Universität Basel

Research Project

CANDY - Comorbid Analysis of Neurodevelopmental Disorders and Epilepsy

Third-party funded project

Project title CANDY - Comorbid Analysis of Neurodevelopmental Disorders and Epilepsy
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Project start 01.04.2019
Probable end 31.03.2023
Status Completed

Early onset neurodevelopmental disorders (NDDs) are common, frequently co-exist with other disorders, come at very high cost, and significantly reduce lifespan. For example, 10–15% of all people in Europe (i.e. 50 to 75 million individuals) are affected by NDDs such as autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), Intellectual Disability (ID), motor problems and language disorders. ăMoreover the number of affected individuals will likely increase – given the rising diagnostic rates of ASD and ADHD. The life-time health and economic burden of these NDDs exceeds that of cancer, stroke or dementia (Gustavsson 2011), and is significantly further increased by their frequent overlap in the same individual and lifetime persistence (Thapar 2017, and **section 1.3**). However, research spend on NDDs is less than 1% of that spend on cancer, stroke or dementia. These NDDs are also often associated with non-mental somatic diseases such as epilepsy, allergies, (auto-)immune and gastrointestinal (GI) diseases, motor problems, and visual and auditory handicaps (Muskens 2017, and **section 1.3**). Patients with ASD or ADHD or ID die on average 20 years younger than individuals in the general population, and this is further amplified by somatic multimorbidity, in particular epilepsy (Hirvikoski 2016; Dalsgaard 2015). Currently, there are no effective treatments for core symptoms of ASD and ID. Existing treatments for ADHD are symptomatic and do not affect either the underlying pathophysiology (which is unknown) or improve long-term outcome (Storebø 2015).

The solution. There is hope, however. A recent fundamental conceptual shift in thinking about NDDs offers new opportunities. There is compelling evidence that some rare genetic variants (e.g. CNVs) increasing risk for ASD, ADHD, and ID are shared (Gonzalez-Mantilla 2016; Short 2018) and converge on relatively few final common pathways (Kiser 2015). Many of them impact on synaptic plasticity and **glutamate and GABA neurotransmission (i.e., excitatory and inhibitory (E/I) balance**) with downstream effects on brain function, cognitive development and risk for somatic multimorbidity, in particular epilepsy. Moreover, outcomes (i.e., symptom profile and severity) are likely moderated by genomic background and environmental factors acting at different time points (critical periods) (Di Filippo 2008). There is in particular emerging evidence that **early maternal immune activation is a shared environmental risk factor across NDDs**, and that its effect varies as a function of interactions between genetic and other environmental factors, such as nutrition and stress (al Haddad 2019; Knuesel 2014; Careaga 2016). Prenatal dietary and immunologic factors not only impact the fetal brain, but also affect the microbiota. Recent work suggests that the **microbiota could be the missing link between environmental "immune" insults in prenatal life and future NDDs** (Kelly 2017; Rudzki 2018; Kang 2018). The interaction between host genetics and gut microbiota could clarify why carrying risk-conferring common variants (i.e. from GWAS) only explain a small part of disease phenotypic variance of NDDs. Basically,

carrying “good” bacteria may in principle overcome the deleterious effect of (i.e.) specific monoamine, glutamate or GABA signalling pathways. On the other hand, “bad” (i.e. pathogenic) bacteria could, in the same way, exacerbate symptomatology even if a protective genetic profile is present. This complex pattern of interaction affects not only neurotransmission (and its precursors) but also endocrine and neuroinflammatory processes observed in NDDs, as shown by us (Aarts 2017) and others (Strati 2017).

Financed by
Commission of the European Union

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