To address this important question, this study investigated the relationship between baseline cognitive performance and functional outcome between 6–12 months in a sample of CHR-P individuals using a machine-learning approach to identify features that are predictive of long-term functional impairments.

**Methods:** Data was available for 111 CHR-P individuals at 6–12 months follow-up. In addition, 47 CHR-negative (CHR-N) participants who did not meet CHR criteria and 55 healthy controls (HCs) were recruited. CHR-P status was assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS) and the Schizophrenia Proneness Instrument, Adult version (SPI-A). Cognitive assessments included the Brief Assessment of Cognition in Schizophrenia (BACS) and the Penn Computerized Neurocognitive Battery (CNB). Global, social and role functioning scales were used to measure functional status. CHR-P individuals were divided into good functional outcome (GFO, GAF ≥ 65) and poor functional outcome groups (PFO, GAF < 65). Feature selection was performed using LASSO regression with the LARS algorithm and 10-fold cross validation with GAF scores at baseline as the outcome variable. The following features were identified as predictors of GAF scores at baseline: verbal memory, verbal fluency, attention, emotion recognition, social and role functioning and SPI-A distress. This model explained 47% of the variance in baseline GAF scores. In the next step, Support Vector Machines (SVM), Linear Discriminant Analysis (LDA), Logistic Regression (LR), Gaussian Naïve Bayes (GNB), and Random Forest (RF) classifiers with 10-fold cross validation were then trained on those features with GAF category at follow-up used as the binary label column. Models were compared using a calculated score incorporating area under the curve (AUC), accuracy, and AUC consistency across runs, whereby AUC was given a higher weighting than accuracy due to class imbalance.

**Results:** CHR-P individuals had slower motor speed, reduced attention and processing speed and increased emotion recognition reaction times (RTs) compared to HCs and reduced attention and processing speed compared to CHR-Ns. At follow-up, 66% of CHR-P individuals had PFO. LDA emerged as the strongest classifier, showing a mean AUC of 0.75 (SD = 0.15), indicating acceptable classification performance for GAF category at follow-up. PFO was detected with a sensitivity of 75% and specificity of 58%, with a total mean weighted accuracy of 68%.

**Discussion:** The CHR-P state was associated with significant impairments in cognition, highlighting the importance of interventions such as cognitive remediation in this population. Our data suggest that the development of features using machine learning approaches is effective in predicting functional outcomes in CHR-P individuals. Greater levels of accuracy, sensitivity and specificity might be achieved by increasing training sets and validating the classifier with external data sets. Indeed, machine learning methods have potential given that trained classifiers can be easily shared online, thus enabling clinical professionals to make individualised predictions.

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**S65. THE ‘STRESS-SENSITIVE SELF’ IN PSYCHOSIS: A PILOT STUDY AMONG HEALTHY INDIVIDUALS OF A CHALLENGE (STRESS) TEST OF SELF-RELATED NEUROCognitive CAPACITIES**

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**Background:** Despite attempts to predict which clinical high risk (CHR) individuals will convert to schizophrenia (SCZ), current neurocognitive tests have yielded only modest results. Stress plays a pivotal role in the inception of psychotic symptoms. Accordingly, we have recently speculated that modest predictive success may be an outcome of the discrepancy between the neutral environment in which testing occurs and the stressful environments in which SCZ outbursts. According to this view, prediction of conversion to psychosis requires ‘stress’ tests analogous to those used in general medicine, such as examining cardiac activity under physical exertion. The purpose of this pilot study was to test this notion by developing and validating a ‘Stress-sensitive Self’ neurocognitive test. The focus on the self was chosen because disturbances of the basic self, such as impaired sense of agency (SoA) are central deficits in SCZ. We examined four hypotheses: (1) subjective ratings of stress will be associated with physiological markers of stress, (2) stress will impair judgments and metacognition of SoA, (3) the effect of stress on SoA will be related to the level of attenuated psychotic symptoms (APS), and (4) based on accumulating evidence relating cardiac signals to the bodily self, accuracy in SoA will be related to cardiac deceleration.

**Methods:** To test these hypotheses 14 healthy controls (HC) performed the ‘Virtual Hand’ (VH) task under two conditions; a neutral block and following a psychosocial stress induction in a ‘stress’ block. In the task they perform a movement with their hand, that is hidden from them, while on a monitor a VH is presented that performs the same movement. The movement is either presented simultaneously or with temporal delays. Participants judge whether the VH’s movement is identical to their actual movement (i.e. agency question) and rate their confidence (i.e. metacognition question). Heart rate (HR) was continuously recorded. Presence and distress associated with APS were assessed via the brief version of the Prodromal Questionnaire (PQ-B).

**Results:** Consistent with our first hypothesis, HR variability captured subjective ratings of stress, and the two were strongly correlated (r = -637, p = .014). Inconsistent with our second hypothesis, stress did not significantly alter sensitivity (d’) in recognition of the VH (F(1,12) = 13.3, p = .003). Moreover, it significantly improved, rather than impaired, metacognitive monitoring (i.e., the association between confidence judgments and the actual correctness of the answers) (F(1,12) = 10.64, p = 0.007, η²p = 0.47). Consistent with our third hypothesis, the beneficial effect of stress on metacognitive monitoring was smaller for HCs with high levels of APS, albeit not significantly so (r = -.28, p = .26). Finally, HR deceleration during VH presentation was significantly predictive of both SoA accuracy (F(1,12) = 13.3, p =.003, η²p = 0.53), and confidence in SoA judgments (F(1,12) = 10.64, p = 0.002, η²p = 0.52).

**Discussion:** The results of this pilot study provide mixed yet promising preliminary support for the notion of a ‘Stress-sensitive Self’ test. More specifically, they suggest that mild stress improves metacognitive monitoring judgments of self-agency, whereas an opposite trend was observed for healthy participants that reported higher scores of APS. In addition, they provide preliminary evidence for a pre-reflexive implicit physiological mechanism supporting the basic self, a mechanism that may be disturbed in SCZ. Ongoing studies are examining CHR’s performance on the ‘Stress-sensitive Self’ test and replicating the current results in a larger sample of HCs.

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**S66. USING UNITIZATION TO CIRCUMVENT RELATIONAL MEMORY DEFICITS IN SCHIZOPHRENIA**

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**Background:** Relational memory (RM) is disproportionately affected in schizophrenia. Unitization is a cognitive strategy that compensates for RM deficits by facilitating the combination of disparate pieces of information to form a single functional unit. Unitization has been effective in circumventing RM impairment in hippocampal amnesia and older adults with RM deficits when performing a Transverse Patterning (TP) task. We developed a brief intervention using unitization to circumvent RM impairment in individuals with schizophrenia when learning arbitrary item-relations in a TP task. We subsequently developed the Relational Trip Task (RTT), which uses pairs of real-life stimuli (faces, places, objects) and a
narrative frame for encoding to investigate if unitization generalizes to a more relatable real-life context.

Methods: Twenty-two individuals with an RM deficit and a diagnosis of schizophrenia or related disorder were pseudo-randomized to either the unitization or control condition, from which 19 completed all TP tasks and 17 completed RTT. TP performance was measured at screening. TP and RTT task performances were measured pre-post learning unitization. During the RTT-unitized task, participants created their own unitizations, with assistance (50% of the task) and on their own. The control group received unitization training following study participation. The TP-unitized control group results were included in the analysis.

Results: TP task performance (percentage of correct trials) did not significantly differ between control (M = 49%, SD = 13%) and unitization groups (M = 60%, SD = 18%) at screening (t(17) = -1.506, p = 0.15). A 2-way mixed analysis of variance (ANOVA) did not reveal a group-task interaction for unitization and control group accuracy in the four TP versions (F(3,51) = 2.38, p = 0.08). A main effect of task (F(3, 51) = 9.43, p > 0.001) was decomposed using Tukey HSD pairwise post-hoc analyses and showed significantly higher TP task accuracy following unitization (M = 85%, SD = 19%) compared to the TP task at screening (M = 55%, SD = 16% p > 0.001), before unitization (M = 61%, SD = 19%, p = 0.001) and when prompting self-unitization (M = 68%, SD = 28%, p = 0.04). No other significant differences in task accuracies were revealed. Group accuracies in the RTT were compared using a 2-way mixed ANOVA, and yielded a significant interaction between group and task accuracy (F(1,15) = 4.93, p = 0.042). Simple main effect analysis showed that accuracy in the RTT post unitization training (M = 90%, SD = 9%) was higher than before training (M = 77%, SD = 14%, p = 0.046), but performance between the same versions of the RTT did not significantly differ in the control group (M1 = 73%, SD = 19%; M2 = 70%, SD = 23%; p = 0.26).

Discussion: TP performance improved when the unitization strategy was provided, but not when the self-generation of unitization was encouraged. Improved RTT performance was limited to the unitization group, suggesting that effects were unitization-specific rather than lead by practice. Logic follows that this strategy may be generalizable to more relatable, real-life contexts. Self-generation of unitization was effective in improving task performance when assistance was provided rather than merely encouraged, suggesting that patients may benefit from guidance generating their own unitizations rather than integrating this strategy on their own. These findings should be replicated in a larger sample, and strategies to provide effective self-generation of unitization should be explored. Moreover, the extent to which the RTT can detect differential relational memory impairment in individuals with schizophrenia when compared to healthy controls warrants further investigation.

S67. TREATMENT-RESISTANCE AFFECTS LONG-TERM COGNITIVE TRAJECTORIES IN SCHIZOPHRENIA: A LONGITUDINAL STUDY

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Background: Schizophrenia is a highly heterogeneous disorder, and despite extensive research progress approximately 30% of patients with schizophrenia show poor response to first-line antipsychotics, denoted as treatment-resistant schizophrenia (TRS). Meta-analytic evidence showed that clozapine is the most effective antipsychotic for TRS, although 40% of TRS patients do not respond even to clozapine (ultra-treatment-resistant schizophrenia -UTR). Recent studies indicated that TRS is neurobiologically and categorically distinct from treatment-responsive schizophrenia, being associated with elevated glutamate levels in the anterior cingulate cortex and unaltered striatal dopamine synthesis. Moreover, the striking majority of TRS patients do not respond to first-line antipsychotic therapy since disease onset and present more severe cognitive deficits since first episode of psychosis, further suggesting the presence of a distinct and more disrupted neurobiological substrate. It is widely known that cognitive impairment is a core feature of schizophrenia and determines a significant detrimental impact on long-term functional outcome, which represents the ultimate treatment goal. However, despite the central role of cognition in schizophrenia, to date no study has investigated longitudinal cognitive outcome among TRS patients.

Based on these evidences, the aim of this study is to evaluate longitudinal cognitive trajectories in a sample of clinically stabilized patients with schizophrenia, stratified according to antipsychotic response. We hypothesized that treatment-resistance is associated with a more severe long-term cognitive decline.

Methods: We enrolled 93 patients with schizophrenia (DSM-V), stratified as follows: 32 first-line responders (FLR), 42 TRS and 19 UTR. Cognition was longitudinally assessed at baseline and at least after 6 years of follow-up (mean: 9.3±2.8 years) using the Brief Assessment of Cognition in Schizophrenia (BACS). From BACS subscores we calculated for each patient a Cognitive Index, as a measure of overall cognitive functioning. In order to quantify global cognitive functioning changes during the course of illness, we estimated effect size score for Cognitive Index using Cohen’s d. Finally, General linear Models (GLM) were performed with overall cognitive index effect size as dependent variable, treatment (FLR/UTR/UTR) as categorical variable and age, duration of illness and education as covariates.

Results: The first GLM (FLR vs TRS+UTR) showed a significant main effect of treatment (F=7.34, p=0.01), with worse cognitive outcome between resistant patients. Consistently, the second GLM (FLR/UTR/UTR) resulted significant as well (F=17.90, p<0.001), with UTR group showing worse cognitive trajectory (Fisher’s post-hoc: p<0.001, UTR Cognitive Index effect size = -0.7).

Discussion: This is the first study to longitudinally evaluate cognitive trajectories of patients with schizophrenia according to their antipsychotic response. We showed that treatment resistance is associated with a more severe cognitive decline, with worse outcome among UTR patients. These data suggest that greater severity of treatment resistance in schizophrenia is associated with greater cognitive impairment, possibly due to the presence of a distinct and more disrupted neurobiological substrate that affects both cognition and antipsychotic response. These findings further highlight the necessity of early individuation and tailored pharmacological treatment for TRS patients, in order to improve long-term clinical, cognitive and functional outcome.

S68. DIFFERENTIAL PATTERN OF SOCIAL COGNITION IMPAIRMENT BETWEEN RURAL AND URBAN DWELLING PATIENTS OF SCHIZOPHRENIA AND ITS FUNCTIONAL CORRELATES

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Background: Cognitive deficits (both neuro & social Cognition) play a vital role in determining functional status in schizophrenia. It has been noted that functional outcomes are relatively better in Indian rural settings. This suggests that cognition might be better in rural patients. Considering the prevailing vast cultural differences there is paucity of research which delineates the differences in social cognition and its impact on the functional outcome, stratified across rural and urban setups. Hence, we aim to explore differential impairment in social cognition in patients with schizophrenia residing in rural versus urban settings and their impact on real-world functioning.