therapeutics mainly target the positive symptoms, cognitive symptoms are often not effectively treated. Our recent discovery that mGlu3 and mGlu5 can act as signaling partners to modulate synaptic plasticity in the prefrontal cortex led us to hypothesize that mGlu3 may subserve similar functions to those of mGlu5 during hippocampal synaptic plasticity and hippocampal-dependent behaviors.
Methods: We directly tested this hypothesis using acute slice electrophysiology to investigate basal synaptic transmission as well as long-term plasticity in hippocampal slices. To test cognition, the associative fear learning behavioral assay, termed trace-fear conditioning, was used. C57bl/6 mice or CaMKII-cre;mGlu5-/- mice were used in all studies.
Results: We report that mGlu2/3 activation enhances hippocampal theta-burst (TBS)-induced LTP but was without effect on group I mGlu agonist-induced LTD The group II mGlu agonist enhancement of TBS-LTP was blocked by antagonists of mGlu3 or mGlu5.
We next tested downstream mechanisms of group II mGlu induced LTP by chemically activating LTP with the group II agonist LY379268 in combination with selective antagonists. We verified the LTP was induced by mGlu3 activation but not mGlu2 using selective negative allosteric modulators of each subtype. Furthermore, mGlu5 negative allosteric modulation with MTEP blocked mGlu3-LTP, and conversely the mGlu5 positive allosteric modulator, VU0092273, enhanced mGlu3-LTP. The cannabinoid receptor type 1 antagonist AM251 was also capable of blocking mGlu3-LTP, suggesting cannabinoid signaling mechanistically drives this LTP.
Having confirmed a role for mGlu5 in the mGlu3-LTP, we next verified that postsynaptic mGlu5 located on pyramidal neurons was necessary for mGlu3-LTP by utilizing CaMKII-cre;mGlu5-/- mice. It was found that hippocampal slices from these mice showed no enhancement of LTP when LY379268 was bath applied alone or in combination with TBS-stimulation. Behaviorally, we discovered that selective activation of mGlu3 by systemically injecting the group II mGlu agonist in combination with a selective mGlu2 negative allosteric modulator, VU6001966, causes an enhancement in the acquisition of trace-fear conditioning learning. This was also confirmed to be dependent on mGlu5 as both systemic pharmacological inhibition or genetic deletion of mGlu5 abolished this learning enhancement. Further testing of the ability of mGlu3 activation to augment other cognitive tasks is currently underway.
Discussion: These results taken together demonstrate mGlu3 enhances hippocampal LTP and hippocampal-dependent learning through mechanisms that involve both mGlu5 and CB1 receptor activation. This work provides a basic biological mechanism and preclinical therapeutic validation for mGlu3 as a target for neurological disorders in which cognition is disrupted such as schizophrenia.

T40. GPR52 AGONISTS REPRESENT A NOVEL APPROACH TO TREAT UNMET MEDICAL NEED IN SCHIZOPHRENIA

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Background: There are currently no treatment options for key symptom domains in certain psychiatric and neurological diseases. For example, antipsychotics effectively treat the positive symptoms of schizophrenia, however both the cognitive impairments associated with schizophrenia (CIAS) and negative symptoms, both key predictors of functional outcome, are not treated by current therapies. Additionally, psychotic symptoms associated with neurological diseases such as Alzheimer's Disease (AD) are not adequately treated with current antipsychotics. Therefore, novel mechanisms to address these unmet medical needs are urgently required and are under investigation.
GPR52 is a Gs-coupled orphan g-protein coupled receptor which has an intriguing pattern of brain expression. In cortex, GPR52 is expressed primarily on glutamatergic neurons and co-localized with the Gs-coupled D1 receptor (D1R). Deficiencies in D1R activation are associated with both cognitive deficit and negative symptoms of schizophrenia. In contrast, in the striatum, GPR52 is almost exclusively co-expressed with the Gi-coupled D2 receptor (D2R), which mediates the reduction in positive symptoms by antipsychotics. Based on GPR52's functional coupling and co-localization, agonists may be predicted to resemble D1R agonists in cortical regions, thus treating cognitive or negative symptoms, while resembling D2R antagonists in striatal regions. Thus, GPR52 agonists have the potential to provide a novel therapeutic strategy for the currently untreated CIAS and negative symptom domains in addition to the psychotic symptoms of AD.
Methods: To assess the antipsychotic potential of GPR52 agonists, they were tested for their ability to decrease psychostimulant-induced hyperlocomotion. The efficacy of GPR52 agonists for CIAS and sociability, an aspect of negative symptoms, was assessed in the sub-chronic phencyclidine (scPCP) model for schizophrenia, known to induce long-lasting cognitive and social behaviour deficits, in addition to a reduction in parvalbumin-positive GABAergic interneurons in hippocampus and pre-frontal cortex. Rats were treated with PCP twice daily for 7 days followed by 7 days washout and then tested in the attentional set shifting task (ASST) for executive function and the social interaction test for sociability respectively following treatment with a GPR52 agonist.
Results: GPR52 agonist 1 dose-dependently reversed psychostimulant-induced hyperlocomotion in rats at doses which were behaviorally quiescent when administered alone. Additionally, GPR52 agonist 2 showed a robust, dose-dependent rescue of scPCP induced deficits in the extra dimensional shift phase of the ASST, achieving significance after a 4 mg/kg p.o. application. Likewise, GPR52 agonist 2 significantly rescued scPCP induced deficits in social interaction at identical doses as in ASST without effects on object exploration or locomotor activity.
Discussion: GPR52 agonists were efficacious in animal models assessing the three main symptoms domains associated with schizophrenia. Efficacy in ASST and SI demonstrate both pro-cognitive efficacy and restoration of an aspect of negative symptoms, respectively, in a well-established model inducing behavioral and neuropathological deficits associated with schizophrenia. Furthermore, GPR52 agonists reduced psychostimulant-induced hyperlocomotion, an effect associated with antipsychotic efficacy. Taken together, these data demonstrate the potential of this innovative mechanism to simultaneously treat the three core symptoms domains of schizophrenia as well as potentially treat the psychotic symptoms associated with other neurological disorders.

T41. MODIFIED COGNITIVE BEHAVIORAL THERAPY FOR ELDERLY PATIENTS WITH SCHIZOPHRENIA: A RANDOMIZED, CONTROLLED PILOT TRIAL

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Background: An European society growing older sets the need to explore treatment options for elderly patients. Here we aimed to gather evidence on the effectiveness of a modified cognitive behavioural therapy (mCBT) in elderly schizophrenia patients as compared to treatment as usual (TAU).
Methods: 43 schizophrenia patients > 55y (mean 60 y), were assessed in a randomized, single blind controlled pilot trial with parallel groups: TAU+mCBT vs. TAU and intention to treat (ITT) last observation carried forward (LOCF) analysis. Subjects were recruited in Germany among

in- and outpatients. MCBT comprised 30 sessions in 9 month, and a 6 month follow-up including a) physical and social activation, b) problem solving c) social skills. Primary outcomes were pre/post change in either PANSS total score, UPSA-brief score or Calgary Depression Scale for Schizophrenia.
Results: From 43 patients, 40 were randomized. 15 mCBT and 16 TAU-patients comprised the ITT sample. None of the primary outcome measures reached significance. When assessing effect sizes we found little pre-/post change in PANSS total score (d=0.14) and the UPSA-brief (d=0.14). Depression symptoms however improved with treatment (pre/post d=0.75 and pre/FU d=0.52). Among secondary outcomes, global assessment of functioning significantly improved in the mCBT-group pre/post (d=.074) and pre/follow-up (d=.080).
Discussion: Our results provide evidence for the feasibility of a sufficiently powered phase-III study targeting depressive symptoms and global functioning in long-term treated elderly schizophrenia patients. A history of about twenty years of pharmacological treatment does not imply there is no room for improvement in depression and global functioning following a modified cognitive behavioral therapy in this specific patient group. Supported by the German Federal Ministry of Education and Research (BMBF-01GV0909); ICTRP/DRKS: DRKS00003623.

T42. WHEN SHOULD EARLY INTERVENTION START, AND FOR HOW LONG SHOULD IT LAST?

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Background: Early intervention in psychosis facilities have often failed to integrate the two main elements of early intervention. While some facilities have focused on early, and have had Duration of Untreated Psychosis (DUP) as their main target, others have focused on the intervention and the treatment provided when patients were diagnosed. As both DUP reduction and specialized early intervention (SEI) has proved to have an effect on the treatment of patients with first-episode psychosis one could hope of a synergetic effect if the two strategies were integrated. In this study, we use data from a randomized clinical trial testing the effect of prolonged early intervention (5 years) compared to standard specialized early intervention (2 years). Overall the study found that both treatment groups remained stable or improved in psychopathology, functioning and cognition and that there was no further beneficial effect of the prolonged the treatment. Participants had a long DUP (median 52 weeks). For this specific sub-study we hypothesized that patients who were treated early in their course of illness would have a beneficial effect of the prolonged treatment compared to those who only received 2 years of specialized treatment.
Methods: 296 participants with a psychotic diagnosis within the schizophrenia spectrum (ICD 10 – F2x, excluding F21) were included. DUP start was assessed from first psychotic symptom equivalent to 3 or above on a global SAPS item. DUP stop was when patients started antipsychotic treatment or specialized early intervention treatment. To assess if there were a delay within the mental health referral system we used the national register to identify when participants first were diagnosed with a schizophrenia spectrum diagnosis and calculated the time until they started SEI treatment. Finally, we added the DUP and the treatment delay together to assess the time from first psychotic symptom until the start of adequate treatment (both antipsychotic medication and specialized early intervention treatment), called total treatment delay. We analyzed if there were a treatment effect for participants with DUP shorter than 3 months (n=79) and if there were an effect for participants with a total treatment delay shorter than 6 months (n=54). We used multiple imputations to correct for missing data at the follow-up. The data were analyzed using binary logistic regression for the dichotomous variables and linear regression for the continuous variables.
Results: At the five year follow-up, the participants who had a short DUP and had received 5 years of SEI treatment had lower psychopathological scores and higher level of functioning and cognition than those who only received 2 years of SEI treatment. The difference was not significant. For the patients who had a short total treatment delay there was a clear trend favoring the prolonged treatment and for negative symptoms there was a near significant effect of the prolonged treatment (estimated mean difference -0.61, 95% CI -1.2;0.006, p=0.05).
Discussion: Our findings are results of a sub-group analysis and should be interpreted with caution. Even if the results from the main trail did not find a significant effect of prolonged SEI treatment this sub-group analysis indicates that some of the explanation could be the delay prior to the start of treatment and that there could be a beneficial effect of the prolonged treatment if it actually were provided within the early years of illness and not just in the early years after diagnosis.

T43. TRANSCRANIAL DIRECT-CURRENT STIMULATION (TDCS) IN PATIENTS WITH ULTRA-TREATMENT-REFRACTORY AUDITORY HALLUCINATIONS

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Background: Transcranial direct-current stimulation (tDCS), a noninvasive neurostimulation treatment, has been reported to show improvements in treatment-resistant auditory hallucinations in patients with schizophrenia. tDCS administered over a limited number of sessions effectively produced lasting attenuation of auditory hallucinations in otherwise stable outpatients. It has also been shown that tDCS may be a useful intervention for ameliorating cognitive deficits in patients with chronic schizophrenia. The purpose of this study was to test tDCS for auditory hallucinations in ultra-treatment resistant schizophrenia to assess if this form of neurostimulation can alleviate treatment-refractory auditory hallucination symptoms up to 4 weeks after the final treatment. In addition, we also wanted to examine the effects of tDCS on cognitive functions.
Methods: 28 inpatients with DSM-V schizophrenia and long-standing treatment resistance and persistent auditory verbal hallucinations were recruited. Each individual participated in behavioral assessments at baseline, endpoint and follow-up [PANSS and Auditory Hallucinations Rating Scale (AHRS) and MCCB cognitive battery] and were randomized to receive active vs. sham tDCS treatments. For active treatment, patients had the inhibitory (cathodal) tDCS electrode placed over left auditory cortex relative to an excitatory (anodal) electrode placed over frontal cortex on the right side. tDCS treatments took place for 20 min twice daily for 5 consecutive days. Assessment batteries were repeated following the 4 weeks of treatment. The Chattanooga, dual channel CHA-1335 stimulator with two 7 × 5 cm (35 cm2) sponge electrodes soaked in a saline solution (0.9% NaCl) was used for the delivery of 2 mA current.
Results: A total of 28 subjects were enrolled (tDCS, n = 13; Control, n = 15). 20 subjects completed the trial. 3 subjects dropped out of the active tDCS treatment group, while 4 subjects did not complete the control treatment due to early discharge from the hospital. Most subjects were male (tDCS n = 10, 76.9%; Control n = 6, 40.0%). Length of present psychiatric admission ranged from 1–25 months, with a mode of 2 months (n = 12) and average of 2.9 months. Participating inpatients were on clozapine, haloperidol, paliperidone depot, fluphenazine decanoate, paliperidone, olanzapine, and risperidone as primary medications. Repeated Measures ANOVA showed a significant difference for the auditory hallucination total score, frequency and number of voices over time ($p < 0.05$) with greater reduction in scores observed for the tDCS group. Improvements were maintained after 4 weeks.