A. Anticevic will present computational microcircuit models, resting state fMRI data and fMRI data using ketamine which provide evidence for a disturbed excitation-inhibition (E-I) balance and resulting in large scale dysconnectivity in schizophrenia in the context of working memory and other cognitive processes.

The research presented in this symposium integrates computational, neuroanatomical, electrophysiological, pharmacological, genetic, behavioural and neuroimaging methods to connect pathophysiological mechanisms at the microcircuit level such as increased neuronal noise and an abnormal E-I balance to disturbances in large scale brain networks at the systems level and to behavioral impairment. Such an integrative approach promises to yield new insights into the pathophysiology of cognitive dysfunction in schizophrenia.

18.1 MITOCHONDRIAL ALTERATIONS WITHIN THE PYRAMIDAL-PARVALBUMIN CELL MICROCIRCUIT IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background: Working memory, a core cognitive function impaired in schizophrenia, depends upon gamma oscillatory neuronal activity in the prefrontal cortex (PFC). Accordingly, individuals with schizophrenia show lower power of gamma oscillations in the PFC during tasks that involve working memory.

Gamma oscillations emerge from the fast and coordinated activity of layer 3 excitatory pyramidal cells and inhibitory parvalbumin (PV) cells. As such, gamma oscillations have a particularly high energetic demand that is met by ATP production via oxidative phosphorylation (OXPHOS) within pyramidal and PV cell mitochondria. PFC layer 3 pyramidal cells have prominent reductions in OXPHOS-related gene pathways in schizophrenia. Importantly, OXPHOS can be regulated by two distinct processes: ATP demand to support neuronal firing, or upstream deficits in OXPHOS enzyme expression.

Layer- and cell type-specific transcriptomic analyses of OXPHOS enzymes and ultrastructural analyses of mitochondrial morphology can help to distinguish between these two possibilities. Reduced ATP demand due to reduced neuronal firing is associated with 1) correlated expression levels of OXPHOS enzyme complexes, 2) lower expression of all subunits comprising Complex IV, the terminal and rate-limiting OXPHOS enzyme complex, and 3) normal mitochondrial morphology. Defective OXPHOS results in 1) elimination of correlated expression of OXPHOS enzyme complexes, 2) variable and inconsistent effects on Complex IV subunit expression, and 3) abnormal mitochondrial morphology.

To determine which upstream factor is likely operative in the illness, we quantified OXPHOS enzyme complex transcripts in layer 3 pyramidal and PV cells, and performed ultrastructural analyses of mitochondrial morphology within pyramidal and PV axon boutons in layer 3 of the PFC in schizophrenia and unaffected comparison subjects.

Methods: For mRNA analyses, frozen tissue sections of area 9 from 36 pairs of schizophrenia and comparison subjects were stained for Nissl substance to identify pyramidal cells, or labeled using immunoperoxidase for aggrecan to identify PV cells. Layer 3 pyramidal and PV somata were dissected using laser capture microdissection. Transcriptome profiling was performed by microarray using Affymetrix GeneChips. Analysis of Complexes I, IV, and V expression in each neuronal population was assessed at $q<0.05$ in covariate- and multiple comparisons-corrected analyses.

Electron microscopic analyses were performed in area 46 of 2 matched pairs of schizophrenia and comparison subjects. Mitochondria in pyramidal and PV cell boutons were classified as normal or abnormal using established criteria. Chi-square analysis was used to examine whether the percentages of each type differed between groups.

Results: The expression of subunits comprising Complexes I, IV, and V in layer 3 pyramidal and PV cells was significantly lower in subjects with schizophrenia relative to unaffected comparison subjects. In both cell populations, expression of Complexes I, IV, and V were correlated (r=0.8-0.9) in unaffected comparison and schizophrenia subjects. Complex IV subunits showed 11–26% reductions in pyramidal cells, and 7-31% reductions in PV cells in schizophrenia. In both unaffected comparison and schizophrenia subjects, ≥99% of mitochondria in pyramidal cell boutons and ≥97% of mitochondria in PV cell boutons exhibited normal morphology.

Discussion: The current findings are most consistent with the interpretation that lower measures of OXPHOS in schizophrenia reflect lower demand for ATP production due to less neuronal firing.

18.2 USING COMPUTATIONAL ESTIMATES OF INTERNAL "NOISE" TO CHARACTERIZE VISUAL PERCEPTUAL AND WORKING MEMORY DEFICITS IN SCHIZOPHRENIA

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Background: Heightened neural noise serves as a promising explanatory framework for schizophrenia (SZ) pathophysiology, yet its specific contribution to working memory (WM) deficits remains unclear. The perceptual template model (PTM), an established human-observer model of visual perception, asserts that a system's internal noise (IN) is due to both background, 'additive' noise and stimulus-driven 'unfiltered' noise. In this study, we assessed levels of PTM-derived additive and unfiltered IN in SZ during basic visual processing and tested their respective relations to patients' visuospatial WM imprecision.

Methods: Individuals with SZ and demographically-matched healthy controls completed a perceptual discrimination task to estimate levels of IN and an analog visual WM task to examine the impact of internal noise on WM precision. The discrimination task involved distinguishing orientations of briefly presented gratings (1 cycle/°; tilted ±45° from vertical) embedded in varying levels of external noise (0–21%). Contrast thresholds were estimated, and additive and unfiltered IN levels were modeled from task performance with the PTM. The WM task required reproducing remembered orientations of high-contrast gratings (same size and spatial frequency as in the discrimination task) with a manual dial at a 1s delay. WM precision was computed as the concentration of the von Mises distribution, fit from subjects' orientation errors.

Results: Additive and unfiltered IN during perceptual discrimination were both significantly increased in SZ compared to HC. WM precision was reduced in SZ compared to HC at every set size. Levels of unfiltered IN negatively correlated with WM precision in SZ, while both unfiltered and additive IN negatively correlated with WM precision in HC. For SZ, unfiltered IN was also negatively correlated with IQ, and WM precision was positively correlated with IQ in both groups.

Discussion: We found evidence of elevated IN levels during visual perception in SZ, though only unfiltered IN was inversely related to patients' visual WM precision. Thus results indicate overall 'noisy' visual perception in SZ, but point to a more precise model of poorer signal filtering or noise suppression as contributing to WM deficits and potentially broader cognitive impairment. Future work must identify the neural drivers of IN levels, as they may shed light on differential implications of the excitation/inhibition imbalance in WM networks. Findings underscore the link between perception and WM encoding in SZ and offer a novel computational strategy for identifying common and unique pathophysiological mechanisms of SZ cognitive dysfunction.