Separate and interactive contributions of weak inhibitory control and threat sensitivity to prediction of suicide risk

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Biobehavioral dispositions can serve as valuable referents for biologically oriented research on core processes with relevance to many psychiatric conditions. The present study examined two such dispositional variables—weak response inhibition (or disinhibition; INH—) and threat sensitivity (or fearfulness; THT+)—as predictors of the serious transdiagnostic problem of suicide risk in two samples: male and female outpatients from a U.S. clinic (N = 1078), and a population-based male military cohort from Finland (N = 3855). INH— and THT+ were operationalized through scores on scale measures of disinhibition and fear/fearlessness, known to be related to DSM-defined clinical conditions and brain biomarkers. Suicide risk was assessed by clinician ratings (clinic sample) and questionnaires (both samples). Across samples and alternative suicide indices, INH— and THT+ each contributed uniquely to prediction of suicide risk—beyond internalizing and externalizing problems in the case of the clinic sample where diagnostic data were available. Further, in both samples, INH— and THT+ interactively predicted suicide risk, with individuals scoring concurrently high on both dispositions exhibiting markedly augmented risk. Findings demonstrate that dispositional constructs of INH— and THT+ are predictive of suicide risk, and hold potential as referents for biological research on suicidal behavior.

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1. Introduction

Suicide is a socially devastating problem that calls for ongoing systematic investigation. In light of compelling evidence for heritable individual difference factors in suicidal behavior, research is needed to clarify how biobehavioral tendencies contribute to the emergence of distinct suicide-promoting processes (Van Orden et al., 2010). The current work addresses this need by demonstrating separate as well as interactive contributions of the biobehavioral constructs of weak inhibitory control and threat sensitivity, operationalized as externalizing proneness (disinhibition) and fear/fearlessness, to prediction of suicidal tendencies.

Although rare, lethal acts of self-harm have antecedents—in the form of ideation, planning, and attempts—that are far more common (Kessler et al., 1999). Thus, suicide risk can be conceptualized as a behavioral continuum ranging in severity from thoughts about death (e.g., “I wish this all would just end” or “I wish I was dead”) through contemplation of self-harm to planning and preparation to attempts. The importance of dispositional vulnerabilities in suicide risk is highlighted by family, twin, and adoption studies demonstrating heritability for suicidal behavior. When broadly defined to include suicidal ideation, plans, and attempts, heritability estimates range from 30% to 50% (Brezo et al., 2008). Notably, heritability estimates vary depending on the aspect of suicidality that is measured, with estimates for death by suicide consistently higher than those for ideation or non-fatal attempts (Brezo et al., 2008).

Evidence for a role of weak inhibitory control in suicidal behavior comes from research on impulsive–aggressive traits,
which show robust predictive relations with suicidal ideation and behavior (Turecki, 2005) and have been characterized as a candidate endophenotype for suicide (Mann et al., 2009; Courtet et al., 2011). Evidence for a role of threat sensitivity in suicidality comes from research demonstrating positive relations of negative emotional tendencies with suicidal tendencies and clinical conditions associated with suicide (e.g., depressive and anxiety-related disorders; Brandes and Bienvenu, 2006). Negative emotional reactivity represents a pre-morbid vulnerability factor for depression (Kendler et al., 2003) and suicide (Khan et al., 2005), and constitutes the key dispositional variable linking internalizing disorders with suicidality. Notably, a diagnostic condition with high rates of suicidal behavior, borderline personality disorder (Sansone, 2004), reflects the conjunction of impulsive-aggressive tendencies and high negative affectivity. Older and newer studies point to reduced levels of the brain neurotransmitter serotonin as related to increased levels of both impulsivity and negative affectivity (Minzenberg and Siever, 2006; See et al., 2008), and in turn borderline personality tendencies (Gurvits et al., 2000) and risk for suicide (Joiner et al., 2005).

To further clarify the biological bases of suicide risk, it will be important to focus research attention on dispositional constructs akin to impulsivity and negative affectivity that connect more clearly to distinct neurobiological systems and can be related to core-suicidal promoting processes (Van Orden et al., 2010). The National Institute of Mental Health’s Research Domain Criteria (RDoC; Sanislow et al., 2010) framework provides an expert-consensus based listing of biobehavioral constructs to serve as targets for psychopathology research. Two such constructs are response inhibition, presumed to reflect variations in the functionality of executive control circuitry, and acute threat (“fear”), theorized to reflect variations in sensitivity of the brain’s defensive system. In trait-dispositional terms, these constructs correspond to inhibitory control capacity and threat sensitivity.

The current work evaluated whether dispositional tendencies toward weak inhibitory control (INH –) and high threat sensitivity (THT +) would predict suicide risk in two large participant samples: (1) clinic outpatients from the U.S., and (2) young men reporting for military call-up in Finland. INH – was assessed using scale measures of trait disinhibition, or externalizing proneness, defined as the general propensity toward problems of impulse control (e.g., antisocial and substance use disorders; Krueger et al., 2007). In terms of biobehavioral correlates, disinhibition defined in this way predicts deficits in brain response to task stimuli in visual–motor paradigms (Yancey et al., 2013) and impaired behavioral performance on cognitive control tasks (Young et al., 2009). THT + was assessed using scale measures of dispositional fear/fearlessness (or boldness; Patrick et al., 2012), defined in terms of reported fear in relation to specific stimuli, events, and contexts (Kramer et al., 2012). Scores on fear/fearlessness defined in this way are uncorrelated with disinhibitory-externalizing tendencies (Patrick et al., 2012), and show robust associations with DSM-defined phobic disorders and symptoms (Nelson et al., in press; Sellbom et al., 2012) and physiological defensive reactivity as indexed by aversive startle potentiation (Kramer et al., 2012; Vaidyanathan et al., 2012).

Operating from a process-oriented theory of suicidal behavior (Van Orden et al., 2010), which emphasizes a role for persisting negative affect in suicidal thoughts/desire and a role for impulsive risk-taking in the capacity for active self-harm, we hypothesized that weak inhibitory control (operationalized as disinhibition) and high threat sensitivity (operationalized as fear/fearlessness) would each contribute uniquely to increased suicide risk. In addition, we postulated that the co-occurrence of these two distinct suicide-promoting dispositions would exert a synergistic (i.e., interactive) effect on suicide-proneness. This hypothesis was based on the markedly elevated rates of suicidality in borderline personality disorder, which entails elevations in both disinhibition and dispositional fear (Patrick et al., 2012), and evidence indicating that the co-occurrence of impulsivity and negative affectivity reflects a distinct neurobiological condition—entailing reduced serotonergic activity—that relates to high suicide risk.

2. Methods

2.1. Participants

2.1.1. Outpatient clinic sample

Outpatient participants were 1078 men and women who underwent psychological evaluations at a university psychology clinic from 2000 to 2010. The clinic serves both students and community residents presenting with clinical problems typical of a community mental health outpatient clinic. The mean age of the sample was 26.7(S.D. = 9.7); 55.2% were female. Most (77.6%) participants were treatment-seeking, with the remainder seen for psychological assessment only. Patients provided informed written consent to participate and underwent an intake screening procedure assessing for psychological problems including suicide risk (Joiner et al., 1999) and psychopathology. Upon admission, patients were assigned to an individual therapist and underwent a diagnostic assessment that included a structured clinical interview assessing for DSM-IV disorders. Study procedures were approved by Florida State University’s Review Board.

2.1.2. Finnish Army recruit sample

This sample consisted of adult men (born mainly in 1991) reporting for call-up to the Finnish military between September and November, 2009. The military call-up is a standard procedure for assessing suitability for military service that all Finnish male citizens undergo at age 18. To ensure a random population-representative sample of this designated age cohort, participants were selected across geographical areas of Finland, with emphasis on the most densely populated southern parts. The target sample included 4910 men attending the military call-up in these four military call-up districts. Altogether, 4324 men (88.1%) returned the questionnaires administered for the study.

At call-up, participants were given the option of completing a set of questionnaires. Participants were advised that this assessment was separate from the military call-up evaluation and was being conducted on a voluntary, research basis. To ensure anonymity, questionnaire responses were coded by number and returned in sealed envelopes. The questionnaire packet included a consent form that participants read and signed prior to completing measures. Data were obtained from 4309 males mainly aged 18 years; 454 (10.5%) of these did not complete all questionnaire measures needed for current analyses, leading to a final sample size of 3855. The study was approved by the ethical committees of Turku University and Turku University Hospital, and authorized by the Finnish Defense Forces.

2.2. Measures

2.2.1. Weak inhibitory control and threat sensitivity

2.2.1.1. Minnesota Multiphasic Personality Inventory -2 - Restructured Form (MMPI-2-RF). The clinic sample completed the MMPI-2-RF, a 338 item global measure of personality and psychopathology with well-documented psychometric properties (Ben-Porath and Tellegen, 2008). Analyses focused on a subset of MMPI-2-RF Clinical and Specific Problems scales developed to index dispositional factors of impulsive-antisociality and fearlessness-dominated (Sellbom et al., 2012), corresponding to weak inhibitory control (INH –) and low versus high threat sensitivity (THT +) reversed; the validity of these factors as indicators of dispositional INH – and THT + has been established in relation to various criterion measures (Sellbom et al., 2012). INH – was scored as a composite with strongest weightings for the Antisocial Behaviors and Hypomanic Activation clinical scales, and (with lesser weighting) Low Positive Emotionality. THT + was scored as a composite with strongest weightings for the following scales: Multiple Specific Fears, Social Avoidance, Styness, and Dysfunctional Negative Emotionality-coded such that higher scores reflected fearful-submissive tendencies.

2.2.1.2. Triarchic Psychopathy Measure (TriPM; Patrick, 2010). The Finnish soldier sample was administered the TriPM, a 58-item measure that assesses for presence versus absence of inhibitory control (disinhibition), fear/fearlessness (boldness), and callous-aggressive tendencies (meanness). Current study analyses focused on two subscales: (1) Disinhibition (corresponding to INH –; 20 items), comprising items from the Externalizing Spectrum Inventory (Krueger et al., 2007; Venables and Patrick, 2012) that index tendencies toward impulsivity and unreliable behaviors; and (2) Boldness (19 items), which indexes low versus high fearfulness (cf. Kramer et al., 2012) in areas of social efficacy, affective experience (immunity versus susceptibility to stressors), and venturesomeness (preference versus avoidance of risk). The Boldness scale was reverse-coded to make higher scores indicative of
fearful tendencies (i.e., THT+; 1) Internal consistency reliabilities (Cronbach’s alpha) for these two scales were 0.77 and 0.89, respectively.

2.2.2. Assessment of suicide risk

2.2.2.1. Clinician-rated suicide risk (Joiner et al., 1999). Clinical participants were assessed for current suicide risk using a brief clinical interview, which codes risk based on current suicidal symptomatology and history of prior attempts on a four-point scale ranging from “low” to “extreme”.

2.2.2.2. Beck Scale for Suicide Ideation (Beck and Steer, 1991). The clinic sample also completed the BSS, a well-validated 21-item inventory designed to assess ideation and plans for suicide during the preceding 2 weeks. Cronbach’s alpha coefficient for the BSS in the current sample was 0.93.

2.2.2.3. Suicide-related items from Young Adult Self-Report (YASR; Achenbach, 1997). The Finnish cohort was administered the YASR, a self-report inventory of clinical problems. Items were answered using a three-point scale to indicate the applicability of the referent characteristic over the past 6 months. Two items that assess for suicidal acts (“I deliberately try to hurt or kill myself”) and ideation (“I think about killing myself”) which were substantially correlated (r=.55) were summed to form a suicide risk index.

2.2.3. Assessment of other psychopathology

Composite indices of internalizing and externalizing psychopathology were available for the outpatient clinic sample. Diagnostic symptoms were assessed using the Structured Clinical Interview for DSM-IV (Axis-I Disorders (SCID-I) (First et al., 1995) by trained clinical psychology graduate students under the supervision of Ph.D.-level psychologists. In addition, indices of antisocial behavior in the form of responses to two questions from the clinician’s standard intake questionnaire, one pertaining to history of violent/aggressive behavior and the second to history of criminal behavior or incarceration, were available for this sample.

Based on prior published work (Kendler et al., 2003), the internalizing psychopathology index was computed as a composite (i.e., sum) of lifetime and current diagnoses of Major Depression, Dysphoria, Generalized Anxiety Disorder, Simple Phobia, Social Anxiety Disorder, Panic Disorder (each coded as present=1 or absent=0, based on SCID-I data), and the externalizing psychopathology index was computed as a composite of Alcohol and Drug Dependence diagnoses (each coded 1= present/0= absent) as assessed by the SCID-I and violent/aggressive and criminal behavior (each coded 1=present/0= absent) as assessed by self-report.

2.3. Data analysis

Pearson correlations and hierarchical regression analyses were conducted to evaluate associations of weak inhibitory control (INH−) and threat sensitivity (THT+) dispositional variables with suicide risk as operationalized in the two study samples. For the clinic sample, separate hierarchical regression analyses were performed for clinician-rated and self-reported (BSS) indices of suicide risk. In each of these analyses, psychopathology composite scores (internalizing, externalizing) were entered in step 1 as predictors of suicide risk, and INH− and THT+ scores were added as predictors at step 2 to evaluate their incremental validity over and above psychopathology scores. Each analysis also included a third step, at which a term consisting of the product of mean-centered INH− and THT+ scores was entered to test for a distinct incremental contribution of the interaction of the two dispositional variables to prediction of suicide risk. For the soldier sample, a single two-step hierarchical regression analysis was conducted in which INH− and THT+ scores were entered as individual predictors of suicide risk at step 1, and a product term reflecting their interaction was entered in the second step.

3. Results

3.1. Outpatient clinic sample

The left and middle sections of Table 1 present, for the clinic outpatient sample, simple correlations for internalizing and externalizing disorder composites along with INH− and THT+ scores as predictors of clinician-rated and self-report assessed suicide risk. As expected based on prior work (Nelson et al., in press; Patrick et al., 2012), the externalizing symptom composite was correlated with INH−, r = 0.39, p < 0.001, but unrelated to THT+, r = −0.01; by contrast, the internalizing symptom composite was robustly associated with THT+, r = 0.35, p < 0.001, and only modestly associated with INH−, r = 0.10. In line with previous research findings, higher levels of internalizing and externalizing problems were each associated with elevated suicide risk.

More crucially, and consistent with primary study hypotheses, INH− and THT+ each predicted suicide risk, whether assessed by clinician ratings or by self-report. When the two were entered together as predictors in a regression model, unique predictive contributions were evident for each as demonstrated by significant regression coefficients (8s for INH− and THT+ were 0.22 and 0.19, respectively, in prediction of clinician-rated suicide risk, and 0.25 and 0.23, respectively, in prediction of report-based suicide risk, all ps < 0.001). As a more stringent test of the distinct predictive contributions of these traits, hierarchical regression analyses were performed for each suicide criterion variable (as described in the last part of Section 2) with internalizing and externalizing composite scores entered as predictors in step 1, and INH− and THT+ scores added as predictors at step 2. The left and middle sections of Table 1 present results from these analyses for the clinic sample.

As shown in the table, internalizing diagnoses and externalizing diagnoses/problems each contributed uniquely at step 1 to prediction of suicide risk, as assessed both by clinicians and by self-report. In the second step, where INH− and THT+ scores were added as predictors, there was a significant increase (as evidenced by significant ΔR2) in the prediction of each index of suicide risk. At this step, INH− and THT+ each contributed uniquely to prediction and also partially accounted for the contributions of internalizing and externalizing psychopathology evident at step 1. In step 3 of the model for each suicide risk measure, where a product-term reflecting the interaction of INH− with THT+ was added as a further predictor, a significant increase in the prediction of risk was again evident. Fig. 1 depicts mean level of suicide risk (left plot=clinician based; right plot=self-report based) for individuals scoring high versus low on INH− and THT+ within this sample, to illustrate effects modeled statistically as continuous score associations. As shown in Fig. 1, individuals at greatest risk for suicide were those scoring concurrently high on both INH− and THT+.

3.2. Finnish soldier sample

Results from analyses for the soldier sample are presented in the right section of Table 1. Mirroring findings from the outpatient clinic sample, INH− and THT+ both showed positive correlations with suicide risk (self-report items pertaining to ideation and attempts), and each contributed distinctively to prediction when entered together in the first step of the regression analysis. When an interaction term consisting of the product of INH− and THT+ was entered in the second step of this analysis, it evidenced incremental contribution to the prediction of suicide risk as indicated by a significant ΔR2. Fig. 2 depicts mean level of suicide risk for participants scoring high versus low on the INH− and THT+ within this sample, to illustrate effects modeled statistically as continuous score associations. Mirroring results for patients shown in Fig. 1, soldiers reporting the greatest degree of suicidal thoughts/behaviors over the 6-month period before testing were those scoring concurrently high on both INH− and THT+.

4. Discussion

The current study provides evidence that dispositional variables of weak inhibitory control and high threat sensitivity (i.e., INH−, THT+), assessed in ways that connect to neurophysiological indicators (Patrick et al., 2012), predict suicide risk more strongly than symptoms of internalizing and externalizing psychopathology individually. Further work is required to determine whether these dispositional variables are markers of risk for suicide, or whether the effect is a function of the role the dispositional characteristics play in the development of symptoms. Given the key role played by dispositional variables in the development of symptoms, further work is required to determine whether interventions targeting these variables show demonstrable efficacy in reducing suicide risk.
et al., 2012, 2013), contribute separately and interactively to prediction of suicide risk. The finding of an interaction is notable because it indicates a synergistic impact of these two dispositions on suicidality. Importantly, findings replicated across distinct samples from two countries (i.e., male/female clinic outpatients from the U.S., males from the general community of Finland), alternative measures/operationalizations of INH− and THT+, and differing assessments of suicide risk (i.e., interview-based clinician ratings, self-report). In line with recent mental health initiatives calling for investigation of biobehavioral constructs with relevance to multiple clinical problems

### Table 1

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<th>Outpatient clinic sample</th>
<th>Finnish soldier cohort</th>
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<td>Clinician-rated suicide risk</td>
<td>Self-reported suicide risk</td>
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<td>Externalizing</td>
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<td>INH−</td>
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<td>THT+</td>
<td>0.19*</td>
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<td>Product of INH− and THT+</td>
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<td>R²</td>
<td>0.22*</td>
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<td>ΔR²</td>
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Note: Internalizing = sum of lifetime occurrences (1 = present, 0 = absent) of the following: Major Depression, Dysthymia, Generalized Anxiety Disorder, Social Phobia, Specific Phobia, Agoraphobia, Panic Disorder. Externalizing = lifetime occurrences (1 = present, 0 = absent) of the following: Alcohol Dependence, Drug Dependence, aggression/violence, other criminal behavior/incarceration; INH− = weak response inhibition; THT+ = threat sensitivity; Product term of INH− and THT+ = interaction term consisting of the product of mean-centered scores for INH− and THT+; r = Pearson correlation coefficient; B = standardized regression coefficient; R = multiple regression coefficient; ΔR² = change in R² (i.e., change in proportion of variance accounted for in the criterion measures).

* N = 957.
* N = 1014.
* N = 3855.
* p ≤ 0.001.
across differing levels of analysis (Insel et al., 2010), the current study provides evidence for INH− and THT+ as biobehavioral constructs of importance to the transdiagnostic problem of suicide.

4.1. Biobehavioral dispositions as bridges between neurobiology and clinical problems

Dispositional variables such as INH− and THT+ can serve as effective vehicles for bridging neurobiology and clinical problems, and as valuable referents for clarifying the biological bases of problem behaviors. When operationalized as disinhibition and fear/fearlessness, these dispositions have been shown to predict externalizing conditions and fear-related internalizing problems, respectively (Sellbom et al., 2012; Vaidyanathan et al., 2012; Venables and Patrick, 2012; Patrick et al., 2013), to relate in distinct, replicable ways to neurophysiological indicators (Yancey et al., 2013, in press), and to be prominently heritable (Kramer et al., 2012; Yancey et al., 2013). Notably, INH− and THT+ dispositional variables are more reliably associated with neurophysiological indicators than DSM disorders and account for observed relations between neurophysiology and DSM symptomatology (Patrick et al., 2013; Yancey et al., 2013, in press).

Current findings further illustrate the predictive power of these trait variables by demonstrating their ability to predict suicide risk over and above DSM diagnoses known to be predictive of suicidality. In turn, knowledge of neurophysiological correlates provides a foundation for developing joint neural/psychometric measures of these dispositions (Patrick et al., 2012, 2013) that can be used to gauge biological risk in prevention studies or programs, serve as targets for biologically oriented treatments, and facilitate selection of subjects for biological (including neuroimaging) studies of psychopathology (Patrick et al., 2012, 2013). In addition, our finding of separate and interactive effects for INH− and THT+ in prediction of suicidality points to the potential importance of configurations of these constructs (i.e., patterns of combined elevations) in predicting mental health problems including suicidality. An intriguing question to be addressed in future research is whether the co-occurrence of INH− and THT+ may signify a distinct condition of affective–behavioral dysregulation (e.g., Davidson et al., 2000; Lang and McTeague, 2009) associated with impaired central serotonergic function (Seo et al., 2008).

4.2. Implications for suicide risk assessment

A potential explanation for the finding that participants concurrently high on both INH− and THT+ exhibited maximal suicide risk may be that these individuals are deficient in the ability to restrain or regulate negative emotional reactions, leading to prolonged states of dysphoria (with affiliated perceptions of social disconnectedness, dependency, and burdensomeness) and acts of risk-taking and self-damage that increase capability for suicide (Van Orden et al., 2010). Conversely, the finding that high INH−, when accompanied by low rather than high THT+, was associated with limited elevation in suicidal risk, appears consistent with clinical accounts of psychopathy and associated empirical findings—which indicate that core affective–interpersonal features of psychopathy reflecting low fearfulness buffer against the facilitatory influence of disinhibitory tendencies on suicidal behavior (Javdani et al., 2011).

Current findings also indicate that scale measures of INH− and THT+ can provide information about patient risk for suicide beyond other known historic predictors. This incremental validity could potentially be enhanced through use of neurophysiological indicators—given evidence for a genetic basis to associations between scale measures of these dispositions and neural indicators, particularly well-established in the case of INH− (Yancey et al., 2013).

4.3. Limitations and future directions

One limitation of the present study is its reliance on self-report based assessment of dispositions. While mitigated somewhat by prior published studies demonstrating reliable physiological and behavioral correlates of report-based measures of INH− and THT+, follow-up work should include indicators of these other types along with scale indicators to evaluate the validity of these dispositional constructs when operationalized biobehaviorally. A second limitation concerns the cross-sectional research design. Future research will need to evaluate the effectiveness of INH− and THT+ in prospectively predicting later suicidal behavior. Lastly, it will be important in future research to include direct assessment of psychological processes posited to contribute to the emergence and escalation of suicidality (Van Orden et al., 2010), in order to clarify the specific sources of impact of dispositional INH− and THT+ on suicidal ideation and action.

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