The symptoms of schizophrenia severely compromise the quality of life of patients and of their families. Although schizophrenia is a heritable disorder, identifying the specific genes involved and the
biological mechanisms they affect has only recently met with some success. Studies by the Psychiatric Genomic Consortium have revealed hundreds of genetic variants bearing minimal effects on risk for schizophrenia. Still, the biology of these genetic variants remains mostly unknown. Genetic variation between individuals is associated with the function of many genes; the genes affected by variants associated with schizophrenia are generally called “risk genes”. The current understanding of the genetics of schizophrenia suggests that gene networks are key to understanding how genes function in the context of brain cells. However, prior work did not account for lifespan changes in gene networks, mostly involving adult subjects only. Therefore, the function of schizophrenia risk genes in neurotypical development and lifespan changes remains undetermined. This information is vital in fighting schizophrenia because it is thought that the disease’s cause lies in brain developmental changes occurring before the onset. FLOURISH aimed to fill this gap by studying how gene networks in multiple brain regions change from fetal life to older adulthood and how they impact neuroimaging measures that can be acquired in subjects at risk.

A methodological objective of FLOURISH was to develop rigorous models of gene networks derived from postmortem brain materials of neurotypical individuals. A further methodological challenge was obtaining gene networks comparable across time points in the lifespan and across brain regions, despite the biological differences existing between early and advanced ages and between brain regions. Then, FLOURISH aimed to identify schizophrenia risk gene networks and assess their changes from fetal life along the lifespan to translate early and later risk into brain function. To understand how gene networks translate into brain changes across the lifespan, FLOURISH collected genetic and neuroimaging data in a young cohort of individuals between 15 and 25 years old and in a cohort of adult participants (aged 30 to 50 years).

FLOURISH successfully generated well-matched networks carefully controlled for confounding variables which revealed a preeminent role of the perinatal and juvenile dorsolateral prefrontal cortex in aggregating risk for schizophrenia dispersed across many genes. Genes co-expressed with schizophrenia risk genes, not detected in previous genetic studies, were identified and could be used as novel targets for drug development. Within functional magnetic resonance imaging data collected in Bari, Italy, FLOURISH identified connectivity patterns characteristic of young ages that appear overly mature in individuals at risk to develop schizophrenia. These results have been communicated in several scientific meetings and in a workshop targeted at families of patients with schizophrenia and other psychotic disorders.

To assess gene network changes along the lifespan, Dr. Pergola analyzed the LIBD repository of postmortem brain mRNA sequencing data from the dorsolateral prefrontal cortex, hippocampus, and caudate nucleus of 562 individuals deceased between fetal and older adult age with a novel pipeline ensuring age-specific networks comparable with each other. Results revealed the centrality of early prefrontal cortical schizophrenia risk gene networks and have been submitted for a presentation at several major conferences in the field of psychiatric neuroscience. Genetic risk for schizophrenia has also been related to dopaminergic function (Braun et al, 2021 Nature Communications 12(1), 3478) and to treatment response in patients with the disorder (Rampino et al, 2021 European Psychiatry 64(1), pp. e39).

To generate neuroimaging and genetic data, FLOURISH recruited 205 participants in Bari, Italy (47 neurotypical adults, 111 neurotypical young individuals, 12 young individuals at high familial risk for schizophrenia, and 35 young individuals at high clinical risk for schizophrenia). We hypothesized that risk for schizophrenia is related with early manifestation of adult connectivity patterns by assessing differences in brain connectivity between the young and adult neurotypical groups; brain connectivity patterns showing an effect of age were tested for differences between young neurotypical and young at-risk participants. Results supporting the hypothesis have been submitted for a presentation at several international meetings. Part of the neuroimaging work has been used for a study of structural brain developmental trajectories (Wierenga et al, 2020 Human Brain Mapping doi: 10.1002/hbm.25204). Clinical risk for psychosis has also been investigated independently of genetic risk, supporting the idea that early life environment plays a role in psychosis (Antonucci et al., 2021 BMC Psychology 9(1), 47).

For the first time, FLOURISH has developed a model of risk gene network changes during the lifespan. Findings revealed that schizophrenia risk genes converge into networks especially in prefrontal cortex between fetal life and 25 years of age, while the prefrontal cortex is still completing its maturation. The evidence supports an early prefrontal and later hippocampal/caudate involvement in the biology underlying schizophrenia. Results on parsed biological pathways and on the genetic architecture of schizophrenia suggest that knowledge about when in life and where, in the brain, these genes are expressed provides us analytic tools to identify novel genetic associations with schizophrenia and, therefore, novel potential molecular targets for treatment.

Compounding these results, the neuroimaging study revealed that the functional connectivity of the prefrontal cortex with the same regions examined in the postmortem study differed between neurotypical age groups; participants at risk for schizophrenia presented connectivity patterns characteristic of adult life and not of young adulthood, thus suggesting altered functional connectivity lifespan trajectories.

The overall impact of FLOURISH consists of providing models of how genetic risk for schizophrenia is intertwined with the biology of brain development. By addressing both heritable components of the
disease and early neuroimaging markers, this project provides a window into schizophrenia that represented an intuition before the project and is now supported by evidence. A relevant aspect of the project is the communication of results to the families of patients via dedicated events in Bari, Italy. This communication constitutes a form of bilateral exchange between scientists and families affected by the burden of schizophrenia that is very much needed for families to see the progress made in research and for researchers to learn from first-hand experience of the disorder.

Ultimo aggiornamento: 9 Maggio 2022
Numero di registrazione: 660292

Permalink: https://cordis.europa.eu/project/id/798181/reporting/it

© European Union, 2022