International Journal of Psychophysiology 148 (2020) 75–83

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Using a co-twin control design to evaluate alternative trait measures as indices of liability for substance use disorders

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ARTICLE INFO

Keywords:
Substance use disorder
Personality
Neurobehavioral
Disinhibition
Conscientiousness
Co-twin control

ABSTRACT

To establish a trait-dispositional variable as an indicator of liability for the development of substance use disorders (SUDs), the trait must share heritable variance with SUDs and its association should not be primarily attributable to a direct impact of SUDs on characteristics that define the trait. The current work applied a co-twin control (CTC) modeling approach to data from two monozygotic twin samples to investigate the degree to which different measures of trait-impulsiveness represent indicants of vulnerability to SUDs (liability indicators), or outcomes or concomitants of SUDs (exposure indicators). The Five Factor Model (FFM) trait of conscientiousness was assessed via self-report, and a counterpart neurobehavioral trait of disinhibition was assessed both through self-report and using self-report and brain response measures combined. FFM trait data were available for one twin sample (N = 298); data for variants of P3 brain response were available along with a scale measure of disinhibition in the other (N = 258). CTC analyses revealed only an exposure effect of SUD symptomatology on FFM conscientiousness, indicating that this self-report assessed trait does not index liability for SUDs. By contrast, the disinhibition scale measure showed pronounced liability and weaker exposure-based associations with SUDs – and when quantified using scale scores together with P3 brain response, the exposure-based association was eliminated, such that this disinhibition measure related to SUD symptoms exclusively as a function of liability influences. These findings highlight a distinct advantage of quantifying traits in neurobehavioral terms – namely, the capacity to effectively index dispositional liability for psychopathological outcomes.

1. Introduction

The prevention of substance use disorders (SUDs) is of critical public health importance. There is widespread evidence of their damaging effects, both societally, costing billions in preventable healthcare costs every year (Rehm et al., 2009; Whiteford et al., 2013), and individually, causing substantial distress and suffering to both afflicted persons and their loved ones. Given these consequences, reliable and efficacious markers of early risk for SUD problems are critically important to identify. Studies investigating trait variables as risk factors for the development and maintenance of SUDs have identified several traits of interest related to impulsiveness or weak inhibitory control. However, due to the progressive nature of SUDs and their impact on psychological and social functioning – including changes in physiological function, behavior, and values, among other effects – it remains unclear to what extent SUD-related traits represent predisposing risk factors for the development of SUDs or altered self-characterizations arising from repeated, heavy use of substances themselves. The current study used a novel behavioral genetics methodology, the monozygotic 'co-twin control' (CTC) design, to evaluate alternative trait-impulsivity measures for their capacity to index pre-existing liability for SUDs, with an eye toward improving early risk-identification and prevention efforts.

A key systematic review on impulsivity and substance use by de Wit (2009) concluded that impulsivity measures can operate as indicators of liability for substance use, but that impulsivity itself can also be exacerbated by heavy substance use. The current study focused on two different impulsivity-related traits that have shown consistent associations with SUDs in cross-sectional studies– the lexical trait of conscientiousness from the Five Factor Model of personality (assessed using a well-established self-report scale) and the neurobehavioral trait of disinhibition (assessed via self-report, and alternatively, through combined use of self-report and neurophysiological indicators). We used a

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https://doi.org/10.1016/j.ijpsycho.2019.11.012
Received 20 May 2019; Received in revised form 18 November 2019; Accepted 20 November 2019
Available online 16 December 2019
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CTC design to extend what is known from common cross-sectional studies and address the degree to which these traits covary with SUD symptomatology due to 1) a non-liability, *exposure pathway* (e.g., shifts in personality related to neural or psychosocial consequences of heavy use, or concomitant effects of experiences such as physical/emotional abuse or social rejection on both personality and substance use), or 2) a shared *liability pathway* between the trait and substance problems (i.e., the trait and substance problems arise from genetic and/or shared environmental influences in common between the two).

1.1. The five-factor model of personality

A substantial body of cross-sectional research – much of it using the NEO Personality Inventory (NEO-PI; Costa and McCrae, 1992) or its abbreviated form, the NEO Five Factor Inventory (NEO-FFI; Costa and McCrae, 1989) – has demonstrated associations of dimensions of the lexically-based Five Factor Model (FFM) with various forms of psychopathology (for a review, see Widiger and Trull, 1992). Of specific relevance to the current work, meta-analytic work indicates that low levels of FFM conscientiousness correlate reliably with SUDs involving use of alcohol as well as other drugs (Kotov et al., 2010; Malouff et al., 2005). As such, low conscientiousness may operate as an indicator of risk for the development of SUDs.

However, different explanations exist for the cross-sectional link between personality traits and SUDs. Widiger and Trull (1992) suggested four possibilities: 1) premorbid traits confer *vulnerability* to future development of SUDs (predisposition model), 2) traits are not directly related to SUDs, but influence their expression (e.g., extent of psychosocial dysfunction, ability to benefit from treatment) or comorbidity patterns (pathoplasty model), 3) traits and SUDs arise from a common etiologic source (spectrum model), and 4) the experience of a SUD alters the way an individual responds to self-report questions regarding characteristic behaviors and attitudes (complication model). The last of these possible explanations, also referred to as the *scar model* (Clark, 2005), posits that the occurrence of psychopathology (e.g., SUD) fundamentally alters psychobiological systems underlying the expression of personality traits. Relevant to the current work, trait measures whose associations with SUDs primarily reflect 'scar' effects would function poorly for purposes of early identification of risk for psychopathology, whereas trait measures related to SUDs as a function of 'predisposition' or 'spectrum' effects would function better for purposes of early identification. From this perspective, innovative approaches are needed for evaluating the effectiveness of particular trait measures as indicators of *liability* for psychopathology.

1.2. Indexing liability through combined use of self-report and neurophysiological measures

While the FFM and other lexically-based models of personality have dominated trait research over the past 3–4 decades, a newer approach to conceptualizing and quantifying traits – through combined use of report-based measures and neurophysiological indicators – may prove advantageous for indexing dispositional liabilities for psychopathology (Patrick et al., 2019). One neurophysiological index that has been shown to capture heritable variance in SUDs is the P3 brain response. Begleiter et al. (1984) presented evidence for reduced amplitude of this brain response – prior to any engagement in alcohol use – in boys at risk for alcohol problems by virtue of a parental history of alcoholism. The authors interpreted this finding as indicating that reduced P3 amplitude operates as an indicator of inherited liability for the development of alcohol problems. Consistent with this, subsequent research demonstrated that small P3 amplitude early in life prospectively predicted the later emergence of substance use and related disinhibitory problems (e.g., Berman et al., 1993; Iacono et al., 2002). Building on these findings, Patrick et al. (2006) presented evidence that reduced P3 brain response operates as an indicator of general proneness to externalizing problems, with subsequent research demonstrating a heritable basis for its association with externalizing proneness (e.g., Hicks et al., 2007).

To the extent that P3 amplitude reduction remains stable over the course of development and indexes the genetic propensity for externalizing psychopathology, measurement of P3 response in childhood may aid in the prediction of susceptibility to SUDs in later life (Burwell et al., 2016; Iacono and Malone, 2011). Relevant to this, a twin study by Yancey et al. (2013) presented evidence that a scale measure developed specifically to index externalizing propensity (termed trait disinhibition), fully captured the heritable variance in common between P3 amplitude and interview-assessed externalizing problems. Taken together, these findings point to the possibility that the variance in common between scale-assessed disinhibition and P3 brain response may specifically reflect dispositional *liability* for SUDs and other externalizing problems. This possibility is central to the emerging neurobehavioral trait model for psychopathology research (Patrick et al., 2019), and evidence supporting it would highlight an important advantage of quantifying traits in "psychoneurometric" terms – that is, through use of indicators from psychological and neural measurement modalities (Venables et al., 2017, 2018; Yancey et al., 2016). As described in detail by Patrick et al. (2019), the psychoneurometric approach provides a research strategy for developing multi-method assessment protocols as called for in recent writings by addictions experts (Kwako et al., 2016).

1.3. Co-twin control design

One approach to distinguishing the degree to which the observed relationship of a trait with substance problems reflects dispositional liability as opposed to environmental exposure is the co-twin control (CTC) design (Begg and Parides, 2003; McGue et al., 2010; Hart et al., 2013). This design capitalizes on the fact that genetic and family environmental influences are shared by monozygotic (MZ) twins reared within the same household to gain insight into whether *nonshared environmental* factors (e.g., experiences related to having versus not having a SUD) contribute to a characteristic of interest (e.g., scores on a trait measure). For example, as applied to investigation of the basis of covariation between SUD symptoms and traits, the MZ twin pair member with lesser SUD symptoms serves as the control case for how the twin with greater SUD symptoms would score on the trait if his/her symptomatology were lower. If the twin with greater SUD symptoms also shows a more deviant trait score (e.g., lower conscientiousness or higher disinhibition), then the trait difference can be inferred to reflect what is termed an "exposure pathway" in the CTC design – that is, an impact of nonshared environmental influences on the relationship between personality and SUD symptomatology. Examples include substance-use related alterations in psychological functioning, values/priorities, or relationship quality that affect personality test responses, or experiences such as abuse or abandonment/rejection that affect both personality and substance use. However, if two co-twins with differing degrees of SUD symptomatology show similarly deviant trait scores, under conditions where deviant trait scores are associated with greater SUD symptoms *across* twin pairs, then it can be inferred that the trait deviation constitutes a liability factor for SUDs (i.e., distinct etiologic influences that contribute to scores on the trait also contribute to SUD symptom scores).

Given ethical issues precluding examination of the effects of excessive substance use on personality traits through experimental means (i.e., manipulation of substance use and observation of its effects on personality), the monozygotic co-twin control design provides an alternative means for evaluating whether changes in personality arise from SUDs or other non-liability related factors that co-influence substance use – or if instead, deviant traits confer liability to SUDs (Harper et al., 2018; Wilson et al., 2015). In terms of the four possibilities identified by Widiger and Trull (1992), the finding of a significant exposure pathway between SUDs and the trait of interest would support

either the complication or scar model, whereas the finding of a significant liability effect for the trait of interest would support either the predisposition or spectrum model.

1.4. Current study

The current study applied the CTC analytic method to data for two types of traits – lexical and neurobehavioral – from two different MZ twin samples in order to clarify the etiologic basis of observed associations of these traits with SUD symptomatology. The lexical trait of conscientiousness from the NEO-FFI operationalization of the FFM was evaluated using data from MZ twins tested in the Human Connectome Project (Van Essen et al., 2013), and the neurobehavioral trait of disinhibition was evaluated using data from a sample of twins recruited through the Minnesota Twin Registry. Disinhibition was operationalized using a self-report scale in the second sample, paralleling that of scale-assessed conscientiousness in the first sample. In addition, given the availability of event-related potential (ERP) data in the second twin sample, disinhibition was also operationalized through combined use of scale and brain-response (i.e., P3) measures in this sample. CTC analyses were used to evaluate the extent to which relations for traits operationalized in each of these ways with SUD symptoms evidenced exposure pathway effects (i.e., nonshared environmental influences accounting for the trait/SUD association) or liability pathway effects (i.e., common etiologic influences accounting for the trait/SUD association).

Our specific study hypotheses were as follows:

1) Traits of conscientiousness (H1a) and disinhibition (H1b) would each show significant phenotypic associations (observed-score correlations) with SUD symptoms across participants – in samples 1 and 2, respectively. These hypotheses were based on prior published evidence for associations of these traits with SUDs (Kotov et al., 2010; Nelson et al., 2016).
2) Clear evidence would emerge for a liability basis to the phenotypic association of scale-assessed disinhibition with SUD symptomatology (H2a), in sample 2. The grounds for this hypothesis were that (a) scale-assessed disinhibition is designed to index general proneness to externalizing problems (Patrick et al., 2013a), which is known to be highly heritable (Krueger et al., 2002), and (b) scale-assessed disinhibition has been shown to capture genetic influences in common with externalizing problems, including SUDs (Yancey et al., 2013). By contrast, for scale-assessed conscientiousness (in sample 1), we predicted that liability influence would account for less (if any) of its observed association with SUD symptomatology (H2b), given that conscientiousness is a language-based trait construct developed without reference to heritable externalizing proneness.
3) Trait disinhibition quantified jointly through self-report and P3 brain response would operate as a purer index of liability for SUDs than disinhibition assessed through self-report alone – such that its expected phenotypic association with SUD symptomatology (H3a) would be accounted for primarily, if not entirely, by etiologic influences in common with SUD symptom scores (H3b). This hypothesis was based on the findings of Hicks et al. (2007) demonstrating a heritable basis to the relationship between P3 brain response and externalizing symptomatology, and those of Yancey et al. (2013) demonstrating that externalizing symptomatology and scale-assessed trait disinhibition relate to P3 brain response solely as a function of shared heritable variance.

2. Material and methods

2.1. Participants

2.1.1. Human Connectome Project (HCP) sample

The Human Connectome Project (Van Essen et al., 2013) is a multisite study that was undertaken to map the human connectome (naturally occurring structural and functional connections between brain regions) in a general community adult sample. In the context of this project, a subsample of 149 monozygotic twin pairs (n = 298 [174 female]) were tested, permitting use of the CTC analytic approach to test the above-noted hypotheses. The application of CTC analysis to personality trait and SUD symptom data for these MZ twins allowed for strong inferences to be made regarding the basis of trait/SUD associations in this subsample of the HCP. The average age of this subsample was 29.3 (SD = 3.3, range = 22–36); its racial composition was 83.2% White, 9.4% Black, 4.4% Asian or Pacific Islander, 2% multiracial, and 1% unreported. All participants provided informed consent prior to data collection.

2.1.2. Minnesota Twin Registry (MTR) sample

The second sample used in the CTC analyses reported here consisted of 129 complete MZ twin pairs (N = 258 participants [132 female]) from an MZ/DZ twin sample (full N = 508) recruited from the MTR registry (Iacono et al., 1999; Lykken et al., 1990). These twins were tested in a study of physiological correlates of biobehavioral traits associated with psychopathological outcomes (for details, see Yancey et al., 2016), without prior participation in any other MTR-based studies. The average age of this MZ twin sample was 29.6 (SD = 5.0, range = 22–38); its racial composition was 95.3% White, 0.8% Black, 0.8% Native American, 0.8% Latino, 1.5% multiracial, and 0.8% unreported. All participants provided informed consent prior to data collection.

Of note, these two twin samples (HCP, MTR) were well matched in terms of age and gender composition, and differed only somewhat in terms of racial composition (i.e., the large majority of participants in each sample were White, though the HCP sample showed greater diversity).

2.2. SUD and trait measures (twin samples 1 and 2)

2.2.1. SUD symptoms

In the HCP twin sample, lifetime SUD symptomatology (i.e., symptoms of alcohol use disorder [AUD] and other drug use disorders [cannabis, cocaine, other stimulants, sedatives, and opioids]) – was assessed according to criteria specified in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000). Symptom assessments were performed by trained PhD- or graduate-level personnel using the interview based Semi-Structured Assessment for the Genetics of Alcoholism-II (SSAGA-II; Hesselbrock et al., 1999). The version of the SSAGA-II interview used for data collection assessed separately for abuse and dependence symptoms, as specified in DSM-IV. However, the current study used data from this interview protocol to operationalize SUD symptoms in a manner similar to DSM-5 (American Psychiatric Association, 2013) by summing across abuse and dependence criteria (=11 symptoms in all for each substance class) for the six above-noted substance classes to create unidimensional symptom composite scores with a maximum possible range of 0–66. The average number of SUD symptoms endorsed by participants in the HCP sample was 1.52 (SD = 2.2, observed range = 0–16). Of the 149 twin pairs comprising this sample, 58.4% (87 pairs) displayed some degree of discordance (≥1 symptom) on this composite (i.e., twin pair members differed in number of SUD symptoms endorsed).

In the MTR twin sample, the Structured Clinical Interview for DSM clinical disorders (SCID-I; First et al., 2002) was used to assess for

lifetime SUD symptomatology (i.e., symptoms of AUD and five other drug use disorders [as per the HCP sample]) according to DSM-IV-TR criteria, with trained PhD- and graduate-level personnel again conducting the assessments. SUD symptom composite scores were computed in the same manner as for the HCP dataset, with maximum possible scores again ranging from 0 to 66. The average number of SUD symptoms endorsed in the MTR sample was 1.96 (*SD* = 3.7, observed range = 0–22). Of the 129 twin pairs comprising this sample, 58.2% (75 pairs) displayed some degree of discordance on the SUD composite (i.e., differed in number of SUD symptoms endorsed). Thus, the two samples of twins were quite similar in terms of rates of SUD symptomatology, as well as in demographic characteristics as noted above.

2.2.2. Personality traits

In the HCP dataset, scores on broad trait dimensions of the FFM were quantified using the 60-item NEO-FFI (Costa and McCrae, 1989), which assesses each FFM dimension using a 12-item scale; internal consistency reliability (Cronbach's α) for the Conscientiousness scale in the HCP sample was 0.81. In the MTR twin sample, the personality trait of disinhibition was assessed using a 30-item scale consisting of items from the Externalizing Spectrum Inventory-brief form (Patrick et al., 2013a; Nelson et al., 2016; Yancey et al., 2013). This ESI Disinhibition (ESI-DIS) scale assesses a reckless-impulsive disposition, which is manifested in boredom proneness, rule breaking, irresponsibility, lack of ability to effectively plan ahead, and difficulty in controlling impulses. Of note, no items of this scale refer to use of alcohol or other substances. The scale evidenced good psychometric properties in the MTR twin sample (α = 0.82).

A second index of disinhibition was computed by combining scores on the DIS-30 with two variants of P3 brain response (see below) previously shown to operate as indicators of trait disinhibition (Patrick et al., 2013b; Venables et al., 2017) – (1) the novelty-P3 response (Friedman et al., 2001) to brief, intermittent picture stimuli occurring within a three-stimulus version of the 'rotated heads' visual oddball task (Begleiter et al., 1984; Iacono et al., 1999), and (2) the probe-P3 response (Drislane et al., 2013; Schupp et al., 1997) to abrupt noise stimuli occurring within a picture-viewing task. The novelty-P3 brain response indexes cognitive-attentional processing of infrequent, salient stimuli occurring within a task sequence; the probe-P3 response indexes allocation of cognitive-attentional resources to the processing of an abrupt, unwarned event (e.g., sudden noise stimulus). For each of these variants of P3, higher trait disinhibition is association with reduced amplitude of peak response (Patrick et al., 2013b). A composite of the psychometric-scale measure of disinhibition (DIS-30) and these two neural-response indicators (novelty P3, probe P3) – henceforth referred to as psychoneurometric disinhibition (Patrick et al., 2012, 2019) – was derived from a just-identified confirmatory factor-analytic model specifying a single latent factor on which these three-indicators loaded. Latent-factor loadings were as follows: DIS-30, λ = 0.34; novelty P3, λ = −0.56; and probe P3, λ = −0.62 (all *p*'s < 0.001). Factor scores (with greater scores indicative of higher disinhibition) were extracted for use in the analyses described below.

2.3. Tasks and brain response measures (twin sample 2)

2.3.1. Tasks

The novelty-P3 response was derived from a visual oddball task administered to participants in the MTR twin sample. The task included presentations of 3 types of stimuli, displayed for 500 ms each and separated by variable intertrial intervals: (1) a frequently occurring nontarget stimulus (simple oval), presented on 70% of (= 168) trials; (2) a rare target stimulus (schematic head), presented on 15% of (= 36) trials and requiring a button-press response; and (3) a rare, salient nontarget stimulus (neutral or emotional picture), presented on 15% of (= 36) trials and not requiring a response. The novel stimuli consisted of 36 different pictorial images (12 neutral, 12 pleasant, and 12 unpleasant) drawn from the International Affective Picture System (IAPS; Lang et al., 1999). The infrequent target (head) and infrequent novel (picture) stimuli each elicited a prominent P3 brain response.

The probe-P3 response to abrupt noise probes was measured in a different task involving passive viewing of neutral and emotional picture stimuli, also selected from the IAPS set. There were 90 pictures presented in total (30 pleasant, 30 unpleasant, and 30 neutral), each for 6 s, separated by variable intertrial intervals. During 81 of the 90 picture presentations, a 50-ms burst of white noise was delivered (at a volume of 105 dB) through insert earphones in order to elicit blink-startle and probe-P3 responses. For purposes of the current work, probe-P3 was quantified as the average stimulus-locked peak-response across the 27 neutral picture trials (cf. Drislane et al. 2013; Patrick et al., 2013b).

2.3.2. Neurophysiological data acquisition and processing

Continuous EEG activity was recorded using 54 Ag-AgCl sintered electrodes positioned on the scalp in accordance with the 10–20 coordinate system (Jasper, 1958). EEG data were referenced online to the midline central (Cz) electrode, and re-referenced offline to the left and right mastoids. Data were epoched from 1000 ms before to 2000 ms after the onset of stimuli of interest (for the novelty-P3, the neutral pictures; for the probe-P3, the white-noise bursts) using version 4.3 of the Neuroscan EDIT software package (Neuroscan, Inc.). A high-pass filter of 0.05 Hz and low-pass filter of 200 Hz were then applied to the epoched EEG data. Next, blinks and other eye movements were corrected algorithmically (Semlitsch et al., 1986) using data for vertical and horizontal electrooculogram activity, measured from electrodes positioned above and below the left eye, and on the outer canthi of the two eyes, respectively. The epoched, eye-movement corrected EEG data were then imported into Matlab for signal-artifact detection using an algorithm-based routine. Data for a given channel on a given trial were set to missing if the signal contained deflections of ± 75 μV or more. Data from particular electrodes containing excessive artifacts were replaced with aggregate mean activity from near-neighboring electrode sites, on a participant-by-participant basis.

Following completion of the foregoing processing steps with the trial-by-trial EEG data, scores for the two ERP components of interest (novelty P3, probe P3) were extracted from relevant stimulus waveforms (rare neutral pictures, white noise bursts) for each participant, computed as point-by-point averages across trials (Figs. 1 and 2). The novelty P3 was quantified as the peak of the average waveform at electrode site Pz within a window of 273–550 ms following presentations of neutral picture stimuli within the oddball task, relative to mean activity during a 150-ms pre-stimulus baseline (cf. Patrick et al., 2013a, 2013b; Nelson et al., 2011). The probe P3 was quantified as the average-waveform peak, also at electrode site Pz, occurring within a window of 250–350 ms following presentations of noise bursts within the picture-viewing task, relative to mean activity over a 300-ms pre-stimulus baseline (cf. Drislane et al., 2013; Perkins et al., 2017).[1] The average amplitude of the novelty-P3 response across participants as a whole in the MTR twin sample was 20.69 μV (*SD* = 6.58) and the average amplitude of the probe-P3 response was 23.05 μV (*SD* = 8.70).

2.4. Data analytic plan

The '*lme4*' (Bates et al., 2007) and '*lmerTest*' (Kuznetsova et al., 2017) packages of version 3.5.1 of the *R* statistical language and environment (R Core Team, 2018) were used to perform the analyses

[1] We used a longer pre-stimulus baseline for scoring the probe P3 because this ERP response, evoked by noise probes presented during viewing of picture stimuli, occurs in the context of picture-elicited brain activity. By contrast, the novelty P3 response is elicited by brief picture stimuli separated by blank-screen intervals, and thus occurs in the context of baseline brain activity.

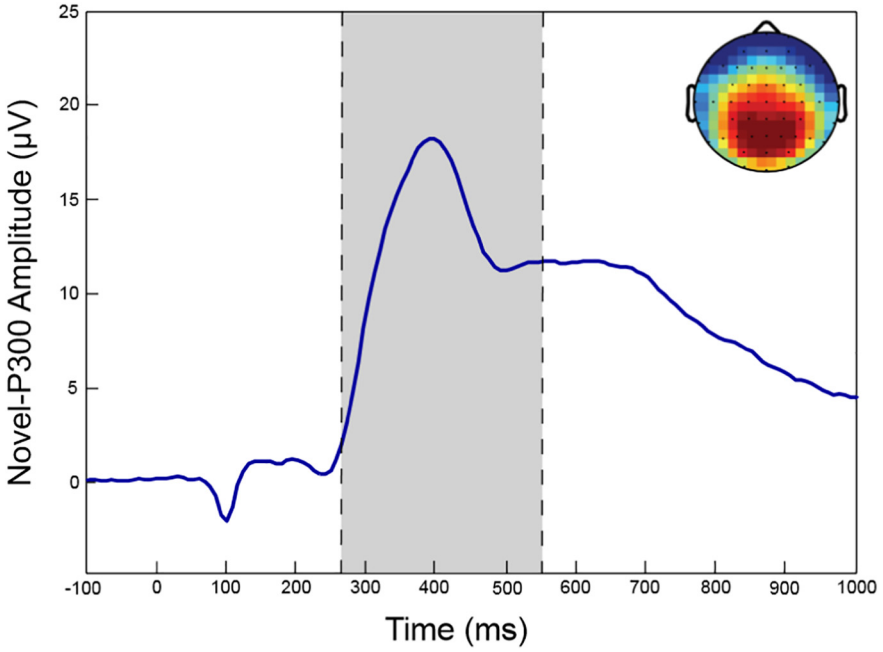

Fig. 1. Waveform plot and topographic map for the novelty-P3 response at electrode site Pz in the MTR sample.

described below. Individual-level (observed-phenotypic) and CTC (exposure versus liability pathway) associations between traits and SUD symptom scores were tested in separate multilevel models (MLM) for each trait variable. As noted below, standardized (z-score transformed) trait scores were used in each analysis to facilitate interpretation of model effects. Within these MLMs, a random intercept was specified for each twin pair to account for nesting of twins from the same family. The "individual level" MLM for each trait variable tested for an observed-phenotypic association between SUD symptomatology and scores on the trait when accounting for non-independence of observations due to the twinness of participants; in this MLM, scores on the trait of interest (NEO-Conscientiousness, ESI-Disinhibition, or psychoneurometric disinhibition) were modeled as $trait_{ij} = \beta_0 + \beta_{individual} SUD_{ij} + \alpha_i + \epsilon_{ij}$, where: β_0 refers to the intercept; $\beta_{individual}$ reflects the association between the trait and SUD symptoms for individual j from family i; α_i refers to the random intercept for twin pair i; and ε_{ij} represents the error term for twin j in twin-pair i.

Significant individual-level effects (reflecting robust phenotypic associations between SUD symptomatology and scores for a given trait variable) were followed by CTC analyses, which distinguish variance in the trait attributable to nonshared (i.e., unique environmental) influences from variance attributable to shared etiologic influences (i.e., common genes and rearing environment). In each CTC MLM, scores on the trait variable were modeled as $trait_{ij} = \beta_0 + \beta_{between}(\overline{SUD_i}) + \beta_{within}(SUD_{ij} - \overline{SUD_i}) + \alpha_i + \epsilon_{ij}$. The β_{within} term of this model denotes the effect of within twin-pair deviations in SUD

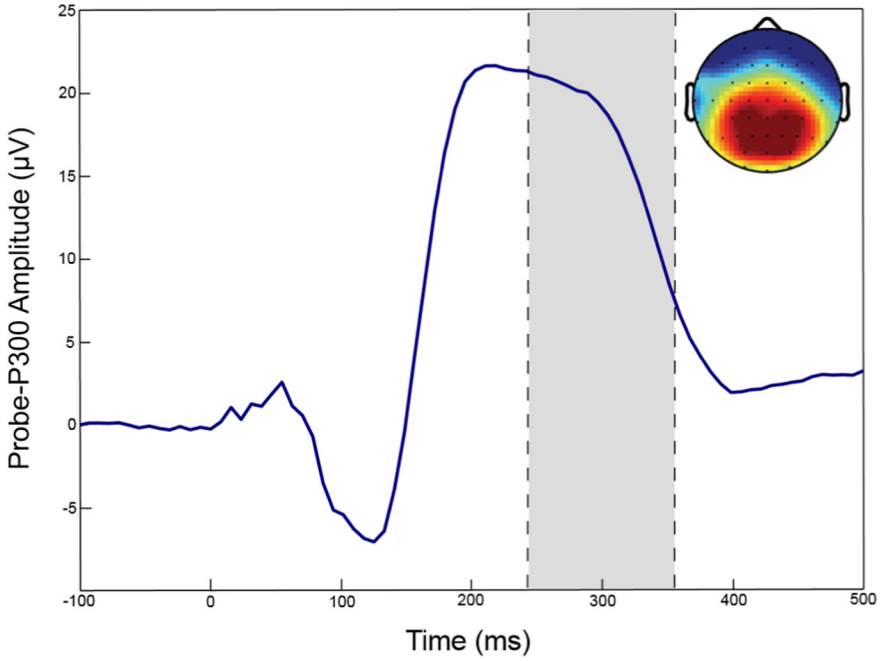

Fig. 2. Waveform plot and topographic map for the probe-P3 response at electrode site Pz in the MTR sample.

symptoms (i.e., SUD_{ij} – SUD_i, where SUD_i is the twin-pair mean in SUD symptoms), which provides an estimate of the effect for the exposure (nonshared environmental influence) pathway between SUD symptoms and levels of the trait, as distinct from the effect for the liability (shared genetic and environmental influence) pathway. A significant β_{within} term in the model can be interpreted as evidence for an exposure effect (e.g., the experience of SUD symptomatology operates as a unique environmental factor affecting scores on the trait of interest, or other environmental factors operate to affect both the trait and substance use behavior); a nonsignificant β_{within} effect provides indirect evidence that shared liability factors (i.e., common genes and rearing environment) account for a significant observed phenotypic association between trait levels and SUD symptoms (Malone et al., 2014). The $\beta_{between}$ term of the model represents the effect of levels of SUD symptoms between twin pairs (where SUD_i denotes the mean SUD symptom score for a given twin pair). A significant $\beta_{between}$ effect provides direct evidence that the observed phenotypic association between SUD symptoms and scores on the trait is attributable to shared liability factors – either partially, if the β_{within} effect is also significant, or entirely, if the β_{within} effect is nonsignificant. The β_0 term of the model refers to the intercept; α_i refers to the random intercept for twin pair *i*; and ε_{ij} represents the error term for twin *j* in twin-pair *i*. Although not shown in the model, age and gender were included as additive fixed-effect predictors due to well-documented effects of these demographic variables on SUD symptomatology (e.g., Brady and Randall, 1999; Kessler et al., 2005).[2]

An alpha level of 0.05 was employed for all analyses. Degrees of freedom and *p*-values for the MLMs were estimated using the Kenwood-Roger method (Kuznetsova, Brockhoff, & Bojesen Christensen, 2016), which provides a more conservative basis for evaluating significance than the *z*-distribution for Wald *t*-values derived from the MLM (Luke, 2017). Beta coefficients (Bs), based on z-transformed trait scores and symptom scores coded from 0 to 66 (i.e., 11 symptoms/SUD x 6 SUDs) in each MLM, are reported as counterparts to β terms in the above-noted model-equations; the B coefficients for each analysis can be interpreted as reflecting the *standardized SD-unit change in scores on the model DV* (i.e., trait score) for each *single raw-unit change in the model IV* (i.e., SUD symptom score). Specifically, for the between-pair effect, a B value of 0.1 would indicate that a 1-symptom difference between twin pairs in SUD score is associated with a 0.1-*SD* between-pair difference in trait score. For the within-twin pair effect, a B value of 0.1 would indicate that a 1-symptom deviation for each twin from a given pair's average level of SUDs is associated with a 0.1-*SD* difference in trait scores from their twin-pair average. Bootstrapped (n = 1000) 95% confidence intervals (CIs) were computed for purposes of (a) evaluating the significance of effects for terms of interest in the two MLM models for each trait variable (i.e., phenotypic association [B_{within}] term in the individual-level model; exposure [$B_{between}$] and liability effect [B_{within}] terms in the CTC model), with significance indicated by 95% CIs not including zero, and (b) comparing the magnitude of effects for these different terms of the two models, with significant differences between effects indicated by non-overlapping CIs.

3. Results

3.1. Trait conscientiousness and substance use disorders in the HCP sample

First, an individual-level MLM was run to test for the expected phenotypic association between NEO-FFI Conscientiousness scores and SUD symptomatology (H1a) when accounting for the twinness of the data. A significant association between the two was evident ($B_{individual}$ = −0.07 (95% CI [−0.12, −0.02]), SE = 0.02, p = .003; see Fig. 3, left bar plot), with greater SUD symptoms evident at lower levels of conscientiousness. Having confirmed this predicted phenotypic association (Hypothesis 1a), a CTC analysis was performed to evaluate the degree to which this observed individual-level effect could be attributed to an exposure pathway between SUD symptomatology and Conscientiousness trait-scores (exposure effect). Average twin-pair levels of SUD symptomatology (i.e., the variance in symptom level indicative of shared liability within this CTC model) were not significantly associated with NEO-Conscientiousness scores, $B_{between}$ = −0.05 (95% CI [−0.13, 0.02]), SE = 0.04, p = .24); however, within twin-pair differences in SUD symptomatology (i.e., indicative of an exposure effect in the model) were significantly associated with NEO-Conscientiousness scores, B_{within} = −0.09 (95% CI [−0.15, −0.03]), SE = 0.03, p = .004 (Fig. 3, left bar plot). This pattern of results suggests that the relationship between SUD symptomatology and conscientiousness is less indicative of a trait-liability effect (H2b), and more primarily indicative of a nonshared environmental (exposure) effect. The implication is that the link between problematic use of substances and the lexically-defined trait of conscientiousness is more consistent with either a scar or complication explanation than a liability explanation.

3.2. Trait Disinhibition and substance use disorders in the MTR sample

An individual-level MLM accounting for the nested structure of the twin data was run to test for a cross-sectional association of SUD symptomatology, including additional terms for fixed effects of age and gender, with scores on the ESI-DIS scale. Consistent with prior published findings, scores on the ESI-DIS scale showed a significant phenotypic association with SUD symptomatology (H1b), $B_{individual}$ = 0.14 (95% CI [0.11, 0.17]), SE = 0.02, p < .001, such that greater SUD symptom levels were associated with higher ESI-DIS scores (see Fig. 3, middle bar plot).

Having confirmed the expected phenotypic association of SUD symptom levels with ESI-DIS scores, a CTC analysis was performed to decompose the covariance between SUD symptomatology and each trait measure into liability versus exposure pathways. Average twin-pair levels of SUD symptomatology (i.e., variance indicative of shared liability within the CTC model) were significantly associated with scores on the ESI-DIS scale, $B_{between}$ = 0.17 (95% CI [0.13, 0.21]), SE = 0.02, p < .001; however, within twin-pair differences in SUD symptomatology (i.e., variance indicative of an exposure effect) also significantly predicted scores on the ESI-DIS scale, B_{within} = 0.10 (95% CI [0.06, 0.15]), SE = 0.02, p < .001 (see Fig. 3, middle bar plot). This suggests that the association between SUD symptomatology and scores on the ESI-DIS scale – in contrast with NEO Conscientiousness scores – *did* reflect a significant portion of liability-related variance (H2a). However, given the accompanying presence of a significant B_{within} term, this model also provides evidence for a contribution of exposure (i.e., unique environmental influence) to the relationship between SUD symptomatology and ESI-DIS scores.

As with scale-assessed disinhibition, the individual-level model for psychoneurometric disinhibition scores revealed a significant phenotypic association for this trait variable with SUD symptomatology, $B_{individual}$ = 0.05 (95% CI [0.02, 0.08]), SE = 0.01, p = .003, such that greater levels of SUD symptoms were associated with higher scale-brain factor scores (H3a; see Fig. 3, right bar plot). However, diverging from the finding of joint liability and exposure effects in the CTC analysis for ESI-DIS scores, the CTC analysis for psychoneurometric disinhibition revealed a robust contribution of between twin-pair differences to the association between SUD symptomatology and scores on this trait variable ($B_{between}$ = 0.10 (95% CI [0.05, 0.14]), SE = 0.02, p < .001), with no contribution of within twin-pair differences, B_{within} < 0.01 (95% CI [−0.04, 0.05]), SE = 0.02, p = .84 (Fig. 3, right bar plot). This indicates a predominant contribution of shared liability to the phenotypic association between SUD symptomatology and trait disinhibition when quantified jointly through scale and brain-ERP indicators (H3b).

[2] The results for the models reported here did not change when age and gender were omitted as predictors.

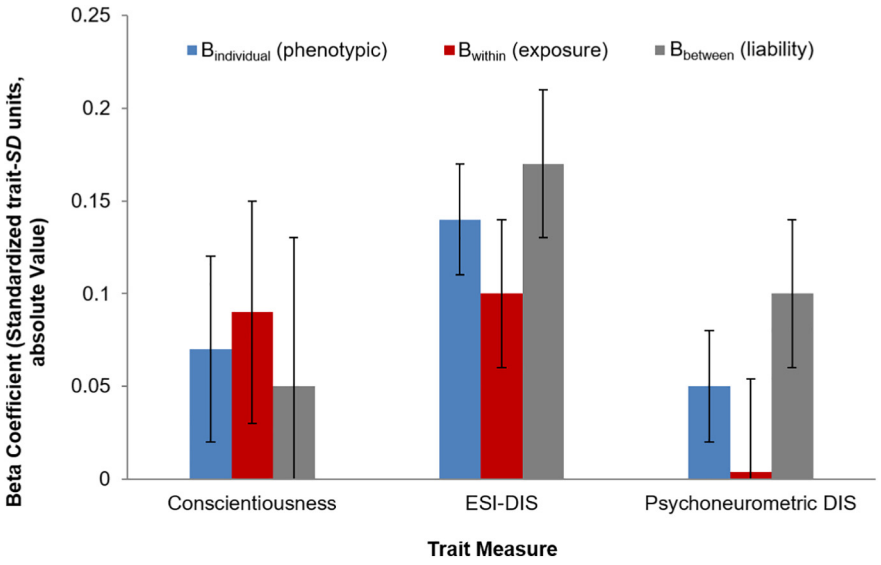

Fig. 3. Bar-plot depictions of results from phenotypic and co-twin control multilevel models for the three trait measures (Conscientiousness = NEO-FFI Conscientiousness scale; ESI-DIS = scale measure of disinhibition composed of 30 items from the Externalizing Spectrum Inventory; Psychoneurometric Disinhibition = composite measure of disinhibition incorporating scores on two brain response indicators (see main text) along with ESI-DIS scale scores. Beta (B) coefficient values (coded on the y-axis) reflect the change in standardized scores for the trait of interest, in *SD* units, for each 1-symptom change in SUD scores. The left (blue) bar within each bar-plot represents the value of B for the fixed effect of SUD symptoms on the trait score (phenotypic effect). The middle (red) bar within each plot represents the value of B for the fixed effect of the within-twin pair deviation in SUD symptoms on the trait score (exposure effect). The right (gray) bar within each plot represents the value of B for the fixed effect of the twin-pair average of SUD symptoms on the trait score (liability effect). The individual (phenotypic) effect for each trait measure (blue bar) is approximately the average of the within- and between-twin pair effects (red and gray bars). Error bars represent bootstrapped 95% confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Thus, by combining scale and brain indicators of disinhibition into a composite psychoneurometric index of trait disinhibition, the liability signal evident for scale-assessed disinhibition was retained, but the corresponding exposure effect for SUDs became negligible.

4. Discussion

SUDs are highly debilitating and costly conditions. Effective prevention efforts are importantly dependent on the identification of individual difference factors that operate as *liabilities* for the subsequent development of SUDs. Conventional personality traits have been widely studied as liabilities for SUDs, and consistent with prior published work (cf. Kotov et al., 2010), the current study demonstrated a significant negative association between the broad FFM trait of conscientiousness and SUD symptomatology (H1a). However, our CTC modeling analysis indicated that this association with SUDs was *not* attributable to a liability pathway (shared etiological influences between traits and SUD symptoms; H2b). Instead, as Malone et al. (2014) reported for the negative relationship between alcohol use severity and performance on a reward based decision-making task, CTC model results were consistent with an exposure relationship between higher SUD symptomatology and lower self-ascribed conscientiousness (i.e., 95% CI for B_{within} term of the model did not overlap with zero, whereas 95% CI for $B_{between}$ term did; Fig. 3). The implication is that the lexically based trait of conscientiousness, operationalized via self-report, does not index dispositional liability for the development of SUDs – or does so only weakly, below the level we had power to detect in the current work.

Of note, the items of the NEO-FFI that index conscientiousness – reflecting perceptions of oneself as orderly, systematic, dutiful, goal-oriented, and hardworking – reference characteristics that appear susceptible to change possibly as a function of having a SUD. While some previous studies have demonstrated longitudinal associations for conscientiousness in predicting substance problems (Chassin et al., 2004; Roberts and Bogg, 2004), findings from the current work suggest that the SUD-related variance in NEO-Conscientiousness, when assessed in adulthood (HCP sample $M_{age} \sim 30$), may be more indicative of the consequences of problematic substance use. Alternatively, a 'third' variable, distinct from a dispositional liability for SUDs, might perhaps account for the relationship between the two. An example of such a variable might be the experience of physical or emotional trauma, unrelated to SUD liability, that exerts effects on both conscientiousness and the propensity toward substance use (e.g., Chilcoat and Breslau, 1998)

Replicating prior findings (e.g., Joyner et al., 2019; Venables et al., 2018), the ESI-DIS scale also showed a robust phenotypic association with SUD symptomatology (H1b). However, in contrast with NEO-Conscientiousness, our CTC-model decomposition of the relationship for ESI-DIS into shared liability versus SUD-related exposure effects revealed both to be significant (i.e., 95% CI did not cross zero for either the $B_{between}$ or the B_{within} term of the model; Fig. 3) – but (cf. H2a) with a larger magnitude of effect for the former, as evidenced by a non-overlapping, higher-range confidence interval (Fig. 3). This indicates that while the ESI-DIS scale is a potent predictor of SUDs and does capture a significant portion of liability-related variance in SUD symptomatology, scores on this scale may also reflect – to a lesser extent – consequences of having an SUD or nonshared environmental factors concomitantly affecting scale scores and SUD symptoms.

Psychoneurometric disinhibition likewise demonstrated a robust phenotypic association with SUD symptomatology (H3a), at a level similar to NEO-Conscientiousness but below that for the ESI-DIS scale (i.e., $B_{individual}$ 95% CIs for NEO-Conscientiousness and psychoneurometric disinhibition evidenced overlap, but neither overlapped with the CI for ESI-DIS; see Fig. 3). However, when decomposing the association for psychoneurometric disinhibition with SUD symptoms into shared liability and exposure effects, only an effect for liability was evident (i.e., $B_{between}$ 95% CI did not overlap with zero, whereas B_{within} 95% CI did; Fig. 3). The fact that evidence of an exposure effect was not found for the association of SUDs with psychoneurometric disinhibition, as was found for ESI-DIS in the same (MTR) twin sample and for NEO-Conscientiousness in the HCP sample, has important implications. It suggests that while the magnitude of the phenotypic (i.e., cross-sectional) association for psychoneurometric disinhibition with SUD symptomatology was smaller in absolute terms than that for the ESI-DIS scale, the variance in SUD symptomatology associated with the psychoneurometric disinhibition variable was more exclusively indicative of a liability influence (i.e., a dispositional factor shared by co-twins). Whereas the etiologic basis of the observed association between trait disinhibition and SUDs remained ambiguous (i.e., evidence was found for exposure as well as liability pathways), incorporation of the P3 indicators into the trait-disinhibition measure resolved this ambiguity (i.e., its observed association with SUDs reflected liability alone).

4.1. Implications for research and applied assessment

An important implication of the current findings is that alternative approaches to quantifying trait dispositions may be useful for differing scientific and applied purposes. The FFM approach has proven extremely useful for characterizing phenomena in the psychological realm and substantial research demonstrates robust relations for FFM traits with a wide range of health and performance outcomes (Malouff et al., 2005). The effectiveness of this trait model for predicting a range of outcomes is likely attributable to the fact that FFM traits tap psychological characteristics or processes in common with clinical problems (see Widiger, 2011; Widiger and Trull, 1992). For example, results from our CTC analysis for the trait of conscientiousness suggest that scores on this FFM trait are sensitive to altered functioning in areas such as orderliness, industriousness, and dependability associated with excessive and disordered use of intoxicating substances.

By contrast, our CTC findings for the trait of disinhibition suggest that it indexes SUD liability – that is, predisposing characteristics of individuals that enhance the likelihood of SUD symptomatology arising. This was particularly the case for disinhibition when operationalized through combined use of self-report (i.e, ESI-DIS scale) and neurophysiological (i.e., P3 response) measures, where the observed association with SUD symptomology was attributable exclusively to a liability effect. This finding accords with an extensive body of published work indicating that the dispositional liability for substance problems has a strong neurobiological component (for reviews, see: Begleiter and Porjesz, 1999; Iacono et al., 1999; Patrick et al., 2016; Vanyukov et al., 2012).

Trait measures that primarily tap liability for problems of particular types are apt to be useful for longitudinal prediction studies because such measures will contain more observed-score variance related to downstream outcomes (Venables et al., 2017). Effective trait-liability measures also have strong potential utility for research aimed at clarifying the biobehavioral nature of dispositional liabilities and the role of experiential factors in determining whether they give rise to clinical problems. For example, selecting subjects based on psychoneurometric disinhibition scores as opposed to self-report trait scores for neuroimaging studies of substance abuse risk would likely enhance power to detect pertinent differences in brain structure or function (i.e., because the selection measure would include neural indicators, and higher scores would index SUD liability more purely). In addition, effective trait-liability measures could provide valuable referents for early prevention efforts, where finite available resources need to be allocated toward individuals at maximum dispositional risk, residing within maximally pathogenic environments.

4.2. Study limitations

Some limitations to the current work warrant mention. First, while the HCP and MTR samples were matched well on demographic and SUD variables, other unassessed differences between the two samples could have contributed to the contrasting results for the traits of conscientiousness and disinhibition. In future research of this kind, it will be valuable to compare the etiologic bases of observed associations for lexical and biobehavioral traits with SUD symptomatology in the same sample of twin participants. A second point is that sample sizes would ideally have been larger. Mitigating this concern somewhat, we found significant phenotypic associations between trait scores and SUD symptom scores in each sample, and significant $B_{between}$ and/or B_{within} effects in the CTC analyses for each. Nonetheless, research with larger-sized samples will be needed to establish whether nonsignificant effects for terms in two of the CTC models (i.e., $B_{between}$ in the analysis for NEO Conscientiousness, and B_{within} in the analysis for psychoneurometric disinhibition) might be attributable to insufficient power. Lastly, the current study samples were limited in terms of racial diversity, as has been the case for many behavioral and molecular genetics studies (Medina-Gomez et al., 2015; Quansah and McGregor, 2018). Future research should prioritize recruitment of more racially diverse samples to address this general limitation in the field.

5. Conclusions

Notwithstanding these limitations, our use of a novel behavioral genetic modeling method to parse liability versus exposure effects in the current work highlights potential advantages to alternative ways of quantifying traits. Our results for the FFM trait of conscientiousness suggest that it is sensitive to alterations in functioning that occur with excessive substance use, or alternatively, that it is affected by adverse experiences that also affect substance use behavior. As such, traits of this type can be viewed as indexing processes proximal (cf. Buchman-Schmitt et al., 2017) to problematic substance use that can serve as referents for research on SUD pathophysiology or as targets for treatment. By contrast, our findings for the neurobehavioral trait of disinhibition – particularly when quantified in part using brain response indicators – suggest that it indexes more distal proclivities that enhance one's likelihood of developing substance problems at some point in life. In research seeking to clarify the nature and bases of SUD liability, selecting subjects based on psychoneurometric trait-disinhibition scores would likely provide clearer differentiation of individuals along a biobehavioral liability continuum than self-report scale based selection. In applied programs focusing on early prevention, use of psychoneurometric trait scores could help to optimize identification of individuals at maximal risk for SUDs prior to their emergence.

Acknowledgements and funding

C. J. Patrick was supported by U.S. Army grant W911NF-14-1-0018. N. C. Venables and S. J. Burwell were supported by National Institute on Drug Abuse Grant T32-DA037183. K. J. Joyner was supported by a Ford Foundation Predoctoral Fellowship administered by the National Academies of Sciences, Engineering, and Medicine. Only the authors of the current work are responsible for the content and any views expressed herein do not represent official views of the U.S. Government, Department of Defense, Department of the Army, Department of Veterans Affairs, or U.S. Recruiting Command. Data were provided [in part] by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. The authors are deeply grateful for the willingness of the HCP PIs to share data openly.

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