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Prof. Dr. med. Dr. rer. nat. Tobias Banaschewski  
Medical Director and Deputy Director, Department of Child and  
Adolescent Psychiatry and Psychotherapy, Central Institute of Mental  
Health, Medical Faculty Mannheim  
Heidelberg University  
Email: [tobias.banaschewski@zi-mannheim.de](mailto:tobias.banaschewski@zi-mannheim.de)

Re: German Center for Child and Youth Health (*CHILDhealth*)

Dear Tobias,

I am very excited about the opportunities for extending our existing collaboration in the context of the proposed *CHILDhealth* research platform.

Needless to say, *CHILDhealth* addresses a critical public-health issue: mental health. Psychiatric disorders account for almost half of all years lived with disability due to non-communicable diseases. To a great extent, this is due to their early onset – over 50% of these disorders begin before 14 years of age. This is why studying brain development – and factors that shape its trajectories – is so important for our understanding of their origin and long-term outcomes.

In the proposed platform, based on a highly integrated network of leading German centers, you propose to focus on studying early risk (preterm birth, childhood adversity) in relation to brain development, and to do so through the use of large cohorts, deep phenotyping and bioinformatics. This conceptual and methodological framework resonates with our **population-neuroscience approach**. As you know, almost 20 years ago, we have pioneered this type of interdisciplinary integration of epidemiology, genetics and neuroscience when designing the Saguenay Youth Study carried out in Canada (<http://saguenay-youth-study.org/>). Later on, we have built on this early experience when contributing to the design and execution of the IMAGEN Study, as well as in our ongoing collaborative work with other cohorts in Europe (ALSPAC, Northern Finland Birth Cohort), USA (Healthy Brain Network based in New York) and the Brazil High Risk Cohort (based in Porto Alegre and Sao Paulo). It would be exciting to work with you and your colleagues on framing some of your questions based on our experience in different countries, helping with replications and – if useful – facilitating integration of relevant datasets in large international consortia, such as ENIGMA.

Above and beyond the general tenor of your platform, there are two ideas in your proposal that caught my eye.

The first one is the focus on long-term consequences of **preterm birth** vis-à-vis mental health. We have been funded recently by the Canadian Institutes of Health Research to work on “Social Environment and Functioning of Adolescents Born Preterm” using two approaches: (1) a population-based aggregate-level analysis linking exposures (preterm birth) and outcomes (mental health), with social environment (assessed at a neighbourhood level) as a moderator of this

relationship; and (2) a targeted individual-level analysis linking exposures (preterm birth) and outcomes (cognition, brain structure) of adolescents living in a selected subset of neighbourhoods. It would be wonderful to work with your colleagues on a similar topic in the German context.

The other idea I find particularly important is your emphasis of **trans-diagnostic** risk signatures. As you know (as a co-author of our recent paper in *JAMA Psychiatry*), we have identified a common inter-regional profile of differences in cortical thickness between healthy controls and patients with six psychiatric disorders; this work was enabled by our collaboration with six working groups of the ENIGMA Consortium (using data from 145 cohorts). We then used our “virtual histology” approach to identify genes showing similar inter-regional profiles of their expression in the human cerebral cortex and, through a number of additional bioinformatics steps, concluded that both prenatal and post-natal development may play a role in giving rise to this “transdiagnostic” signature. It would be fairly straightforward to implement this strategy in your platform; should you decide to do so, we would be happy to provide the scripts and expertise to facilitate this. I should also note that this is an example of how important it is to include pre-clinical work on experimental models, both to validate “virtual histology” with “true histology” but also to inject causality to otherwise observational data yielded by human studies. I see this as yet another strength of your proposal.

As you can see, I am very excited about the prospects of your application succeeding in the final stage of the competition. If successful, this would open opportunities for moving our existing collaborations to the next level.

Wishing you and your colleagues good luck!

Yours sincerely,



Tomáš Paus MD, PhD

Professor of Psychology and Psychiatry  
University of Toronto