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TITLE The language of astrocytes: multilevel analysis to understand astrocyte communication and its role in memory-related brain operations and in cognitive behaviour **(ERC Advanced Grant FP7)**

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In the 90s, two landmark observations brought to a paradigm shift about the role of astrocytes in brain function: 1) astrocytes respond to signals from other cells with transient Ca2+ elevations; 2) Ca2+ transients in astrocytes trigger release of neuroactive and vasoactive agents. Since then, many modulatory astrocytic actions were described, forming a complex - partly contradictory - picture, in which the exact roles and modes of astrocyte action remain ill defined (Araque et al., Neuron, 2014; Volterra et al., Nat Rev Neurosci, 2014). Our project aims to bring light into the "language of astrocytes", i.e. into how they communicate with neurons and, ultimately, address their role in brain computations and cognitive behavior. To this end, we perform 4 complementary levels of analysis using innovative methodologies. We study:

1. the subcellular organization of astrocytes underlying local microdomain communications by use of correlative light-electron microscopy;
2. the way individual astrocytes integrate inputs and control synaptic ensembles using 3D two-photon imaging, genetically-encoded Ca2+ indicators, optogenetics and electrophysiology (Bindocci et al, Science, 2017);
3. the contribution of astrocyte ensembles to behavior-relevant circuit operations using miniaturized microscopes capturing astrocytic population dynamics in freely-moving mice during memory tests;
4. the contribution of astrocytic mechanisms to cognitive behavior using new mouse lines with conditional, astrocyte-specific genetic modification of signaling pathways (Habbas et al., Cell, 2015).

This combination of groundbreaking ideas, innovative technologies and multilevel analysis makes our project highly attractive to the neuroscience community at large, bridging aspects of molecular, cellular, systems and behavioral neuroscience, with the goal of leading from a provocative hypothesis to the conclusive demonstration of whether and how "the language of astrocytes" participates in memory and cognition.