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Polderman, Tinca J.C.

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Editorial: The Genetic Overlap Between Cognitive Abilities and a Transdiagnostic Vulnerability for Psychopathology

Tinca J.C. Polderman, PhD

Cognitive abilities, such as working memory, selective attention, inhibition, alertness, and flexibility, are collectively known as executive functioning (EF), which is essential in daily life routines. For instance, EF is important when planning a series of actions, in novel situations, or during the performance of complex tasks. General intelligence, or g , is a related construct and involves, for instance, the ability to reason, plan, solve problems, think abstractly, and learn from experience. The concept g is usually measured with a psychometric intelligence test. It has been known for more than a decade that EF and, in particular, g are negatively correlated with psychopathology. Yet, the underlying source of this correlation is largely unknown.

Twin studies are commonly used to disentangle genetic from environmental sources that contribute to the correlation between two traits. Monozygotic (MZ) twin pairs are genetically identical, whereas dizygotic (DZ) twin pairs share on average half of their genetic material. Yet, both types of twins are similar in how they share their environment. When so-called “cross trait/cross twin correlations” (eg, the correlation between EF of twin 1 and anxiety of twin 2, and vice versa) are on average higher within MZ twin pairs compared to DZ twin pairs, this indicates that genetic factors partly explain the correlation between both traits. Studies investigating genetic and environmental influences on the association between psychopathology and EF and g have so far focused mainly on attention problems and attention-deficit/hyperactivity disorder (ADHD) symptoms. Phenotypic correlations between g and attention problems typically vary between -0.25 and -0.35 , and part of this correlation appears to be explained by shared genetic factors.^{1,2}

However, the association of EF and g with psychopathological disorders is not specific for one or two disorders. Instead, these cognitive abilities are associated with a range of psychopathological problems. Moreover, comorbidity

between disorders is often the rule rather than the exception; for example, anxiety and ADHD symptoms often co-occur. In addition, several recent genetic studies have reported genetic correlations between psychopathological disorders (eg, r_g of 0.42 between ADHD and major depression³), suggesting that these disorders share biological underpinnings. Therefore, Harden *et al.*⁴ decided to examine the association of EF and g with a phenotype that covers a broad spectrum of internalizing, externalizing, and attention-related psychopathological behaviors. In their study, this phenotype represents a “transdiagnostic dimension of vulnerability to psychopathology” that is measured in a general population. The impressively large sample of this study consisted of almost 2000 MZ and DZ Texan twins, varying in age from 7 to 20 years. Psychopathological problems were assessed with well-known self- and parent-rated behavioral questionnaires, and g was measured with a shortened psychometric IQ test. EF was administered in half of the sample, with 12 tasks covering the abilities inhibition, switching, working memory, and updating. A first set of analyses showed that the different behavioral reports, the various EF tasks, and the four psychometric IQ tests each clustered in one factor. Subsequent analyses of these factors showed that EF and g were both negatively associated with psychopathological problems. For parent-reported psychopathology specifically, a nonlinear association was observed: the strongest associations with psychopathology were observed in children with very low scores on g and weak EF abilities. This quadratic pattern of associations was not observed for child-reported psychopathology, leading the authors to speculate that children with low cognitive abilities might be less competent to properly reflect on their own feelings and behavior.

Another notable finding was the unique association between attention-related problems and EF, and g , above and beyond the association with the general psychopathology factor. This is a rather surprising finding, as only about

a decade ago researchers were rather skeptical about the relation between attention problems and EF: “Deficient attention is hard to find” reported Huang-Pollock *et al.*,⁵ when investigating selective attention in a sample of children affected with ADHD. Other studies also suggested that the evidence for impaired cognitive functioning was not unambiguous.⁶ The current study, however, suggests that a general factor, capturing several forms of EF, does correlate specifically with attention-related problems in the general population. This is an important finding, encouraging new hypotheses about the association between the total spectrum of EF and attention deficits in behavior.

Finally, it was shown that the general psychopathology, EF, and *g* factor were highly heritable (>70%), and that the observed associations resulted mostly from shared genetic influences. Interestingly, for EF and general psychopathology, a significant unique environmental correlation was observed as well. This might suggest a causal relation between EF and general psychopathology, yet, with the direction being unknown. Alternatively, it might imply that both factors share the same unique environmental influences without any causal relationship. Thus, although noteworthy, based on the current study, this particular finding is hard to interpret, and future studies in longitudinal genetically informative designs are needed to shed some light on the pattern of causality.

The findings of the current study⁴ are more and more supported by recent genetic studies that use results of large genome-wide association studies to test the genetic overlap between traits. A first hint of the nature of the shared biological mechanisms is that the majority of genes implicated for psychopathology (eg, ADHD³) and IQ⁷ are

expressed in the brain. In addition, these latest genetic findings for IQ showed negative genetic correlations with ADHD ($r_g = -0.36$), depression ($r_g = -0.27$), and schizophrenia ($r_g = -0.21$). These genetic studies can also be used to test for causality using mendelian randomization (MR) analyses (for a clear guide on MR, see Davies *et al.*⁸). This type of analysis for IQ revealed a bi-directional causal link between IQ and schizophrenia, and a protective effect of higher IQ on ADHD.

All in all, accumulating evidence from twin, family, and molecular genetic studies shows overlap in genetic factors between cognition and psychopathology. Not surprisingly, recent molecular genetic research suggests that the shared genetic factors appear to derive from mechanisms in the brain. This type of study also starts to address questions of causality, which is a very welcome addition to twin and family studies. The latter need extensive longitudinal, genetically informative designs with a comprehensive data collection to address this question, and these data are, as yet, scarce.

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Dr. Polderman is with the Center for Neuroscience and Cognitive Research, Vrije Universiteit, Amsterdam, The Netherlands.

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Correspondence to T.J.C. Polderman, Vrije Universiteit Amsterdam, Center for Neurogenetics and Cognitive Research, Complex Trait Genetics, De Boelelaan 1085, 1081 HV, Amsterdam, The Netherlands; e-mail: tinca.polderman@vu.nl

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