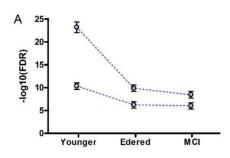
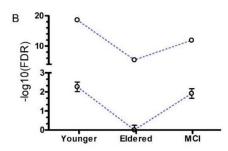
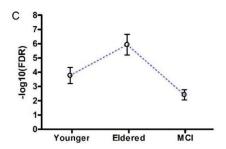
## **Supplementary Materials**



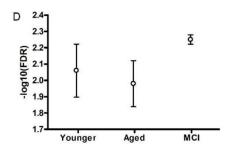
Group 1. Decreased in aging, but falling was kept in the MCI. The upper curve represents the evolution of the "somato-dendritic compartment", "dendritic tree", "axon", "synapses", and "post-synapses". The lower curve represents the evolution of ontologies categories as "pre-synapses", "dendritic shafts", and "dendritic spines".



<u>Group 2</u>. Decreased in aging, but compensated in the MCI. The upper curve represents the evolution of "glutamatergic synapses", whereas the lower curve represents the evolution of ontology classes as "CA3 pyramidal cell dendrites", "Schaffer collateral synapses", "guanylate complex soluble", and "Calcium channel complex".

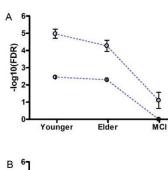


<u>Group 3</u>. Up-regulated in aging, but decreased in the MCI. This group includes ontology classes as "synaptic vesicles", "exocytic vesicles", and "secretory vesicles".

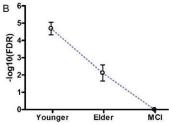


Group 4. Ontology classes only significant in a given stage. Younger Group: "astrocyte projection", "Ranvier nodes", "caveola", "voltage-gated Na+ channels", "rough endoplasmic reticulum", "synaptobrevin2-SNAP25-syntaxin 1a-complexin II complex", "PML body", "Golgi apparatus"; Eldered Group: "dense core granule", "voltage-gated K+ channel", "death-inducing signal complex", "Bim-Bcl2 complex", "caspase complex", "pore complex", "amyloidß complex", "y-secretase complex", "cAMPdependent complex", "NURF complex", "neuronal ribonucleoprotein complex"; MCI Group: "heterotrimeric G protein complex", "GTPase complex", "excitatory synapses", "ionotropic selective glutamate receptors", "AMPA selective glutamate receptors".

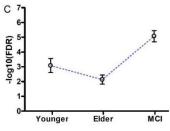
Figure S1. Main profiles across the three stages analyzed (Younger, Eldered, and MCI) as derived from the cell-component ontology analysis. The ontologies found significant were grouped by hierarchical cluster analysis using  $(1-R_{\text{Spearman}})$  as metric of correlation distance, and "average" as criterium of linkage function. The error bars cover the confidence intervals for a level  $(1-\alpha) = 0.95$ . The significances in the y-axis are quantified as  $-\log 10(\text{FDR})$ , where FDR is the false discovery rate. For details about the gene composition corresponding to each ontology class, see the Supplementary Tables S1–S3.



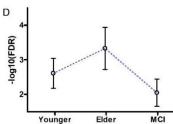
<u>Group 1</u>. Initial plateau, but sharp decreasing in MCI. The <u>upper curve</u> includes "NMDAR activation & post-synaptic events", "neurotransmitter receptors in post-synaptic transmission", "nervous system development", "IL-3 signaling". The <u>lower curve</u> includes "serotonin", "pluripotency mechanisms", "sumoylation of intracellular receptors", "oxidative stress induced senescence", and signaling pathways corresponding to "GPCR", "CCR5", "TSP1", "NTRKs", interleukins (IL-2/6/7/17), "NRF2/ARF", "IGF1", "insulin", "Wnt", "estrogens", "PDGF1", "Met receptor", "TLR4/9 receptors", "TGFbeta", "BAD", and "Apoptotic factor mediated response".



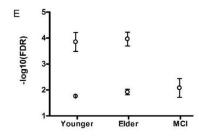
<u>Group 2</u>. Continuous decreasing across the three analyzed stages. The group comprises the evolution of "G protein mediated events", "myogenesis", "MAPK signaling", and "DREAM pathway".



<u>Group 3</u>. Lower plateau in aging, but overshooting in the MCl stage. This group comprises the evolution of ontology classes as "neuronal transmission across chemical synapses", "Protein-Protein interactions at the synapses", "neurexin & neuroligins" and "thrombin-proteinase-PAR receptors".



<u>Group 4</u>. Slight increment in aging but normalized in the MCI. This group comprises the evolution of the following pathways: "BDNF", "NOS1", and "synaptic adhesion molecules"



Group 5. Exclusive ontology categories detected in each group. Younger Group: the upper part includes "Gastrin-CCK-CREB signaling via PKC &MAPK", "Opioid signaling" and "ERK5 signaling". The lower part includes "EGFR1 signaling", "SLIT-ROBO receptors", "ErbB2", "TPO", "p38MAPK", "NCAM signaling for neurite outgrowth", "NO-guanylate cyclase stimulation", "senescence", "LIS1 pathway", "(E-SC)pluripotency", "CREB1 activation by NMDAR-RAS", "GDNF/Ret signaling", "FGFR3-SPRY", "Netrin 1", "EPH-Ephrin", "SP1R", "Glutamate neurotransmitter releasing cycle", and "hemostasia". Elder Group: the upper part includes "apoptosis (intrinsic mechanism)", "cell death (via NRAGE, NRIF, NADE)", "p75NTR", "p53". At the lower part "TNRF1", "inactivation of BCL2", "FAS", "splicing factor NOVA", "HSP90 & HSP27", "cytoskeleton cleavage by caspases", "MEF2D", "CREB activation by PKA", "pyroptosis", "caspase activation (extrinsic mechanism)", "stress pathway", "oxidative damage response", "NLR signaling", "fibrin-C3R", "NFAT", "apoptosis execution phase", "NRAGE receptor", "CREB activated by CaMKIV". MCI Group. It includes "pre-synaptic depolarization & Ca2+ion channel opening", and "SMCs contraction".

Figure S2. Main profiles across the three stages analyzed (Younger, Eldered, and MCI) as derived from the pathway analysis. The ontologies found significant were grouped by hierarchical cluster analysis using (1- $R_{\text{Spearman}}$ ) as metric of correlation distance, and "average" as criterium of linkage function. The error bars cover the confidence intervals for a level (1- $\alpha$ ) = 0.95. The significances in the y-axis are quantified as  $-\log 10(\text{FDR})$ , where FDR is the false discovery rate. For details about the genes involved in each pathway, see the Supplementary Tables S1–S3.