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Published in:
Twin research and human genetics

DOI:
10.1017/thg.2012.112

Publication date:
2013

Twin Research and Human Genetics
Volume 16 ▌ Number 1 ▌ pp. 268–270 ▌ © The Authors 2012 ▌ doi:10.1017/thg.2012.112

The Twin Interdisciplinary Neuroticism Study

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The Twin Interdisciplinary Neuroticism Study (TWINS) is a three-wave study including >800 twin pairs from the northern part of the Netherlands. The aim of the study is to unravel why neuroticism reflects vulnerability to mental disorders. In this study, we focus on possible mechanisms underlying this vulnerability and their genetic and environmental origins. In total, 125 female twin pairs visited our psychophysiological laboratory. From these twin pairs DNA was isolated and both candidate gene and genome-wide genotyping were conducted. Future work includes studies of candidate genes. The study also participates in several meta-genome-wide association study (GWAS) consortia.

■ **Keywords:** neuroticism, DNA, psychophysiology, cardiac autonomic nervous system, HPA-axis, cognitive bias

Major Research Focus

The Twin Interdisciplinary Neuroticism Study (TWINS) is a three-wave study including >800 twin pairs from the northern part of the Netherlands (see Appendix A Table A1 for an overview of the study). The aim of the study is to unravel why neuroticism is a marker of vulnerability to affective disorders (e.g., depression and anxiety). The unique aspect of this twin study is the a priori selection of studied underlying mechanisms that may (partly) explain neuroticism's association with affective disorders. We hypothesize that biased cognitions for negative (emotional) stimuli and the major physiological stress mechanisms (cardiac autonomic nervous system and the hypothalamus-pituitary adrenal axis function) represent mechanisms that underlie the relationship between neuroticism and onset, maintenance, or recurrence of affective disorders. More specifically, we hypothesize that cognitive deviations in capacities for decoding and encoding negative (emotional) stimuli (Rijsdijk et al., 2009), and deregulated physiological stress mechanisms account for part of the association (Riese et al., 2007, 2009). Classic behavioral genetic analyses were used to test if a single common genetic factor can account for the phenotypic correlation between neuroticism, and each of the cognitive and physiological stress measures.

Recruitment and Zygosity Determination

The sample for TWINS was selected from the Groningen Twin Register (GTR). To establish the GTR, in 2001 nine municipalities with more than 31,000 inhabitants in the north of The Netherlands were requested to provide addresses of inhabitants born between 1972 and 1992, from the same mother with an identical date of birth. All the twins identified in this way received an invitation to participate in the GTR. In 2002 (T1), 1,047 participants filled out a survey, which included, among others, a zygosity questionnaire (Nichols & Bilbro, 1966) and the NEO Five Factor Inventory (NEO-FFI) neuroticism scale (Hoekstra et al., 1996). In 2003 (T2), 125 female twin pairs aged between 18 and 30 years old were invited to visit our psychophysiological laboratory to perform various tasks (Riese et al., 2006; Rijsdijk et al., 2009). At T2, neuroticism was evaluated again with the NEO-FFI inventory, and additionally with the Eysenck Personality Questionnaire (Sanderman et al., 1991), along

RECEIVED 19 July 2012; ACCEPTED 12 October 2012. First published online 28 November 2012.

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TABLE 1

Overview of Measures Assessed in the Groningen Twin Register (GTR) and Twin Interdisciplinary Neuroticism Study (TWINS)

T1 (2002) GTR survey	
Questionnaires	Zygosity, neuroticism (NEO-FFI), temperament (ATQ), life events, coping (self-report and co-twin report), psychosomatic symptoms
T2 (2003/2004) Selected female twin pairs for the TWINS study	
Survey	
Questionnaires	Neuroticism (NEO-FFI, EPQ, NEO-PI-R impulsiveness, NEO-PI-R Vulnerability), aggression (Buss-Perry), anxiety/depression (SCL8), social (support, contacts), interpersonal sensitivity (IPSM), lifestyle (drug use, physical activity), birth/early youth, education, health status (GHQ)
Experimental session	
Questionnaires	Neuroticism (NEO-FFI cotwin report), temperament (ATQ cotwin report), anxiety/depression (SCL8 cotwin report), social desirability (EPQ), intelligence (GAT-B), mood (POMS, STAI-DY1, Manakin)
Fasting blood measures	DNA (zygosity, GWAS), glucose, insulin, total cholesterol, HDL-C, triglycerides, C-reactive protein, fibrinogen, IgG, free fatty acids, hematocrit
Psychophysiological measures	BMI, WHR, skinfolds, armcuff SBP and DBP, heart rate, heart rate variability, baroreflex sensitivity, cortisol awakenings response, attention bias, memory recall bias
T3 (2006) GTR survey	
Questionnaires	Zygosity, neuroticism (NEO-PI-R impulsiveness, NEO-PI-R vulnerability, NEO-PI-R hostility, NEO-PI-R self-consciousness), life events, coping, DSM-IV diagnosis (self-rated vignettes)

with a co-twin report on the earlier mentioned NEO-FFI scale. Zygosity of this target group was determined using 10 micro-satellite markers. Due to technical failures, zygosity of three twin pairs could not be determined by DNA genotyping; for these pairs, survey data on zygosity were used instead. In 2006, all registered and additionally recruited twins aged 15–35 ($N = 1{,}128$) were asked to fill out a survey, which 815 (72%) twins returned. This survey included a zygosity questionnaire (Nichols & Bilbro, 1966), and four facets (hostility, self-consciousness, impulsiveness, and vulnerability) of the neuroticism scales of the NEO-PI-R inventory (Hoekstra et al., 1996). A more detailed overview of the measures assessed is given in Table 1.

Major Achievements

The genetic relationship between neuroticism and the psychophysiological variables and cognitive deviations were tested. The psychophysiological variables measured were the cortisol awakening response (CAR) and cardiovascular measures (inter-beat interval, heart rate variability [HRV] and baroreflexsensitivity [BRS]). Neuroticism and the CAR were both found to be heritable, but did not share any genetic influences (Riese et al., 2009). The three cardiovascular measures were found to be heritable (Riese et al., 2006, 2007). Neuroticism was moderately negatively correlated with BRS and HRV. For BRS, this correlation with neuroticism was entirely determined by shared genetic influences; for HRV largely by genetic influences. We concluded that high neuroticism is associated with a deregulated cardiac autonomic nervous system, which may be partly due to pleiotropic genetic effects. Cognitive deviations were measured by means of cognitive tasks tapping into memory recall bias and an attention bias for emotional stimuli (Rijsdijk et al., 2009). At the higher end of the distribution of the neuroticism scale, neuroticism was correlated with the proportion of recalled unpleasant words. This effect was due to shared environmental influences, rather than genetic influences. There was no evidence that the cognitive predisposition to focus on negative (emotional) stimuli is a possible underlying genetic mechanism of neuroticism.

Future Plans

From the target group (e.g., the 125 female twin pairs) DNA was isolated and both candidate gene and genome-wide genotyping were conducted. Future works include candidate gene studies and the study participates in several meta-genome-wide association study consortia.

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Appendix A

TABLE A1

Overview of the Twin Interdisciplinary Neuroticism Study (TWINS)

Country	The (north of the) Netherlands
Sample	General population
Opposite sex twins (yes or no)	Yes (survey data only)
Number of twins	Circa 800 twins
Variables measured	Survey data. For the female target group ($n = 125$ pairs; 74 MZ, 51 DZ), among others, repeated measures and co-twin reports on neuroticism, and psychophysiological and cognitive measures.
DNA/blood samples	For the female target group ($n = 125$ pairs) GWAS data are available
Contact	Harriëtte Riese
E-mail	h.riese@umcg.nl
Major publications	(Riese et al., 2006, 2007, 2009; Rijsdijk et al., 2009; Tops et al., 2008)
Major source of funding	NWO, Medische Wetenschappen (0804/904-57-130)
Comments	No future assessment waves are currently planned