Disruption of the spatio-temporal dialogue between migrating cortical neurons as underlying factor in Autism Spectrum Disorder (nEUrotalk)

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Although the precise etiology of Autism Spectrum Disorder (ASD) is unknown, one of the most accepted theories is an abnormal proportion of excitatory projection neurons (PNs) and inhibitory cortical interneurons (cINs). During cortical development, migrating PNs and cINs interact in such a way that impaired migration of each of these major classes of neurons affects the number and location of the other.
In the present project we propose an impaired spatio-temporal crosstalk between migrating PNs and cINs as shared pathomechanism in ASD. We will test this hypothesis by studying several ASD-linked genes (Cntnap2, FMR1, Agtpbp1) involved in neuronal migration of PNs and/or cINs at different levels, which all show increased PNs/cINs ratio. We will carry out a multidisciplinary approach to study different systems, from animal models to state of the art in vitro cultures including 'next generation' patient-derived brain organoids harboring mutations in each of these ASD-associated genes. We will characterize the contribution of these genes to the reciprocal interaction of migrating PNs and cINs by conditionally deleting them in each of these major classes of neurons in animal models. Brain organoids will be used to study patient's molecular and cellular specific features and their contribution to the abnormal circuit wiring. In short, we will be able provide important new insights into a potential new signature driving neurodevelopmental pathological mechanisms in autism.