DOES THE COGNITIVE HETEROGENEITY WITHIN AUTISM SPECTRUM DISORDER REFLECT THE UNDERLYING GENETIC HETEROGENEITY?

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Background: Numerous studies have shown impairments in cognitive functioning in individuals with autism spectrum disorder (ASD) compared to typically developing (TD) controls. However, when looking at specific cognitive characteristics, large inter-individual differences have been found. This cognitive heterogeneity within ASD is thought to (at least partially) reflect the underlying genetic heterogeneity. As such, genetically distinct ASD subgroups are expected to show distinct cognitive profiles. The cognitive function under study is executive functioning (EF).

Aim: Firstly, we charted the heterogeneity of EF within our ASD sample. Secondly, we investigated whether two genetically distinct ASD samples show differences in EF, compared to a TD group. Finally, we examined whether clustering of the individuals from both ASD samples, based on their EF profile, resulted in different clusters for both groups.

Method: Five EF domains (i.e., inhibition, cognitive flexibility, working memory, generativity, and planning) were measured in 58 TD controls, 58 individuals with ASD and 19 individuals with neurofibromatosis type 1 and co-occurring ASD (NF1+ASD group) (aged 8-to-18 years). NF1 is an autosomal dominant disorder caused by a mutation in the NF1 gene. To examine the cognitive heterogeneity, a multiple case series analyses was used to calculate the percentage of individuals with ASD that showed impaired / superior performance compared to the TD group, for each EF domain separately. K-means cluster-analyses were performed for both ASD samples to delineate clusters with a more similar EF profile.

Results: We found that none of the EF impairments were present in all individuals with ASD, with large inter-individual differences in the number and type of cognitive domains on which they show deviations. Interestingly, some individuals even performed better than controls on some of the EF measures. When comparing both ASD samples, the NF1+ASD group displayed more EF problems compared to the ASD group. Finally, by performing cluster-analyses, different clusters emerged, each with a different EF profile. Interestingly, the distribution of both ASD samples over the different clusters differed significantly, with two clusters mainly containing individuals with ASD, one cluster containing mainly individuals with NF1+ASD and one cluster with an equal percentage of individuals from both groups. However, each cluster contained individuals from both groups.

Discussion: Although the genetically distinct ASD groups showed group differences on some EF domains, both groups did not emerge as clearly separated clusters with a distinct EF profile. Hence, EF characteristics alone do not allow to differentiate between individuals with ASD with and without a dominant monogenetic mutation. This might be due to the large distance between genes and EF and the complex gene-gene and gene-environment interactions that influence the EF profile. Based on these findings, we want to discuss the utility of cognitive subtyping to reveal biologically distinct ASD subgroups. Furthermore, we want to consider the value of cognitive characteristics as potential intermediate phenotypes linking brain and behavior and how future research could elucidate this further.