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Evidence of a prominent genetic basis for associations between psychoneurometric traits and common mental disorders☆

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ABSTRACT

Threat sensitivity (THT) and weak inhibitory control (or disinhibition; DIS) are trait constructs that relate to multiple types of psychopathology and can be assessed psychoneurometrically (i.e., using self-report and physiological indicators combined). However, to establish that psychoneurometric assessments of THT and DIS index biologically-based liabilities, it is important to clarify the etiologic bases of these variables and their associations with clinical problems. The current work addressed this important issue using data from a sample of identical and fraternal adult twins ($N = 454$). THT was quantified using a scale measure and three physiological indicators of emotional reactivity to visual aversive stimuli. DIS was operationalized using scores on two scale measures combined with two brain indicators from cognitive processing tasks. THT and DIS operationalized in these ways both showed appreciable heritability (0.45, 0.68), and genetic variance in these traits accounted for most of their phenotypic associations with fear, distress, and substance use disorder symptoms. Our findings suggest that, as indices of basic dispositional liabilities for multiple forms of psychopathology with direct links to neurophysiology, psychoneurometric assessments of THT and DIS represent novel and important targets for biologically-oriented research on psychopathology.

1. Introduction

The National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) initiative seeks to reorient psychopathology research toward the study of core biobehavioral constructs such as threat or reward sensitivity and cognitive control, in order to advance neurobiological understanding of psychiatric conditions and improve methods for preventing and treating them (Kozak and Cuthbert, 2016). To facilitate this endeavor, new approaches for assessing mental health problems are needed (Lilienfeld, 2014; Patrick and Hajcak, 2016). One approach, termed *psychoneurometrics* (Nelson et al., 2011; Patrick et al., 2013; Patrick et al., 2012; Yancey et al., 2016), involves combining indicators from different assessment domains (e.g., neural, behavioral, psychological-scale) to quantify individual characteristics that relate to mental disorders. Two such characteristics are threat sensitivity (THT) and weak inhibitory control (or disinhibition; DIS). Prior work has shown that joint psychological-scale/neurophysiological (psychoneurometric) assessments of these dispositions show robust relations with patient-reported clinical problems of various types and outperform scale measures in predicting neurophysiological criterion measures (Patrick et al., 2013; Yancey et al., 2016). As a next step in evaluating their substantive nature and scientific utility, the current study used data from an adult twin sample to examine the contributions of genetic and environmental influences to variance in psychoneurometric THT and DIS variables and clarify the etiologic bases of their relations with differing forms of psychopathology.

Dispositional fear/fearlessness, corresponding to "acute threat" in the Negative Valence Systems domain of the RDoC framework, and

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inhibitory control (inhibition/disinhibition), corresponding to "response inhibition" in the Cognitive Systems domain, are biobehavioral dispositions with potential relevance to many common forms of psychopathology. Dispositional fear (or threat sensitivity; THT), reflecting heightened negative emotional reactivity to threatening situations and stimuli, appears most relevant to focal fear disorders such as specific phobia, social phobia, and panic disorder. Weak inhibitory control (or disinhibition; DIS), reflecting impaired capacity for behavioral restraint, appears most relevant to externalizing conditions such as alcohol and drug dependence and antisocial behavior problems. Both dispositions may play a role in distress (Watson, 2005; or "anxious misery" Krueger, 1999) conditions such as major depression, dysthymia, and generalized anxiety disorder—which are characterized by pervasive, dysregulated negative affect.

Nelson et al. (2016) reported on relationships of THT and DIS assessed using self-report scales alone with symptoms of multiple DSM-IV clinical disorders in a large community adult sample. Robust associations with internalizing disorder symptoms were evident for both trait variables, with THT more predictive of fear disorder symptoms and DIS more predictive of distress disorder symptoms. For substance use disorders, prediction was evident only for DIS. Additionally, interactive effects of THT and DIS were found for distress disorders, and to a lesser extent, fear disorders—with participants scoring high on both trait variables exhibiting markedly elevated levels of symptomatology relative to those scoring high on one or the other. The implication is that the presence of both traits is associated with the pervasive, dysregulated negative affect that characterizes conditions such as recurrent depression, generalized anxiety disorder, and posttraumatic stress disorder. Of note, work with community and clinical samples has shown that THT and DIS also predict separately and interactively to suicidal behavior (Venables et al., 2015).

Other research has shown that these trait dispositions remain predictive of disorder symptoms when assessed using self-report scale and neurophysiological indicators combined (i.e., psychoneurometrically), at levels comparable to prediction using scale measures alone. Importantly, psychoneurometric assessments of these traits show appreciably higher associations with neurophysiological criterion measures. Specifically, Patrick et al. (2013) reported that DIS quantified as a composite of two trait-relevant scale measures and two variants of the P300 brain response (known to correlate reliably with disinhibitory tendencies; Patrick et al., 2006; Yancey et al., 2013) outperformed self-report DIS substantially in predicting cognitive-brain criterion measures, while predicting externalizing disorder symptoms to an equivalent degree. In parallel with this, Yancey et al. (2016) reported that THT quantified as a composite of scores on a fear/fearlessness scale (Kramer et al., 2012) along with three lab physiological measures of reactivity to discrete aversive stimuli (in a picture-viewing task) outperformed self-report THT by over 30% in predicting separate criterion measures of fear-cue reactivity, with no reduction in prediction of fear disorder symptoms. These results illustrate the potential utility of a cross-domain ('multi-unit') approach to assessing psychopathology-related constructs, as advocated by RDoC: Individuals who score high on dispositional dimensions quantified partly by lab neurophysiological indicators can be expected to differ more reliably in other neurobiological characteristics of interest (e.g., brain activations measured using neuroimaging; responsiveness to pharmacological interventions) than those scoring high on dimensions indexed by self-report alone.

Given findings indicating that THT and DIS assessed in this manner show robust associations with clinical problems of various types, an important question is whether and to what extent these observed associations reflect common genetic influences, as opposed to overlapping environmental influences. A prominent genetic basis to observed relations between psychoneurometric measures of these traits and clinical outcomes would support the notion that these cross-domain trait measures index constitutionally-based liability factors for psychopathology. A more appreciable environmental basis to overlap between the two, on the other hand, would suggest that traits quantified this way reflect shaping influences of experiential factors on self-perceptions and reactivity patterns in common with experiential factors that contribute to the occurrence of clinical problems.

The current study addressed key questions regarding the etiological bases of observed relations between psychoneurometric measures of THT and DIS (Patrick et al., 2013; Yancey et al., 2016) and common forms of psychopathology (cf. Krueger, 1999) by undertaking biometric analyses of multi-domain data (self-report, clinical-diagnostic, psychophysiological) from a mixed-gender sample of adult twins. In line with the focus of the RDoC initiative on problem dimensions rather than discrete disorders (Kozak and Cuthbert, 2016), and following prior published work utilizing DSM-based symptom dimensions as clinical criterion measures (e.g., Lang et al., 2016), our analyses focused on broad symptom factors (i.e., fear, distress, substance; Nelson et al., 2016) rather than binary diagnoses or symptom counts for individual disorders. Major study hypotheses were that: (1) psychoneurometric trait variables and clinical symptom variables would each show appreciable heritabilities, and (2) the observed (phenotypic) covariation between psychoneurometric and symptom variables would be accounted for largely by common genetic influences. In addition to examining the etiological bases of observed relations for THT and DIS with broad symptom dimensions, we also assessed contributions of genetic and environmental influences to the relationship for the interaction of the two traits (quantified as a product term) with distress and fear disorder symptoms. Though we did not have specific hypotheses for this interaction term, we expected that knowledge regarding the etiological basis of its association with affective symptomology would help to clarify the construct represented by the product of the two traits.

2. Method

2.1. Participants

The base sample for the study consisted of 508 adult twins (133 female monozygotic [MZ], 124 female dizygotic [DZ], 127 male MZ, and 124 male DZ) recruited from the greater Twin Cities metro area. Most participants were tested concurrently with their same gender co-twin on the same day, but by different experimenters in separate laboratory testing rooms. Participants were selected for participation in lab testing based on levels of THT as indexed by scores on a 55-item Trait Fear scale as described below (see also: Yancey et al., 2015; Yancey et al., 2016), and as being free from visual or hearing impairments as assessed by a screening questionnaire. (Further information regarding the sampling strategy for the study is provided in Nelson et al. (2016)). Twenty-two members of the base sample were excluded from analyses due to missing individual difference data; 32 others were excluded due to missing or artifact-ridden data for two or all three of the main physiological indicators of THT or DIS. These exclusions resulted in an N of 454 for data analyses involving psychoneurometric variables (51.3% female; M age = 29.5 years, SD = 4.84). Data for the 471 participants reported on by Nelson et al. (2016) were utilized in biometric analyses focusing on diagnostic variables per se. All participants provided informed written consent and were compensated $100 for participation. Study procedures were approved by the University of Minnesota's Institutional Review Board.

2.2. Experimental paradigms and physiological recording procedures

The data for the current analyses were collected as part of a larger physiological assessment protocol that included affective picture-viewing and visual oddball task procedures. Participants were seated in a padded recliner, and completed a series of questionnaires while an elastic cap fitted with electroencephalographic (EEG) sensors was attached along with peripheral electrodes to record brain and other physiological reactivity. During testing, participants viewed the task stimuli on a 21″