Three haplotype blocks were defined: 1) rs2208870, rs12333117, rs582186, 2) rs645649, rs582262, 3) rs3763180, rs10484320, rs4960155, rs9379002, rs9405890, rs1475157. PLINK-v1.06 was used for the tabulation of possible individual haplotype phases and for the family-based association analyses (Transmission Disequilibrium Test). To explore the brain functional correlates of NRN1, the subjects belonging to case-control sample underwent a single MRI scanning session and performed a virtual reality spatial navigation task (Salgado-Pineda et al. 2016). The standard atlas provided in the FSL package was used to define three separate ROIs (left and right hippocampus and medial frontal region (mPFC)) and the mean value of activation per each subject was used to test the effect of each SNP/haplotypes by means of a linear regression. All the analyses were adjusted by age, sex and premorbid intelligence coefficient (IQ-TAP).

Results: Two haplotypes including SNP4 and SNP5 (rs645649-rs582262) were associated with early onset SZ-SD: the haplotype CG was undertransmitted from parents to patients (p=0.011, OR (95%CI=0.08(0.01-0.71) - protective haplotype), while the haplotype GG showed an overtransmission trend (p=0.055, OR (95%CI=3.83 (1.40–10.48)). No effect was observed in the adult onset subsample.

No differences between patients and controls were observed in the activation of the three ROIs. Within patients, an effect of the haplotype CG (SNP4-5) was detected in the mPFC: carriers of no copies of the protective haplotype showed a higher mean activation (n=15, mean(SD)=1.17(1.73)) than individuals with at least one copy of the haplotype (n=9, mean(SD)=21.19(21.94)) (t(24)=0.507 p=0.035).

Discussion: First, our family-based results are consistent with evidence of a genetic association between NRN1 gene and SZ-SD and extend the knowledge on that NRN1 has a selective impact on early age at onset (Fujio-Vilas et al. 2016). Second, our data suggest that NRN1 is involved in the regulation of the de-activation of mPFC in patients with SZ during a spatial navigation task. This result is of special interest since mPFC is an area included in the Default Mode Network (DMN) and alterations in this network have been highly documented in SZ patients during performance of different tasks (Pomarol-Clotet et al. 2008; Mannell et al. 2010; Salgado-Pineda et al. 2011).

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T153, CAN COGNITIVE TRAINING DECREASE REACTIVE AGGRESSION IN SCHIZOPHRENIA?

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Background: Cognitive deficits contribute to aversive social behaviors such as impulsive aggression. Studies have shown that cognitive training interventions may decrease the risk for impulsive aggression. The current study sought to illuminate the underlying mechanism of cognitive training effects on impulsive aggression—particularly, changes in the neural circuitry and in behavioral expressions of emotion regulation and emotion-based impulsivity.

Methods: Participants (N=28) with schizophrenia or schizoaffective disorder were recruited from New York Presbyterian Hospital and Manhattan Psychiatric Center and randomized into one of two cognitive training groups—a cognitive remediation training plus social cognition training (CRT+SCT) group versus CRT alone. At baseline and following 36 hours of training, participants completed the MATRICS Consensus Cognitive Battery (MCCB), Eyes Task, and the Emotion Recognition-40 (ER-40) as measures of neurocognition, mentalizing, and facial affect recognition. We indexed emotion regulation capacity using the Positive and Negative Affect Scale (PANAS) and by obtaining heart rate, respiration, and electrodermal activity while participants viewed pictures selected from the International Affective Picture System (IAPS). A subsample of participants completed fMRI scans during the completion of the emotion regulation task. The Go No-go task and the Emotional Stop Signal task served as measures of impulsivity. Aggression was measured using the Overt Aggression Scale (OAS), the Point Subtraction Aggression Paradigm (PSAP), and the Taylor Aggression Paradigm (TAP).

Results: Participants were 31.93 years old (SD=10.46) and had completed 12.07 (SD=2.59) years of education. Both groups showed improvements from baseline on the composite cognition score of the MCCB with a slight edge to the combined CRT+SCT group (Cohen’s d=0.22). Both groups showed pre-to-post reductions in aggression with only minimal differences. Although both groups showed pre-to-post improvements in affect recognition and mentalizing, the CRT+SCT group showed greater improvements in affect recognition (Cohen’s d = 0.21) and mentalizing (Cohen’s d = 0.39). Both groups showed reductions in negative affectivity scores from baseline (Cohen’s d = -0.48) but reductions were greater in the CRT+SCT group (Cohen’s d = -0.24). Both groups demonstrated pre-to-post reductions in their Low Frequency/High Frequency heart rate variability ratio (Cohen’s d=0.83) and pre-to-post reductions in skin conductance (Cohen’s d = -0.48). Pre-to-post differences in HRV and skin conductance were very minimal.

Both groups demonstrated large pre-to-post reductions in misses on the No-Go trials of the Go No-Go Task (Cohen’s d = -1.74). Reductions were greater in the CRT+SCT than the CRT only group (Cohen’s d=0.49) suggesting that the CRT+SCT group show greater improvements in impulse control after cognitive training.

Baseline fMRI scans showed that amygdalofrontal network activation was greater when emotionally evocative pictures were preceded by a reappraisal statement compared to conditions in which they were preceded by negative descriptions. This shows that the emotion regulation task engages relevant neural targets. The presentation will include accumulated follow-up fMRI scans. It is expected that there will be increased BOLD signaling following cognitive training.

Discussion: The study adds to evidence of cognitive training prospects for decreasing aggressive impulses. A mechanistic model with improved emotion regulation and impulse control contributing to reduced aggression may characterize cognitive training effects. Change in neural circuitry of emotion regulation will demonstrate strong proof-of-concept.

T154, RESTING STATE PERFUSION IN THE REWARD SYSTEM LINKED TO DIMENSIONS OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA?

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Background: Negative symptoms (NS) are central for the symptomatology of schizophrenia associated with poor functional outcome. Two dimensions of NS have consistently been proposed: apathy and diminished expression. Even though distinct pathophysiological mechanisms have been hypothesised rest state perfusion and dimensions of NS have not been studied. Here, we therefore focused on dimensions of NS and the link to whole brain resting state perfusion in schizophrenia patients.

Methods: We included 45 schizophrenia spectrum patients and 44 age- and gender-matched healthy controls. We assessed NS with the Scale for the Assessment of Negative Symptoms (SANS) and imagining on a 3T MRI scanner. Apathy was currently present in 31 patients and diminished expression in 27 patients. Patients did not differ in antipsychotic medication or positive symptoms. We compared whole-brain perfusion over all, and between the groups using 1-way ANCOVAs (F and T tests). A uniform threshold of p < 0.5 (FWE-corr) was applied.

Results: Diminished expression was most prominently associated with perfusion within the right orbital cortex, insula, ventral striatum and head of caudate nucleus, while apathy was associated with perfusion bilateral within the SMA, the insula and the thalamus.
T155. SEPARABLE AND REPLICABLE NEURAL STRATEGIES DURING SOCIAL BRAIN FUNCTION IN PEOPLE WITH AND WITHOUT SEVERE MENTAL ILLNESS

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Background: The case-control design and disease heterogeneity may be major limiting factors impeding biomarker discovery in brain disorders, including serious mental illness such as schizophrenia spectrum disorder (SSD) or bipolar disorder (BDP). We propose that this heterogeneity represents an opportunity for discovery by uncovering relevant biologically driven sub-types within disorders. Individuals with schizophrenia spectrum disorder (SSD) have deficits in social cognition related to poor functional outcome.

Methods: A total of 109 SSD and 70 matched healthy controls (HC) were recruited across three sites. Participants performed an fMRI task in which they observed or imitated emotional faces. For each participant, an individual pattern of activity (Imitate > Observe for emotional faces) was identified. Hierarchical clustering (Ward’s method) identified clusters of individuals with similar patterns of activity. We then examined whether new data-driven groups of participants (based on patterns of brain activity) demonstrated performance differences on a battery of social and neurocognitive tests completed out of the scanner. As a validation of the importance of cluster membership, Euclidean distance was compared between participants to members of their own cluster, diagnosis, or site. The clustering analysis was repeated on a replication sample consisting of 32 SSD, 37 HC and 35 SSD.

Discussion: Three clusters with distinct patterns of neural activity were found. Cluster one (24 HC and 44 SSD) represented ‘typical activators’ (lateral frontal and parietal activity). Cluster two (21 HC and 31 SSD) were identified as ‘hyper-activators’, showing more intense and extended activity. This group also had improved social cognitive performance relative to the replication sample, the same three patterns (typical activators, hyper activators, and deactivators) were identified. When clustering was applied to the replication sample, the same three patterns (typical activators, hyper activators, and deactivators) were identified.

Discussion: Our findings demonstrate different patterns of neural activity among individuals during a socioemotional task that were independent of DSM-diagnosis or scan site. Our findings may provide objective neuroimaging endpoints (or biomarkers) for subgroups of individuals in target engagement research aimed at enhancing cognitive performance independent of diagnostic category.

T156. IN VIVO CHARACTERIZATION OF THE FIRST AGONIST DOPAMINE D1 RECEPTORS PET IMAGING TRACER [18F]MNI-968 IN HUMAN

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Background: D1 receptors, which couple to inhibitory G-proteins, have been shown to regulate neuronal growth and development, mediate some behavioral responses. Its function has been shown to be altered in both neurologic and psychiatric disorders. To date, there is a lack of agonist PET tracers for the D1 receptors labeled with 18F with relevance in clinical studies. We report the evaluation in non-human primates of [18F]MNI-968 (PF-06730110), a novel PET radiotracer of the D1 receptors.

Methods: Four brain PET studies, 2 baselines and 2 blockade studies using FP-2562, a D1 partial agonist compound, were conducted for 90 min in two rhesus monkeys with [18F]MNI-968 (169 ± 31 MBq). [18F]PF-06730110 was administered at the same dose level for both monkeys as a bolus followed by a 2-hour infusion, with [18F]MNI-968 administered 30 min into the infusion. Additionally, six brain PET studies were conducted over 180 min (317 ± 49 MBq) in 6 healthy human volunteers (3 test/retest and 3 test). PET data were modeled with 2-tissue compartmental model (2T), Logan graphical analysis (LGA), and non-invasive Logan graphical analysis (NI-LGA) with cerebellar cortex as reference region to estimate total distribution volume VT, and binding potential BPND.

Results: In rhesus monkeys, [18F]MNI-968 (PF-06730110), penetrates the brain with a peak whole-brain uptake to ~3% of the injected dose at ~6 min post injection and showed a fast washout. The highest signal was found in the caudate, putamen, with moderate estrastral uptake. The lowest signal was in the cerebellum. BPND values were up to ~1.4 in the putamen. All three quantification methods (2T, LGA and NI-LGA) were in excellent agreement, with a similar estimated D1 receptors occupancy of ~040% for both monkeys in the caudate and putamen. In human, [18F]MNI-968 kinetics appeared to be faster compared to non-human primates, with a BPND in the putamen of ~0.8. Initial measurement of test-retet reproducibility was ~3% for the striatal regions.

Discussion: Our work showed that [18F]MNI-968 (PF-06730110), is a promising agonist PET radiotracer for imaging D1agonist receptors that can be quantified non-invasively. Studies are currently ongoing both in non-human and human primates to further characterize the tracer.

T157. FRONTOSTRIATAL CONNECTIVITY IN TREATMENT-RESISTANT SCHIZOPHRENIA: RELATIONSHIP TO POSITIVE SYMPTOMS AND COGNITIVE FLEXIBILITY

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Discussion: In independently collected samples, our findings demonstrate different patterns of neural activity among individuals during a socioemotional task that were independent of DSM-diagnosis or scan site. Our findings may provide objective neuroimaging endpoints (or biomarkers) for subgroups of individuals in target engagement research aimed at enhancing cognitive performance independent of diagnostic category.