater LPP during threat extinction (*M* = 4.19, *SD* = .300) than adults (*M* = 2.77, *SD* = .324), $F(1,91) = 10.29$, $p = .002$.

These results suggest that LPP may represent sustained attention to a threat cue, which is less sensitive to extinction especially among youth. Findings may expand our knowledge on neural differences in threat-learning processes across development and their possible role in pediatric anxiety.

FAMILY ACCOMMODATION AND PARENTAL STRESS: A PARENT-BASED TREATMENT FOR CHILD ANXIETY AND OCD, SPACE

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Family accommodation of child's anxiety refers to changes that parents make in their own behavior to help their child avoid or alleviate distress related to the anxiety disorder. In recent years, there has been rapidly increasing interest in the construct of family accommodation in anxiety disorders, generating data on the underlying theoretical and biological mechanisms related to this parental behavior, and associations with anxiety disorders. Today, family accommodation is considered a key factor impacting child anxiety. Although it is intended to reduce anxiety in the short-term, family accommodation is associated with greater symptom severity, functional impairment, and parental stress.

Supporting these theoretical understandings and empirical findings, novel parent-based interventions of child anxiety have shown much promise. SPACE (Supportive Parenting for Anxious Childhood Emotions) is an evidence based, theory-driven intervention informed by research into parental entanglement in the symptoms of childhood anxiety and by mammalian parental behavior. SPACEE is a parent-based treatment which teaches parents to recognize their accommodating behaviors, and to implement specific plans for reducing the accommodation while maintaining an empathic and supportive attitude towards the child.

This presentation will briefly describe associations between family accommodation, parental stress and child anxiety and provide a brief overview of SPACE. A large randomized controlled trial (N = 124, ages 6-14 years) comparing SPACE with CBT will be presented. This clinical trial showed SPACE to be as efficacious as CBT. Additional ongoing research further establishing the efficacy of SPACE as an evidence-based treatment for child anxiety will also be presented.

WHAT DOES GIDI GOV AND CLOZAPINE HAVE IN COMMON?

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Studies all around the world have shown that both psychiatrists and patients are reluctant to use clozapine. Despite the evidence that show its advantages in treatment-resistant schizophrenia (TRS), clozapine administration entails prominent concerns. Most famously, it might lead to serious adverse effects such as myocarditis, neutropenia, salivation and obesity. Another common patients' concern is the national requirement of 4 months of weekly blood-monitoring, deterring them from clozapine initiation. An additional clinicians' concern is the difficulty to ensure long-term adherence, due to lack of equivalent long-acting agent. Therefore, it's hardly a surprise that clozapine usage rates are lower by over 50% than expected, if everyone operated with accordance to the international guidelines for treatment-resistant schizophrenia.

This talk will cover several recent studies that may enhance clinicians' and patients' confidence when considering clozapine. In particular, the talk will focus on some of the most deterring obstacles - neutropenia, myocarditis, and long-term adherence.

All these obstacles, as it seems, have an important common denominator – it's just a matter of time.

MECHANISMS UNDERLYING THE EFFECTS OF MDMA ON FEAR EXTINCTION IN A RAT MODEL FOR PTSD

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Background: 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') combined with psychotherapy shows promising results for treating PTSD. Studies in rodents suggest that these effects can be attributed to the enhancement of fear memory extinction. However, the mechanisms through which MDMA acts to enhance extinction are not well understood. Here, we examined whether the effects of MDMA on extinction in a rat model for PTSD are mediated via serotonergic and oxytocinergic pathways.
Methods: Male rats were exposed to the shock and reminders model of PTSD. Prior to the first extinction training, rats were unilaterally microinfused with MDMA (1µg/0.5 µl/side), MDMA combined with OXY antagonist L-369,899 (250 ng/ 0.5 µl/side), MDMA combined with the 5-HT1a antagonist WAY 100635 (50 pmoles/0.5 µl/side) or vehicle (PBS) into the infralimbic area of the prefrontal cortex (IL-PFC). Brains were taken for mRNA analysis of OXY and 5HT1a in the PFC.
Results: Intra-IL MDMA infusion facilitates fear extinction in a rat model for PTSD and we have preliminary results for the involvement of serotonergic and oxytocinergic mechanisms.
Conclusions: Our findings show that MDMA can facilitate fear extinction learning in a rat model for PTSD and the underlying mechanism are still under examination.

FUNCTIONAL MOTOR DISORDER - NEUROBIOLOGICAL AND PSYCHODYNAMIC CONSTRUCTIONS

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1 - Case report of hypnotherapy of a patient with Functional Motor Disorder (FMD) presenting with tremor Eyal Limony

2 - Impaired Semantic Inhibition in Subjects with Conversion Disorder
Shani Zach

3 - Predictive Coding and Conversion Disorders
Kobi Tiberg

4 – Conversion Diosrders – Between Somatic Compliance and Symbolization
Iftah Biran

Conversion tremor belongs to functional neurological disorders which are at the neuro-psychiatric interface and are typified by neurological inconsistency and inadequacy. Psychodynamic theories, such as conversion-mechanism, dissociation, and neurobiological theories, are all implicated in the diagnosis and therapeutic approaches. The biological theories suggest the involvement of various brain networks related to attention, limbic, and agency. Other theories look at Bayesian explanations. In this session, four lectures will be presented based on a case of hypnotherapy of conversion tremor formulating it through the neurobiology of conversion, hypnosis, cognitive theories of executive regulation, Bayesian theories, and the neuropsychoanalytic interface.

The first talk describes the clinical presentation and the course of hypnotherapy alongside neurobiological formulations of conversion and hypnosis.

The second talk will expand on an empirical study looking at a frontal-dysexecutive model in conversion disorders according to which there is a dysregulation of inhibitory semantic-symbolic functions culminating in positive conversion signs such as the tremor.

In the third talk, we will describe how the 'Predictive Coding' theory explains the appearance of functional symptoms as a result of giving an excess weight (precision) that can be predicted (priors) at intermediate levels of the brain hierarchy. We will analyze the case accordingly.

In conclusion, in the fourth talk, we will review how the psychoanalytic conceptualizations of conversion disorders vary between referring to the "body" and "neurology" as the main generator of the disorder (the somatic compliance) as opposed to the "psychomental" as the generator of the disorder (the symbolic model). We will summarize the case while emphasizing the dialectic between these two concepts.

IMPAIRED SEMANTIC INHIBITION IN SUBJECTS WITH CONVERSION DISORDER

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Background: Previous studies suggest that patients with Conversion disorders are impaired at inhibitory tasks. This was studied mainly in motor FND and tasks looking at motor inhibition, problem-solving, and inhibition of automatic reading. As traditional psychoanalytic thinking suggests that the symptoms of conversion disorder are related to a dysregulated semantic-symbolic representation of a psychological conflict transposed onto the body, we postulated that subjects with conversion disorder might suffer from dysregulated semantic inhibition compared with other types of inhibition.
Methods: Population: Subjects with conversion disorder were recruited from the department of Neurology at Tel Aviv Medical Center (PT) and compared to matched healthy control subjects (CON). Tasks: We administered three inhibition tasks: (1) Hayling task for semantic inhibition; (2) Stroop task for inhibition of automatic reading; (3) The bead task for inhibition of problem-solving.
Results: Population: 16 subjects with conversion disorder and 16 matched controls. The two groups were matched for sex, age, and education (Sex: 12F/4M in each group; Age (years): CON-30.6±13.0, PT-30.2±12.9, P=0.925; Education (years): CON-13.4±1.3, PT-12.7±1.8, P=0.217). Experimental Tasks: The patients' performance was significantly worst compared with the control group in the semantic inhibition (Hayling task) (CON-2.94±1.8, PT-6.8±5.1, P=0.013) but not in the other inhibitory tasks.
Conclusions: The results demonstrate that semantic inhibition abilities are relatively more impaired among conversion patients. The results emphasize the role of impaired inhibition as a possible mechanism for conversion symptoms and are in accordance with the psychoanalytic understanding of the role of aberrant symbolization and semantics in the generation of conversion disorder

PREDICTIVE CODING AND CONVERSION DISORDERS

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Background: Predictive Coding Theory formulates the brain as a 'predictive machine' that creates a model of the world, and whose task is to constantly minimize 'prediction errors' or sensory input that does not fit the model's predictions. The goal of this process is to maintain homeostasis. This is achieved in two ways: by perception, in which the model or predictions are 'corrected' or updated according to the prediction errors, and by action, a process by which the 'sensory sample' is changed in a way that fits the predictions. The brain is structured as nested hierarchical levels so that each level minimizes or explains the prediction errors of the level below. Precision weighting is the process by which the weight or level of accuracy attributed to each prediction is determined against those attributed to the prediction errors.

CONVERSION DIOSRDERS – BETWEEN SOMATIC COMPLIANCE AND SYMBOLIZATION

Iftah Biran

Background: DSM-5-TR names the disorder previously recognized as hysteria with two competing terms: 'Functional Neurological Disorder' and 'Conversion Disorder'. This duality is at the root of an inherent tension in this diagnosis: What is the source of this disorder - the (neuro)soma or the (psycho)mental? This echoes a psychoanalytic tradition that differentiates between the neurological – the 'somatic compliance' related to the term 'Functional Neurological Disorder and the symbolic that links to the concept of conversion – the conversion of the (psycho)mental into the physical.

Psychoanalytic models: On the one hand, the 'somatic compliance' emphasizes the neurosubstrate: there is a neurological nidus around which the mental conflict is crystallized. On the other hand, the symbolic mechanism emphasizes a psychic mechanism operating according to a dictionary of emotions and their bodily manifestations. No prior neuronal impairment is needed to produce these symptoms. The neurological systems involved are selected not according to their mechanism or function but rather according to a system of meanings that are not necessarily physiologically or functionally related. These two mechanisms, 'somatic compliance' and symbolization, are not mutually exclusive, and in each case of conversion disorder, there is a relative contribution of each mechanism.

Conclusion: We will look at the relative contribution of each of the above mechanisms to the creation of the tremor in the case presented, integrating the various theories (hypnotic – network-based model, the dysexecutive model, predictive coding theory). We will further formulate the case through Freud's model of psychogenic visual disturbances, according to which the neurological infrastructure can serve either an emotional or a physiological-neurological function but not both simultaneously. The two functions compete for who will utilize (or exploit) the anatomical substrate. We argue that the therapeutic process enabled the physiological function to regain control of the motor apparatus leading to recovery.

CROSS-SPECIES HOMOLOGIES IN PATTERNS OF LARGE-SCALE FUNCTIONAL BRAIN NETWORK DECLINE ACROSS AGING MICE AND HUMANS

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Background: Suicide attempt is a psychiatric emergency that can be treated with different approaches. Understanding of patient- and physician-related determinants of selected treatment may help to identify sources of bias and improve clinical care.

Objective: To evaluate the demographic predictors of psychiatric intervention in the emergency department (ED) following a suicide attempt.

Methods: We analyzed all ED visits following suicidal attempts carried out by adults between 2017-2022. Two logistic regression models were built to examine whether patient and psychiatrist's demographic variables can predict 1) the clinical decision to provide a continued psychiatric intervention and 2) the setting for the psychiatric intervention (inpatient or outpatient)

Results: In total, 1,325 ED visits were evaluated, corresponding to 1,227 unique patients (mean age; 40.47±18.14 years, 550 men [41.51%]; 997 Jewish [75.25%]), and 30 psychiatrists (9 men [30%]; 21 Jewish [70%]). Demographic variables had a minor effect on the decision to intervene. However, the type of intervention was strongly associated with demography, with a significant interaction between patient and psychiatrist's ethnic identities. Further analysis revealed that Arab psychiatrists preferentially referred Arab patients to outpatient over inpatient treatment.

Conclusions: The results indicate that while demographic variables, and specifically patient and psychiatrist's ethnicity, do not affect clinical judgement for psychiatric intervention following a suicide attempt, they do play a major role in selecting treatment setting. Further studies are required to better understand the causes underlying this observation and its association with long-term outcomes. Yet, acknowledging the existence of such bias is a first step towards better culturally mindful psychiatric interventions.

CHILDREN AND ADOLESCENTS WITH ADHD DURING THE COVID-19 PANDEMIC IN ISRAEL

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Emerging research points to great ramifications of the COVID-19 pandemic on various aspects, including children's mental health and functioning. The present article consists of two studies, aimed to explore the pandemic implications on Israeli children and adolescents diagnosed with Attention Deficits Hyperactivity Disorder (ADHD). A total of eighty-one youth aged 6-18 participated in these two studies, recruited from the psychiatric outpatient clinic at SCMC in Israel. Study 1 (n=39) prospectively examined total difficulties, emotional, hyperactivity/inattention, conduct, and peer relationships problems before the pandemic outbreak and twice more during the pandemic, among a group of youth with ADHD and a psychiatric control group. Study 2 (n=42) examined clinical severity and functioning, through parental and therapists' reports, among a different group of youth with ADHD, during the two pandemic waves. In study 1, both groups experienced a significant increase in peer problems, nevertheless, children diagnosed with ADHD improved in hyperactivity/inattention symptoms over time. In study 2, children's clinical severity was significantly improved in the second wave, as reported by their parents, however, no change over time was reflected in therapists' reports. These findings strengthen and support previous literature, that mental health professionals and parents' notion the child's mental health differently. The integration of the two studies enabled an extensive outlook from various perspectives, at the impact of a chronic stressor on ADHD youth. A parental perceived improvement during a global health crisis, illuminates the daily familial challenges involved in coping with a child's ADHD and encourages the development of focal interventions.

LEARNING AND COGNITIVE FLEXIBILITY PROTOCOLS IN THE INTELLICAGE SYSTEM

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Developing and investigating rodent models through behaviour-based paradigms has successfully facilitated the understanding of complex psychological disorders. The IntelliCage (IC) (TSE Systems) is an apparatus which eliminates many of the non-experimental variables impacting rodent behaviour which traditional methods involve, including subjective scoring of behaviour, manual transportation from the home environment, and misalignment with biological activity cycles caused by running tests at pre-determined times and during their inactive daylight hours. These are all eliminated by automating experimentation and data collection in the rodent's home environment. The cage includes four corner pieces with two drinking points each, and a control unit that enables setting up experiments that runs constantly. This allows tracking the rodent's performance continuously while they have complete autonomy as to when they engage with the experiment.

The versatility and consistency of the IC have allowed for the successful competition of a wide variety of behavioral essays such as long-term and circadian activity, learning and learning reversal (spatial and temporal learning tasks), anhedonia and taste aversion, among plenty other essays, both traditional and novel. This make the IC a great tool for behavioral phenotyping in both healthy and disease model animals such as Alzheimer, Schizophrenia, Autism, and other cognitive and social phenotypes are relevant.

One flexibility protocol based on drinking access is the side preference protocol, in which the mice are presented with an alternating rule to learn. They are first granted access to drinking water on the right side of either of the four corners, and then presented with a left-to-right rule change, with an alternation occurring after all mice indicate an understanding of the new rule (passing chance level of success with significance), usually every two days. The number of trials each mouse took to pass the learning criteria was used to rank the performance of the mice. This experiment was run on two groups of mice, control vs ketamine-treated schizophrenia model, with the expectation of deficits in the cognitive flexibility of the treated group. The initial learning of the treated group was indistinguishable from that of the control ($t(12.19)=0.4543, p=0.6576$) but the average ranks of the mice in the following three rule changes were significantly higher in the treated group ($t(14)=2.616$, $p=0.0203$), indicating cognitive flexibility deficit. Additionally, the treated group showed a different, slower, learning curve for the alternating sessions from that of the control group.

CLOZAPINE PLASMA LEVELS ASSESSMENT USING A POINT OF CARE DEVICE: FEASIBILITY AND VALIDITY

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Background: Clozapine is the only drug approved for refractory-psychosis; however, the compound is underused. Therapeutic drug monitoring (TDM) can assist overcoming some of the barriers through personalized dosing. Blood levels are associated with clinical response, identification of drug-related toxicity and adherence monitoring. Clozapine TDM is usually performed by LC-MS/MS, hence requiring venous blood sample and multi-step laboratory outsourcing. New and advanced technologies can enable rapid and easier measure of clozapine serum levels. MyCare InsiteTM by Saladex© is a Point of Care (POC) device based on capillary sampling immunoassay. The test is conducted as an office procedure and the results are received immediately following finger prick.

In this exploratory study we assessed the validity of the device in comparison to the standard LC-MS/MS method. Additionally, we assessed the feasibility of this methodology among patients and healthcare practitioners.

Methods: Study population included 44 patients, diagnosed with schizophrenia-spectrum disorders and treated with clozapine of a stable dose. Participants were assessed using questionnaires. Thereafter venous and capillary blood samples were collected and analyzed. Additionally, healthcare providers filled clinical and feasibility questionnaires. Clozapine plasma levels were compared between methods using linear regression model.

Results: Of the total sample (44 patients), 61% were males and 39% females. Mean age was 43±12 years and mean daily clozapine dose was 293±134 mg/day (ranging between 50-600 mg/day). According to clinical global assessment, most of the patients (79%) presented moderate to severe psychotic symptoms as well as negative symptoms. Moderate or severe side effects were reported among 37% of them. Linear regression model of TDM measurements from the two methods demonstrated high correlation with R2=83% ($p<0.0001$) and mean dispense of 26±162 ng/dl (median of 4.5 ng/dl). More than 60% of the patients found the TDM to be important. Most of the participants (58%) favored the capillary sampling, with 11% even claimed that testing method would affect their adherence to TDM. A larger portion (72%) strongly preferred to be tested in the physician's office. Healthcare providers also thought patients would prefer the capillary testing.

Discussion: Clozapine TDM is a valuable tool to ascertain efficacy and safety of treatment. The POC device offers a rapid, accessible and satisfactory measure of clozapine serum levels. Both patients and healthcare providers reported preference of capillary sampling as well as office procedure TDM. Using POC immunoassay may contribute to increase treatment adherence and therefore improving rate and outcome of clozapine treatment among this difficult-to-treat population.

THE IMPLEMENTATION OF CHROMOSOMAL MICROARRAY TECHNOLOGY AND FRAGILE X CARRIER TESTING IN THE GENETIC DIAGNOSIS OF PATIENTS DIAGNOSED WITH SCHIZOPHRENIA

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Objectives: To elucidate the diagnostic yield of chromosomal microarray (CMA) and Fragile X testing in patients with Schizophrenia.

Schizophrenia is a genetic disease, and about 11 sites of chromosomal Copy number variants have been discovered.

Fragile X syndrome (FRAX) is an X- linked neurodevelopmental condition caused by a CGG triplet repeat expansion within *FMR1* (> 200). 55 to 200 repeats- *FMR1* premutation, with psychiatric symptoms including schizophrenia in females.

CMA detects submicroscopic chromosomal changes and is pathological in 10–30% of schizophrenia patients.

Methods: Patients with schizophrenia (10 adults aged 18-60 YO, and 2 children aged 9-10 YO) were tested for FRAX and CMA findings. The children also underwent epilepsy and neurodevelopment genetic panel.

Results: 7 adults with CNVs and 2 female patients with FRAX permutation were detected. One child's CMA showed 22q11 microdeletion, the other child's CMA was normal, but genetic panel for epilepsy and neurodevelopment showed CLCN6 c.1622C>T (p.Thr541Met) de novo mutation (associated with epilepsy and neuropsychiatric disorders). The detection rate by CMA was 70% among adults, and 50% among children. Among the abnormalities detected- the CNVs 22q11 microdeletion, 21p22.3 duplication, 15q11.2 duplication, del6q26, 5p15.33 duplication, 3q24 duplication, 2q32.1 microdeletion and microduplication. FRAX testing was positive in 2 female patients.

Conclusions: The CMA diagnostic tool can be used in diagnosing schizophrenia, assessing prognosis, adjusting pharmacological treatment and medical follow-up and providing genetic counseling. Female FMR1 premutation carriers are at increased risk of developing schizophrenia and could benefit from carrier testing and subsequently- from improved medical follow up and assistance with family planning.

THE LONG SHADOW OF PRENATAL SYMBOLIC PARENTING: DISENTANGLING PARENT AND CHILD INFLUENCES ON CHILD MENTAL HEALTH OUTCOMES

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Background: The notion that parenting has a critical influence on child mental health (MH) outcomes has dominated the field of developmental research for decades. However, current approaches emphasize the role of the child in shaping their environment, including the parenting they receive (Davidov et al., 2015). Parenting is thus perceived to be (to a substantial degree) a response to child behaviors and temperament tendencies (Avinun & Knafo, 2014). At the same time, our previous work has documented associations between parents' expected parenting practices, referred to as symbolic parenting *in utero*, and the child's expected temperament already in the prenatal stage (Abramson et al., 2016).

Therefore, the question of whether (and to what extent) parent-driven elements of parenting affect children is particularly challenging. To address this question, following parent-child dyads from the prenatal period could hold important promise. More specifically, we suggest examining expecting-parents' symbolic parenting: ideations of their own parenting practices, including intentions, plans and beliefs of how individuals imagine themselves to feel and behave towards their future. Such symbolic parenting could be viewed as the initial substrate, which has yet to become intertwined with (and affected by) the child itself; thus, it represents effects individuals bring to parenting prior to any actual influence by the child. This could help disentangle parent-originated influences on child MH, from parental influences that operate as a response to the child. This will shed light on causality and mechanisms of parental influences on children, by identifying the unique influence stemming from parents to child MH.

Methods: We longitudinally followed families from the prenatal stage (N=400 families with postnatal data in at least one wave). Israeli pregnant women and, when possible, their partners, were recruited while awaiting a prenatal ultra-sound test at a number of clinics and were asked to fill out questionnaires. Families were followed at 9, 18, 36 and 60 months. Importantly, we have incorporated both maternal and paternal reports, a critical issue given the neglect of studying fathers in developmental research.

Symbolic parenting was assessed using adjusted prenatal versions of the Parent Acceptance-Rejection/Control Questionnaire-Short Form (Rohner & Khaleque, 2005), administered to mothers and fathers prenatally.

Child MH was assessed using the Strengths and Difficulties Questionnaire (Goodman, 1997), which assesses internalizing (emotional symptoms and peer relationship problem) and externalizing (hyperactivity/inattention and conduct problems).

Findings: The PARQ includes subscales of the following parental behaviors: warmth/affection, hostility/aggression, indifference/neglect, undifferentiated rejection, and control. Items are rated on a 4-point Likert-type scale (1=almost never true to 4=almost always true). A principal component analysis with oblimin rotation yielded two factors explaining 61% and 66% of the variance for mothers and fathers, respectively. The first factor contrasted hostility/aggression, indifference/neglect, and undifferentiated rejection, which loaded positively on it (loadings ranging from .65 to .81), with warmth, which loaded negatively (–.63, for mothers, –.73 for fathers). This factor was therefore referred to as *parental negativity*. The second factor reflected mainly the control variable, which loaded strongly on it (mothers, .87, fathers, .95). This factor was therefore referred to as *parental control.* Factors for both mothers and fathers had acceptable internal consistency (α=.64–.65). Maternal symbolic negativity predicted both internalizing scales at age 5 (peer problems, $r(152)=.19$, $p<.05$; emotional problems, $r(152)=.18$, $p<.05$). Paternal symbolic negativity, and symbolic control (maternal and paternal) did not predict child outcomes.

Implications: By examining symbolic parenting, we will address an important controversy in the field of child MH: to what extent parent-originated influences effect child outcomes. Incorporating paternal influences has importance for both research and practice, as studying fathers has been substantially neglected in developmental research. These findings could also have important implementations in designing informed interventions and policies, by studying parents as early as the prenatal stage, while accounting for the different components of parental behavior, as well as possible differences between mothers' and fathers' effects.

STIGMA AND LEVEL OF FAMILIARITY WITH MEDICATION ASSISTED TREATMENT (MAT) AMONG ALL SPECIALIST PHYSICIANS IN ISRAEL

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Background: To minimize the risk of an opioid epidemic in Israel, preparedness is essential. We evaluated physicians' objective knowledge, level of stigma, and approach with respect to prescribing opioids, and their self-reported familiarity with substance use disorder risk factors, identification of patients with substance use disorder, and knowledge about medication assisted treatment (MAT) for opioid use disorder.

Methods: Anonymous computerized questionnaires were distributed nationally to physicians by the Israel Medical Association (IMA). Knowledge, stigma and approach were scored (ranged between 0 and 100%). High scores were defined as being in or above the 75th percentile.

Results: 18,651 emails were sent, but only 249 physicians responded. Of them, 58.6% prescribe opioids, 32.1% prescribe cannabis, and 18.5% knowingly encounter patients who suffer from substance use disorder. 42.6% of them self-reported having limited knowledge about MAT. Using logistic regression, the high knowledge group (scored≥60) was characterized by daily encounters with patients who suffer from substance use disorder, and those who are very familiar with MAT. The high stigma group (scored≥35) was characterized by physicians who prescribe opioids, but who self-reported having limited knowledge regarding MAT. The high approach group (scored≥40) was characterized by those who prescribe opioids and/or cannabis, but who self-reported having limited knowledge regarding MAT despite reporting being able to identify substance use disorder.

Conclusions: Notable gaps in knowledge and approach were observed among the minority of physicians who participated in this survey. High stigma was most evident among physicians who prescribe opioids but, importantly, who had limited knowledge specifically regarding MAT. An educational intervention is highly recommended to reduce stigma and increase referrals of patients for MAT, the most effective treatment for opioid use disorder.

THE THERAPEUTIC POTENTIAL OF CANNABIDIOL (CBD) IN ALZHEIMER'S DISEASE

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Background: Progressive impairment of memory and cognition is a key clinical feature of Alzheimer's disease (AD), which is characterized by the accumulation of amyloid β-protein (Aβ) plaques, tau hyperphosphorylation, neuroinflammation, and neuronal degeneration that eventually manifest in the form of neuropsychiatric symptoms including depression and anxiety.

Cannabidiol (CBD) is a safe, non-psychoactive phytocannabinoid that exhibits immunomodulatory activity in neurodegenerative disease and may ameliorate AD symptoms and slow cognitive decline.

In this study, we aimed to examine whether chronic treatment with CBD can prevent cognitive deficits and neuropathology changes in a rat model of sporadic AD pathology.

Methods: Adult male rats received intracerebroventricular (ICV) injection of streptozotocin (STZ, 3 mg/kg) followed by 10 mg/kg CBD treatment for 2 weeks. After which, cognitive and emotional functions were tested, and correlated with alterations AD markers and neuroinflammation in the hippocampal-prefrontal (PFC) pathway.

Results: Rats that were injected with streptozotocin (STZ), a widely used rat model of sporadic AD, exhibited impaired performance in hippocampal-dependent object location and PFC-dependent recognition tasks. In the social interaction test, STZ-vehicle rats demonstrated decreased sociability index, and increased anxiety-like behavior in the open field test. Importantly, chronic treatment with CBD restored these STZ-induced impairments in behavior. We are currently studying the correlation between the behavioral phenotype and specific inflammatory mediators in the hippocampal-PFC circuit.

Conclusions: Our findings show that CBD can prevent STZ-induced impairment in cognitive and emotional functions. Further research is ongoing to understand the underlying mechanism.

THE ASSOCIATION BETWEEN AUTISM SPECTRUM DISORDER AND CONGENITAL MALFORMATIONS: A POPULATION-BASED NESTED CASE-CONTROL STUDY

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Background: Early intervention can improve prognosis and functioning in individuals with Autistic Spectrum Disorder[1,2], and more than 60 perinatal and neonatal factors have been identified so far as risk factors for later occurrence of ASD[3,4]. Our goal in this study is to test whether specific congenital malformations (CM) detected at birth are associated with increased likelihood of autism spectrum disorder (ASD).

Methods: A case-control study nested within a 12-year (1993-2005) birth cohort derived from the Israel National Birth Registry. The study cohort included all registered ASD cases (n=2,099) and 1:1 age- and sex- matched controls. Cases were ascertained using the autism registry of the Israeli Ministry of Social Affairs (MoSA). Registration of a childhood autism in MoSA required in order to received government founded health and social services.

Results: Overall, CM were more prevalent in the ASD group as compared with controls [odds ratio (OR) 1.75, 95% confidence interval (CI) 1.29-2.38]. This association remained robust after adjusting for birth weight, parental age, parental ethnicity, and maternal immigration [adjusted OR (aOR) 1.71, 95% CI 1.17-2.50]. The most prevalent CM types among the ASD group were circulatory system (2.1% vs. 1.2% among controls) and urogenital organs (1.8% vs. 0.8%). The association between ASD and genital CM was limited to males and persisted in the adjusted models (aOR 2.24, 95% CI 1.16-4.34). In the stratified by sex analysis, we found a strong association between all non-genitourinary CM and ASD in females, (aOR 3.47, 95% CI 1.31-10.65). A trend for increased risk for circulatory malformations in females with ASD was observed in crude and adjusted models.

Conclusion: CM, most notably genitourinary in males, and circulatory in females, are more prevalent in newborns later diagnosed with ASD, as compared with age- and sex- matched controls. Confounding by sex is implausible because of the matched design. Our results might be explained in part by unmeasured or hidden confounders, such as maternal medical conditions and in-utero exposure to medications. However, given strong crude associations, CM may be important markers for the need of early screening and intervention. These sex-specific CM might represent useful pre- and postnatal markers of ASD, and their presence in newborns at-risk of ASD might indicate earlier and more frequent neurodevelopmental assessments. Our findings might also guide future research of plausible genetic, epigenetic, and prenatal underpinnings of ASD.

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MICROGLIA AND MYELIN ALTERATIONS: A POTENTIAL LINK IN WILLIAMS SYNDROME PATHOLOGY

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Microglia are the immune cells of the brain, involved in circuit sculpting, myelination, plasticity, and cognition along the development. Our lab recently showed multifaceted myelination deficits related to Williams syndrome (WS), a genetic neurodevelopmental disorder caused by a heterozygous microdeletion on chromosome 7q11.23. These myelination deficits, a result of general transcription factor II-i (*Gtf2i*) deletion in forebrain excitatory neurons, were mediated by neuron-glia abnormal interactions and were shown to be ameliorated following administration of the promyelination FDA-approved drug, clemastine. Here, we studied microglial properties in the cortex of this mouse model for WS (referred to herein as *Gtf2i* cKO) and unveiled multifaceted deficits in microglial properties. In early postnatal stage of our mouse model, microglia in the cortex were found to be in higher number, increased activation state, and altered inflammation-related properties as compared to controls. In young adult mouse model, microglia in the cortex demonstrated an under-activated state compared to controls, as demonstrated by altered transcripts expression and impaired morphology. Because clemastine was effective in improving myelination, and since clemastine was previously shown to bind directly to microglia and reduce their activation, we administrated systematically clemastine from early postnatal stage and examined its effects on microglia. Clemastine decreased microglial inflammation in the treated mouse but not in treated controls. Our data implicate that microglial properties are altered at early postnatal stage in mouse model for neurodevelopmental disorder, and that manipulating microglia at early postnatal stage may be beneficial in reducing their inflammation state and neurobiological deficits associated with brain development.

REAL LIFE COURSE AND EFFECTIVENESS OF MELATONIN TREATMENT FOR SLEEP DISORDERS IN CHILDREN WITH ASD

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Introduction: Sleep disturbances are reported in >50% of children with autism spectrum disorder (ASD). Melatonin is considered the most effective pharmacological treatment for sleep disturbances however, real life data about the course and effectiveness of melatonin in children with ASD is lacking.
Methods: We evaluated the course and effectiveness of immediate-release melatonin treatment among 78 children with ASD from the Azrieli National Center for Autism and Neurodevelopment Research. Parents of these children completed a phone-questionnaire about the course of treatment (e.g. treatment duration, doses, side effects etc.) and its effectiveness (in a scale of 1-5) on sleep quality and behavior. Key demographic and clinical characteristics, including the severity of sleep disturbances based on the CSHQ questionnaires, were compared between melatonin “responders” ("overall effectiveness score">3) and non-responders.
Results: Overall, 72% of the children who were treated with melatonin, were defined as responders. Of these, 86% had an improved sleep onset while only 43% reported its effectiveness on night awakenings. Furthermore, 32% of these children discontinued treatment, mostly due to lack of effectiveness (31%) or due to mild side effects (15%). Interestingly, melatonin responders did not differ from non-responders in their overall CSHQ score. However, they required more “very substantial support” according to the DSM5-A criteria (60% vs. 32%; p-value=0.04), and had higher tendency to have comorbid ADHD and to be prescribed other psychoactive drugs.
Conclusions: Our findings suggest that melatonin treatment is mostly effective in children with more severe autistic and comorbid symptomatology. This may be due to the greater melatonin deficiency in these children, a factor that has been shown to be associated with more severe autistic symptoms. Further studies are needed to validate these findings in larger samples and further explore additional biological and clinical factors associated with melatonin effectiveness in children with ASD.

AGE RELATED DUAL EFFECT OF ULTRA-LOW DOSE THC ON LONG-TERM MEMORY

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Δ9-tetrahydrocannabinol (THC) is emerging as a promising therapeutic agent. While cannabis has its negative effects, including anxiety and cognitive functions. In a recent study, we found that a single injection of an ultra-low dose of THC (ULD-THC; 0.002mg/kg) significantly improved cognition in 24 month old mice, and had a negative effect on young mice. In order to better understand the age dependent dual effect of ULD-THC, this study aims to characterize the cognitive response to ULD-THC at several time-points, and its underlying biological mechanism. This could help in understanding when the therapeutic effects of THC can be helpful and when they can be harmful.

ICR female mice (20 mice per group) were given a single dose of ULD-THC (0.002mg/kg) or vehicle i.p. and examined for short and long-term memory, spatial memory and strategy shifting at 3 different time points: early adulthood (6 months), late adulthood (12 months) and old age (18 months). After which, Hippocampus and Preforntsal tissues were collected and will be examined for the expression of various genes (using qPCR) and proteins (using western blot) involved in the neurotrophic and serotonergic system. Our results indicate that the shifting point between the harmful and beneficial effect of ULD-THC is around 12 months. Healthy Mice receiving ULD-THC at 6 months showed cognitive decline after the ULD-THC treatment, while mice at the age of 18 months with age-related cognitive decline benefited from the treatment. To conclude, ULD-THC may be used in the future as a medicine for neurodegenerative diseases associated with old age, but with caution as we saw that it can cause cognitive damage at a young age. We discovered that the critical age for reversing the cognitive response to THC is 12-month-old mice. More research is needed to understand the mechanism underlying this phenomenon.

QUANTITATIVE MRI BIOMARKERS OF PATHOLOGY IN A POLY I:C RAT LACTATIONAL MODEL OF SCHIZOPHRENIA AND DEPRESSION – TOWARDS RADIOLOGIC IDENTIFICATION OF PSYCHIATRIC DISORDERS

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Schizophrenia and depression have a significant impact on the quality of life. Despite the lack of objective clinical markers of these conditions, it is clear that the pathophysiology of these conditions reflect brain pathology that is yet to be revealed. Quantitative MRI (**qMRI**) can map various properties linked to the tissues' microstructure and biochemistry and improve MRI's accuracy and sensitivity to these pathologies and their manifestations. Post-natal Poly I:C is an established neurodevelopmental rat model for schizophrenia and depression. The essential advantage of this model is the ability to include sex as a variable by inducing sex-dependent functional brain changes in rats.

In this, we investigated the utility of qMRI to identify new radiologic markers of schizophrenia and depression in a Poly I:C rat model. Forty rats were included: male versus female and Poly I:C versus control (10 rats per group). qMRI features were collected for all groups, and a logistic regression classifier was trained using multiparametric multi-region data. The model's accuracy reached 80%, identifying specific features and brain regions that differed between poly I:C and the control group and between males and females. Above all, the mean diffusivity (**MD**) map returned in both males and females as a vital indication. MD is a measure of membrane density that may be damaged by demyelination, axonal damage, and inflammation.

The added value of this new multi-parametric, multi-region, radiomic approach lies in identifying pathology beyond structural deformations and improving the sensitivity to microstructural and neurochemical pathology.