SUPPLEMENTARY MATERIAL 3

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Nicotine exposure in a phencyclidine-induced mice model of schizophrenia: Sex-selective medial prefrontal cortex protein markers of the combined insults in adolescent mice

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Short title: Adolescent nicotine and schizophrenia mPFC proteomic profile

Isolated sub-networks

mPFC interactome map of PCPNIC male mice

The only sub-network that was not linked to *Amph* in the male interactome map was the Energy metabolism, composed of 2 proteins: Phosphoglycerate kinase 2 (*Pgk2*) and Malate dehydrogenase cytoplasmic (*Mdh1*). *Pgk2* acts in the first ATP-generating step of the glycolytic pathway converting 1,3-diphosphoglycerate into 3-phosphoglycerate. In the gluconeogenic pathway, *Pgk2* catalyzes the reverse reaction. As for *Mdh1*, it catalyzes the reversible oxidation

of malate to oxaloacetate in the citric acid cycle and is a major participant in the malate-aspartate shuttle, a passage from the cytosol to the mitochondria essential for energy production. The presence of these proteins in the male interactome map corroborates previous studies that demonstrate impaired energy metabolism in SCHZ patients (Henkel et al., 2022; Martins-De-Souza et al., 2011). *Mdh1* is downregulated in the dorsolateral prefrontal cortex of SCHZ patients, which may decrease energy production via glycolysis (Martins-de-Souza et al., 2009; Middleton et al., 2002). Also, in a preclinical study that used MK-801 (an NMDA receptor antagonist) to model SCHZ, there were significant changes in the levels of glycolytic enzymes, including *Pgk*, with oligodendrocytes being more severely impacted (Guest et al., 2015).

mPFC interactome map of PCPNIC female mice

In the female interactome map, there were 2 isolated sub-networks. Septin-8 *(Sept8*) and Septin-10 *(Sept10*) formed the Septin cytoskeleton sub-network. Septins compose a conserved family of GTPases involved in various cellular processes, including synaptic vesicle trafficking, exocytosis, cell signaling, and apoptosis (Benoit et al., 2023; Peterson and Petty, 2010). Thirteen paralogs have been identified and clustered into 4 subgroups. Both *Sept8* and *Sept10* are components of the SEPT6 group, together with Septin 6, Septin 11 and Septin14 (Werner and Yadav, 2022). *Sept8* contributes to neurite development and branching (Werner and Yadav, 2022) and its depletion disrupts neurite elongation (Ageta-Ishihara and Kinoshita, 2021). It was shown to inhibit neurotransmitter release, as a result preventing overexcitation (Ageta-Ishihara and Kinoshita, 2021). In addition, septins including the SEPT6 subgroup, are enriched in the postsynaptic density (Ageta-Ishihara and Kinoshita, 2021; Werner and Yadav, 2022). These data corroborate previous reports that link altered cytoskeleton components to SCHZ and nicotine exposure (Ehlinger et al., 2017; Jung et al., 2016; Marchisella et al., 2016) and suggest a role of septin dysregulation.

Ras-related protein Rab-37 (*Rab37*) and HMG box transcription factor BBX (*Bbx)* composed the Cell cycle subnetwork. When considering trafficking pathways, the Rab GTPase family stands out. This family is composed of a very heterogeneous group of proteins that, through their effectors, regulate vesicle formation, actin- and tubulin-dependent vesicle movement, and membrane fusion (Stenmark and Olkkonen, 2001). *Rab37* gene promotes cell division but also the differentiation of neuronal cells (Hagag et al., 1986; Noda et al., 1985). These roles are closely related to those assigned to *Bbx. Bbx* is a member of the high mobility

group (HMG)-box proteins, a superfamily of architectural proteins (Chen et al., 2014). It is a sequence-specific transcription factor and is expressed in progenitor cells of the developing neocortex ventricular zone, promoting progenitor cell self-renewal (Dixon et al., 2013). Its role in cell cycle progression has also been shown in yeast, in which *Bbx* promotes the G1/S phase transition (Sanchez-Dias Az et al., 2001).

Besides previous evidence that associate the proteins that compose the Energy metabolism subnetwork of males (*Mdh1* and *Pgk2*) with SCHZ, no previous data describe specific contributions of the proteins that compose the female Septin cytoskeleton (*Sept8* and *Sept10)*, and Cell cycle (*Rab37* and *Bbx)* subnetworks to SCHZ or the comorbidity. Accordingly, possible deleterious outcomes of their disbalance await further investigation. Notwithstanding, the fact that these 3 sub-networks are isolated from the main nets of proteins described in the text of the manuscript suggests independent mechanisms of interference in the comorbidity.

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