neurons and perineuronal nets (PNN) were conducted, and pyramidal and dopamine neuron activity was recorded in vivo in the hippocampus and VTA respectively.

Results: Rats exposed to MAM gestationally were found to exhibit increased VTA DA neuron population activity, hyper-locomotion to amphetamine, and disruption in novel object recognition as adults. In contrast, exposure to either the antianxiety agent diazepam (PD31-40) or environmental enrichment (PD 21–40) prepubertally prevented this occurrence. Furthermore, combined footshock + restraint administered at PD31-40 in normal rats lead to a similar pathology in the adult. In contrast, combined stressors administered at adults (PD65-75) led to a short-term attenuation of DA activity similar to that observed in depression models. However, if the developmental critical period was re-opened in adults using either VPA or SAHA to resemble the prepubertal state, combined stressors now led to a persistent loss of PV-PNN labeling in the hippocampus, resulting in persistent hippocampal hyperactivity and a persistent increase in VTA DA neuron activity.

Conclusions: These data demonstrate that the timing of environmental stress is critical in determining the pathophysiological consequences. The fact that MAM can be circumvented via alleviation of stress prepubertally and that prepubertal stress can lead to a similar pathophysiology suggests that the predisposition to schizophrenia is based on increased impact of stress prepubertally, when the PV neurons are in a vulnerable state. In contrast, in the adult when PV neurons have a protective PNN, the same stressors now lead to a depressive state. However, reopening the critical period via histone deacetylase inhibition now causes the adult rat to be susceptible to stress-induced hyperdopaminergic phenotype. This suggests that depression and schizophrenia may share a common genetic predisposition leading to increased stress susceptibility at different developmental stages, with the pathophysiology dependent on the timing of the stressor.

3.2 NEURAL MECHANISMS OF SOCIAL ENVIRONMENTAL RISK FOR SCHIZOPHRENIA

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Background: Urban birth, urban living, and ethnic minority status are established risk factors for schizophrenia, but the mechanisms are unclear. Previous evidence suggests a causal role of social exposures and adverse experiences, but experimental evidence is scarce.

Methods: We combine multimodal neuroimaging with ecological momentary assessment, geolocation and geospatial analysis in an epidemiological longitudinal sample in Germany.

Results: We find that established risk factors converge on the perigenual cingulate-amygdala-ventral striatal pathway as shown by structural and functional imaging, supporting a role for the amygdalostriatal system in psychosis risk. Using a combination of PET and fMRI data, we suggest a mechanistic link to psychosis by increased dopamine release and synthesis in striatum secondary to prefrontal dysregulation. Moreover, environmental context, such as greenspace, can mitigate these impacts.

Conclusions: This work shows a convergent risk circuit that could guide primary prevention of schizophrenia through reduction of manifestation risk by environmental manipulation.

3.3 CIRCADIAN EXPRESSION OF STRESS AND ANXIETY MOLECULAR FACTORS IN THE HUMAN AMYGDALA: ABNORMALITIES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Converging evidence points to a key role played by the amygdala in stress responses and anxiety. Several molecular pathways have emerged as potential regulators of these amygdala functions, with anxiolytic as well as anxiogenic effects, raising the possibility that a disruption of the balance between these pathways may cause increased anxiety, a symptom shared by a large number of psychiatric disorders. Somatostatin (SST) represents a key candidate for these mechanisms. It is expressed in a population of interneurons in the deep amygdala nuclei, where it exerts powerful anxiolytic effects. SST has been involved in the pathophysiology of schizophrenia (SZ) and bipolar disorder (BD), disorders in which anxiety is often comorbid. A population of SST-positive neurons co-express neuropeptide Y also postulated to play a role in stress response. Several other molecules, including Pituitary adenylate cyclase-activating polypeptide (PACAP) and corticotropin releasing factor (CRF), have been shown to play a key role in stress response and anxiety, potentially interacting with SST and increasing anxiety. We tested the hypothesis that SST-immunoreactive (IR) neurons are decreased in the amygdala of subjects with SZ and BD, while PACAP and CRF may be increased. Evidence for circadian SST expression in the amygdala and disrupted circadian rhythms and rhythmic peaks of anxiety in BD suggest a disruption of rhythmic expression of SST in this disorder.

Methods: Postmortem tissue samples from the amygdala from a well characterized cohort of healthy control, SZ and BD subjects were included in these studies. Immunocytochemistry combined with quantitative microscopy and Western blotting were used to measure expression of these molecules. Time of death (TOD) was used to test associations with circadian rhythms. Step-wise ANOVA analyses included several potential confounds such as exposure to pharmacological agents and substance abuse.

Results: Neurons expressing SST were overall decreased in the lateral nucleus of the amygdala in subjects with BD ($p=0.005$) and SZ ($p=0.03$). In normal controls, numbers of SST-IR neurons in the amygdala varied according to TOD, showing a circadian rhythm equivalent to that predicted on the basis of rodent studies. This pattern was altered in BD, with significant decreases of SST-IR neurons selectively in subjects with a subjective day TOD ($p=0.0009$). Numbers of NPY-IR neurons were not affected. Expression of CRF was significantly increased in both disorders ($p<0.02$), while expression of PACAP receptor 1 (PAC1) was decreased ($p<0.005$).

Conclusions: Decreased SST-IR neurons in the amygdala of SZ and BD, interpreted here as decreased SST expression, may disrupt responses to fear and anxiety regulation in these subjects. In BD, our findings raise the possibility that morning peaks of anxiety depend on a disruption of circadian regulation of SST expression in the amygdala. Overall, altered expression of molecular pathways involved in stress responses and anxiety supports a dysregulation of these functions in the amygdala of subjects with SZ and BD.

3.4 CHANGES IN AMYGDALA AND HIPPOCAMPAL FUNCTIONAL CONNECTIVITY IN SUBCLINICAL PSYCHOSIS: RELATIONSHIP TO SYMPTOM PERSISTENCE, PARANOIA AND ABERRANT SALIENCE

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Background: Prior studies have found evidence for abnormalities of medial temporal lobe structures in patients with psychotic disorders. It has been hypothesized that these abnormalities, which have been linked to dysregulation of dopaminergic neurotransmission in animal models of psychosis, may be associated with a cognitive bias to mislabel neutral events or objects in the environment as salient, which may, in turn, give rise to delusional beliefs and other psychotic symptoms. One persistent challenge for this line of research arises from the confounds associated with testing such models in psychotic disorder patients who have been treated with antipsychotic

medication. In light of recent evidence for a neurobiological continuum between clinical and subclinical psychosis, in the current study, medial temporal lobe connectivity was measured in non-help-seeking young people (college students) with a range of severity of subclinical delusional beliefs (n = 131). We sought to determine whether changes in medial temporal lobe connectivity are associated with such beliefs, in particular persecutory ideas, as well as with a bias to mislabel neutral information as negatively-valenced. We also sought to better understand the phenomenology and antecedents of delusional beliefs in this young adult population, by examining relationships to other subthreshold psychotic experiences and childhood adversity in a larger cohort of subjects (n = 399).

Methods: Participants with a range of severity of delusional beliefs were identified and recruited from college campuses in the Boston area. Associations among symptoms and childhood trauma were examined using hierarchical regression modeling. Resting-state functional magnetic resonance imaging data were collected in a subset of these subjects, and seed-based functional connectivity analyses were conducted using atlas-based amygdala and hippocampus seeds. Also, biases to mislabel neutral information were measured using a validated word classification task. Lastly, a portion of the cohort was followed longitudinally, via on-line assessments.

Results: A history of childhood trauma was highly associated with both delusional beliefs and hallucinatory experiences, which were highly correlated with each other. The severity of delusional beliefs in this cohort strongly correlated with the strength of the connectivity of the amygdala to early visual cortical areas. This effect remained significant after accounting for symptoms of depression, anxiety and hallucinatory experiences. Moreover, the effect was stronger when the analyses were limited to those participants with delusional beliefs that had persisted over a period of one year. Further analyses revealed that these effects were mainly accounted for by the presence of persecutory beliefs, rather than other delusion types. The hippocampal seed showed a similar, but less robust, pattern of effects. Lastly, a significant association between the tendency to mislabel neutral information as negatively-valenced and delusional belief severity was mediated by the strength of amygdala-visual cortex connectivity.

Conclusions: Subclinical delusional beliefs, particularly persecutory ideas, are associated with a history of childhood trauma and increased connectivity between the amygdala and visual cortex, which was linked to a tendency to mislabel neutral information as negatively-valenced. These findings suggest a mechanistic path by which early stress-induced abnormalities in medial temporal lobe function could give rise to misperceptions and misinterpretations of incoming sensory stimuli.

4. THE NEUROBIOLOGY OF COGNITION ACROSS THE PSYCHOSES: EVIDENCE FROM DIVERSE MODALITIES AND ACROSS ILLNESS PHASES

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Cognitive dysfunction is a major feature of the psychotic disorders that is evident even prior to illness onset, and persistent throughout the illness course. Although it is intuitive that such dysfunction is biologically-based, its precise foundation is not currently well understood. Cognitive impairment has been linked to inflammation as well as altered brain structure and function in an increasing number of studies, but inconsistencies in findings across cohorts suggests that the nature of relationships between these variables is complex and potentially influenced by factors that differ from patient-to-patient. In this symposium, we will present data offering novel insights into biology-cognition relationships in psychosis, with an emphasis on new work that addresses heterogeneity within psychosis phenotypes and that focuses on the dynamics of biology-cognition relationships across different phases of the lifespan and illness course.

Dr Van Rheenen (Australia) will chair the session and introduce the topic. She will present data that reconciles inconsistent findings of temporal stability in fluid cognitive deficits in psychosis, but accelerated age-related structural brain deterioration in regions known to support it. She will highlight cognitive reserve as an important moderator of the presence and strength of brain-cognition relationships on the schizophrenia-spectrum.

Assistant Professor Lewandowski (USA) will present data examining whether different cognitive profiles in psychosis are reflective of differential resting state network connectivity changes. She will discuss the possibility that associations between cognitive impairment and functional connectivity may be more reflective of discreet phenotypes than a continuum of impairment.

Ms Wannan (Australia) will present data indicating that initial deterioration in visuospatial associative memory ability in psychosis may be related to left hippocampus atrophy in the stratum layers in early psychosis, whereas ongoing deterioration in chronic schizophrenia patients may be related to the spread of pathology to the previously unaffected right hippocampus. The potential that these hippocampal abnormalities and subsequent memory impairments arise from chronic stress exposure and inflammation will be discussed.

Associate Professor Burdick (USA) will present data indicating the role of the immune system in cognitive outcomes in patients on the schizophrenia-bipolar spectrum, highlighting the influence of primary and secondary inflammatory mediators and discussing the role that illness course variables play in the inflammatory response.

Professor Susan Rossell (Australia) will act as the discussant, synthesising the content of these presentations in an interactive discussion focused on the implications that these data have for our understanding of cognition in psychosis.

Together, this geographically diverse, cross-institutional panel brings a range of experience to the topic. This will ensure an offering of fresh ideas grounded in an established knowledge base that is expected to stimulate lively dialogue focused on the neurobiology of cognition across the psychoses.

4.1 COGNITIVE RESERVE ATTENUATES AGE-RELATED COGNITIVE DECLINE IN THE CONTEXT OF ACCELERATED BRAIN AGEING IN SCHIZOPHRENIA-SPECTRUM DISORDERS: EVIDENCE FOR ACTIVE COMPENSATION

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Background: In schizophrenia, relative stability in the magnitude of fluid cognitive deficits across age and illness duration is inconsistent with evidence of accelerated deterioration in brain regions known to support these functions. These discrepant brain-cognition outcomes may be explained by variability in cognitive reserve (CR), which in neurological disorders has been shown to enable resilience against brain pathology and minimize its impact on cognitive or clinical indicators of illness.

Methods: Age-related changes in fluid reasoning, working memory and frontal brain volume, area and thickness were mapped using regression analysis in 214 individuals with schizophrenia or schizoaffective disorder and 168 healthy controls. In patients, these changes were modelled as a function of CR.

Results: Patients showed exaggerated age-related decline in brain structure, but not fluid cognition compared to controls. In the patient group, no moderation of age-related brain structural change by CR was evident. However,