Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Multimodal neural network connectivity and genetic risk factors for Psychopathology

Autor: Anais Buhl
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktormutter: Prof. Dr. Dr. H. Tost

Most neuropsychiatric disorders are at least moderately heritable. Two functional candidate variants affecting monoaminergic neurotransmission are MAOA and 5HTTLPR. Earlier neuroimaging studies connected genetic variance in these polymorphisms with alterations in brain function and structure mainly in corticolimbic circuits. However, these initial findings have been questioned because of failure to replicate in larger cohorts and lack of clear meta-analytic evidence. Therefore, the current work investigated the following hypotheses: 1) Network phenotypes are more sensitive to the subtle effects of typical genetic risk variants than traditional neuroimaging approaches. 2) Applying a whole-brain, connectomic approach will detect widespread effects. 3) Genetic variance in the serotonergic system impacts structural and functional connectivity patterns even without an active task. However, a task that challenges a significant cognitive domain might increase sensitivity. 4) Networks showing altered connectivity patterns in carriers of serotonergic risk variants are also associated with differences in emotion regulation. We examined a sample of 223 healthy subjects with an emotional face processing task to re-evaluate the association between 5-HTTLPR and amygdala activation, explore potential network-based functional connectivity phenotypes for associations with 5-HTTLPR, and probe the reliability, behavioral significance and potential structural confounds of the identified network phenotype. Our results show that the number of risk alleles was significantly correlated with functional connectivity of a visual-limbic subnetwork (PFWE=0.03). This subnetwork cluster included brain regions that are pivotal to emotion regulation.
Notably, individuals with lower subnetwork connectivity had significantly higher emotion suppression scores (P=0.01). In the second study, we included healthy individuals using multimodal neuroimaging (sample size range: 219-284 across modalities) and network-based statistics (NBS) to probe the specificity of MAOA-L-related connectomic alterations to cortical-limbic circuits and the emotion processing domain. We assessed the spatial distribution of affected links across several neuroimaging tasks and data modalities. Our results revealed a dstributed network of node links with a significantly increased connectivity in MAOA-L carriers compared to the carriers of the high expression (H) variant. The hyperconnectivity phenotype primarily consisted of between-lobe network links and showed a pronounced involvement of frontal-temporal connections. Hyperconnectivity was observed across functional magnetic resonance imaging (fMRI) of implicit emotion processing (pFWE = 0.037), resting-state fMRI (pFWE =0.022), and diffusion tensor imaging (pFWE = 0.044) data. The current work extended on earlier research linking serotonergic genetic variants with altered neural connectivity. Our novel, connectomic method showed that serotonergic genetic variance affects large brain networks that include but are not limited to frontotemporal regions. The present work confirmed that connectomic, unbiased methods are more sensitive to the often subtle effects of genetic risk polymorphisms. Whereas the effect of 5HTTLPR was only evident during an emotion processing task, MAOA genotype had an effect on resting state connectivity and anatomic connectivity in addition to connectivity during emotion processing. One possible explanation for this more general effect of MAOA genotype is that in contrast to the 5HTTLPR polymorphism which selectively affects serotonergic neurotransmission, MAOA is not only involved in serotonergic neural signaling but catalyzes the metabolism of other monoaminergic neurotransmitters including noradrenaline and dopamine.