Article

Personality, Psychopathology, and the Neurotransmitter Attributes Questionnaire (NAQ)

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Abstract

In this study, 901 participants completed an anonymous Internet-based survey, including a new instrument, the Neurotransmitter Attributes Questionnaire (NAQ), indicating possible dysfunction of the serotonergic or dopaminergic circuits. NAQ items were derived from questions prescribing professionals commonly ask new patients whose symptoms call for psychopharmacological treatments, sometimes in combination with psychosocial interventions. Rasch modeling was used to establish item quality, subscale reliability, and unidimensionality. In addition, the items in each subscale were found reliable when judged by three blind raters who were experienced psychopharmacologists. Standard measures of mental disorders and self-reported diagnoses were used to validate the NAQ subscales. These questions that form the subscales on the NAQ may be helpful when determining the class of medication likely to be most effective. Variations in mood and anxiety-disordered patients call for a case-specific approach to pharmacological treatment. Some patients are best helped by serotonergic agonists, others have a better outcome from treatment with dopaminergic agonists, and some patients seem to be best served by a combination of both. The NAQ was designed to aid decision-making early in treatment, potentially leading to greater compliance and better outcome. The NAQ may be used to standardize protocols in outcome research, and in addition, it may provide a new perspective on personality studies.

Keywords

neurotransmitters, dopamine, serotonin, personality, psychopathology, psychopharmacology

Introduction

Decades ago, the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.; *DSM-III*; American Psychiatric Association [APA], 1980) was developed to standardize diagnoses of mental disorders, improve reliability between clinicians, and facilitate research across situations and psychopathologies (Horwitz, 2002). Although *DSM-III* was an improvement over preceding editions, the effort to standardize diagnoses was less successful than hoped. The DSM-III, DSM-IV (4th ed, APA, 1994), including multiple revisions, and the recently released DSM-V describe categories of symptom clusters; however, not all patients within a symptom-cluster share similar underlying pathophysiology (Feighner et al., 1972; Guze, 1989; Möller, 2009). Furthermore, diagnoses have remained somewhat unreliable across locations, theoretical perspectives, and the era in which diagnosing is taking place (Aboraya, 2007).

Patients sometimes do not "fit" in a clear diagnostic category because they fail to demonstrate enough of the required criteria. In addition, mental disorders overlap with one another, with the same criterion found in different disorders.

For example, anxiety is present across many diagnostic categories, although it may differ in intensity and manifestation. People with mental illnesses often exhibit criteria from multiple disorders, leading to diagnostic confusion. These limitations have made it difficult to diagnose in accord with the specific illnesses in the *DSM* model.

Personality and Psychopathology: Recent Dimensional Perspectives

In contrast to taxonomic models of psychopathology (exemplified by the *DSM* tradition), an alternative tradition emphasizes a dimensional understanding of common psychological

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disorders. Dimensional models highlight continuity between psychological disorders and highly prevalent, adaptive, biologically based temperament and personality factors. Here, behavioral, mood, and personality disorders are conceptualized as spectrum disorders defined within multidimensional frameworks. Among more influential approaches in this tradition are Eysenck's PEN (psychoticism, extraversion, and neuroticism) perspective (1990), Cloninger's biosocial model of personality (Cloninger, Bayon, & Svrakic, 1998; Cloninger & Svrakic, 1997), K. K. Akiskal and Akiskal's (2005) theory of affective temperaments, and various models emphasizing continuity between psychopathology and the Big Five personality factors (Nigg, John, Blaskey, Huang-Pollock, Willcutt, Hinshaw, & Pennington, 2002; Widiger& Frances, 1994).

Akiskal and colleagues (Lara & Akiskal, 2006; Lara, Pinto, Akiskal, & Akiskal, 2006) recently developed an integrative, bi-dimensional theory of temperament with implications for the assessment and treatment of psychological disorders. This model incorporates neurobiological evidence for serotonergic and dopaminergic systems underlying normal affective traits and their symptomatic exaggerations in mood and personality disorders.

In this bi-dimensional model, the fundamental human affective systems are posited to relate to fear and anger, evolutionary adaptations to the ubiquitous demands of detecting and responding to danger and environmental challenges. Broadly speaking, the fear system regulates the inhibition of behavior, while the anger system promotes the initiation of behavior. Each system is responsible for a set of transient emotional states and enduring temperamental traits. Fear traits relate to harm avoidance, with high fear reflected in cautiousness, pessimism, need for security, and low energy. Persons low in fear exhibit optimism, confidence, high energy, low perception of danger cues, and reckless risk-taking. Lara and Akiskal (2006) provide evidence that fear traits are linked primarily to amygdala functioning (with secondary involvement of other limbic and precortical and paralimbic structures) and to serotonergic systems (as well as gamma-aminobutyric acid [GABA] and noradrenergic systems).

In contrast, anger relates to traits such as appetitive motivation, with high anger associated with novelty- and stimulation-seeking, impulsivity, extravagance, and dominance. Low anger is associated with apathy, passivity, submissiveness, and low appetitive and exploratory motivation. Lara and Akiskal (2006) identify the nucleus acumbens as the primary neuroanatomical structure involved in the regulation of anger traits, with prefrontal cortical structures playing secondary roles. Although the neurochemistry of anger is complex, the authors describe dopaminergic circuits involved in anger regulation. This model is reminiscent of Gray's theory of Behavioral Inhibition Systems (BIS) and Behavioral Activation Systems (BAS), derived from research in animal learning and motivation (Gray, 1982, 1991). Dopaminergic and serotonergic circuits may play important roles in the BAS and BIS, respectively (Depue & Iacono, 1989).

Fear and anger traits, as conceptualized by Akiskal and colleagues (Lara & Akiskal, 2006; Lara, Pinto, Akiskal, & Akiskal, 2006), are orthogonal dimensions, with high and low fear and anger co-occurring in combination. Many psychological disorders are located within this two-dimensional framework, with disorders identified by extremes on at least one dimension. Bipolar disorders are characterized by elevation on anger- and fear-related traits. Without the modulation by high fear, an individual with high anger is prone to manic and hypomanic states, with less frequent depressive episodes. Major depression is associated with high fear characteristics and low anger; with higher fear traits, depression merges into the anxiety disorders. According to this model, ADHD may be located at low levels on the fear and anger dimensions. However, the frequent comorbidity of ADHD with anxiety, oppositional, and other disorders makes this hypothesis difficult to assess (Biederman, Faraone, & Lapey, 1992; Cantwell, 1996; Jensen et al., 2001). Akiskal's bi-dimensional model is similar to the perspective adopted in the NAQ (Neurotransmitter Attributes Questionnaire) reported in the present study.

A Dimensional Perspective in Clinical Practice

Most frustrating to clinicians is the failure of diagnostic categories to point the way to effective treatments. Despite hopes for standard psychopharmacological treatment, Trivedi, Rush, et al. (2006) report the results of the STAR*D, a massive multisite study designed to assess the outcome of a standard psychopharmacological treatment for depression. Depressed patients were treated with citalopram (Celexa), a selective serotonin reuptake inhibitor (SSRI) often used as a first-line agent. Results demonstrated that only 28% of the patients achieved remission and only 47% responded to an adequate trial of citalopram, underlining the finding that many depressed patients fail to respond to common first-line agents; more than half showed no response, and more than two thirds failed to achieve remission. The utility of being able to identify which patients will respond to a given antidepressant agent before beginning treatment is evident. The low remission rate in the face of treatment with adequate serotonin reuptake inhibition agonists suggests that other neurobiological systems play a role in some or even many cases of depression and associated symptoms such as anxiety. While agents most commonly used in first-line treatment of depression rely on the selective blockade of serotonin receptors, Nutt (2006) pointed to evidence linking dopamine and norepinephrine in depression and the role of dopamine in treatment. Primary dysfunctions of the dopamine circuits may account for subtypes of depression not effectively treated by serotonergic agents (Dunlop & Nemeroff, 2007; Nutt et al., 2006).

Driven by the need to match specific patients to effective treatments, many clinicians are moving away from the symptom-cluster orientation of *DSM-IV*, which fails to

identify effective treatment agents. Instead, clinicians are attempting to correlate specific clinical data with underlying pathophysiology, natural history, patterns of unique correlates, and treatment response, to arrive at treatment approaches designed to match hypothesized abnormalities in individual neural circuits and neurotransmitter systems (Stahl, 2000). This approach takes into account not only the patient's symptoms, but also pre-morbid personality traits and past history of response to different pharmacological agents in an attempt to identify dysfunction in specific neurotransmitter systems that might be redressed with pharmacological intervention. A medication trial may be viewed as a "probe" of a patient's individually constituted nervous system; such trials can therefore be diagnostic as well as therapeutic. We refer to this model as "circuits based," in contrast to the *DSM* approach, the "symptom cluster" model.

The disappointing results of outcome studies encouraged us to reconsider the neurobiological systems responsible for dysfunctions and to tailor treatments with a patient-specific method (Trivedi, Fava, et al., 2006). Experienced clinicians develop an implicit method of diagnosing and determining optimal treatment after observing multiple patients' personality traits and their reactions to medications, using "clinical intuition." However, this necessitates knowledge and understanding of psychopharmacology and in some settings, practitioners may lack the background or relevant experience in psychopharmacology. Some treatment providers have not been trained to think of biological considerations linking treatment to personality factors associated with psychopathology or sustained problems in living. In addition, while primary care physicians are among the most frequent prescribers of antidepressant medications in the United States, they often miss the diagnosis of major depressive disorder (Coyne, Fechner-Bates, & Schwenk, 1994). Thus, there is a need for a secondary, systematized means by which to link personality traits and clinical data to treatment approaches that might help physicians make informed choices between different types of antidepressant agents and psychosocial approaches. Such a method might also help direct the course of nonpharmacological treatment by making more explicit the nature of the illness.

A patient-specific method may ultimately include a variety of nonpharmacological treatments such as therapist-designed cognitive and behavioral treatment (CBT), self- or computer-administered CBT, telephone counseling, or graded programs of exercise (Tylee, 2006). Because little data exist regarding the effects of psychosocial treatments on specific neurotransmitter circuits, there are no established protocols linking nonmedication treatments with either serotonergic or dopaminergic system-based symptoms. Several exceptions to this include the efficacy of Exposure and Response Prevention (ERP) in the treatment of obsessive-compulsive disorder (OCD), and CBT in the treatment of depression. In these, there have been studies comparing ERP and CBT with pharmacological treatment. In some studies psychosocial treatments appear more effective alone, in others, a combination of medication and psychosocial treatments lead to better outcome (Menchetti et al., 2010). Recent outcome data on ERP for OCD are not always so optimistic, and the lack of case specificity in medication practices has lead to a pervasive weakness in clinical trial studies (Furukawa et al., 2011). In each study comparing psychopharmacological with psychological treatments, all patients are given the same in class of pharmacological agent, without taking into account whether a given patient might be more responsive to a serotonergic or dopaminergic agonist. Every patient in the comparative studies receives the same type of medicine. Therefore, outcome must necessarily be lower for medication treatments than it might be if patients were treated with the medication most appropriate, in a case-specific manner.

In longer-term studies, the learning process that takes place in CBT appears to promote a greater reduction in symptoms over time than medication without behavioral treatment. However, for many, medications are helpful in jump-starting treatment, offering patients enough hope to begin the work of a CBT (Baxter et al., 1992; Conte, Plutchik, Wild, & Karasu, 1986). Clinicians working with a circuits-based model might consider patients' presenting symptoms as representing "dysfunctional" dopaminergic or serotonergic systems, while viewing neurotransmitters as functioning in nonlinear, complex, adaptive systems in continuous interactions. A dopamine agonist may be most helpful for a symptom suggestive of low dopaminergic tone, such as distractibility or decreased motivation. A serotoninergic agonist might better address a symptom suggestive low serotonergic tone, such as anxiety proneness or chronic sadness. In clinical contexts in which patients manifest relatively nonspecific symptoms of depression but have evidenced lifelong personality traits suggestive of, for example, low dopaminergic tone, clinicians may find dopaminergic agonists preferable, although serotonin circuits may secondarily be involved in a patient's presentation, and treatment may be most successful when using serotonergic and dopaminergic agonists. Beyond consideration of psychopathology, normal personality traits and individual differences may be investigated and characterized by this model and fit into a broader evolutionary perspective (H. S. Akiskal, 1998; Cloninger, 2002; DeBattista, Solvason, Poirier, Kendrick, & Schatzberg, 2003; O'Connor, Berry, Weiss, & Gilbert, 2002).

Present Study

Currently there is a lack of effective measures to aid case-specific approaches to pharmacological treatment that take into account the individual differences in personality traits often informing decision making by experienced psychopharmacologists. This study was designed to evaluate a new measure, the NAQ, based on a "circuits" model of psychopathology, extended to include common psychological

problems and individual differences in personality traits. The NAQ was developed with an eye to potential clinical applications, making explicit an implicit process for experienced prescribing providers. The items capture informal criteria used by seasoned specialists intuitively, in determining optimal treatment. NAQ items are related to behavioral, affective, and cognitive traits on which people show individual differences, and for which extreme elevations on clusters of traits (related to either serotonergic or dopaminergic influence) might be associated with distress, psychological problems, or ongoing difficulties in living. Each of the two NAQ subscales, the D-scale (dopaminergic) and S-scale (serotonergic), thus comprise these traits made explicit. While elevations on each classification of traits may not always be associated with specific diagnoses, they commonly represent clusters of traits noted in patients successfully treated with dopamine agonists such as bupropion (Wellbutrin), methylphenidate (Ritalin), and others, or with serotonin agonists such as floxetine (Prozac), citalopram (Celexa), or escitalopram (Lexapro). This study examines the psychometric properties of the NAQ items and subscales, including their reliability and validity in distinguishing differences between patients who may have the same diagnosis but need different treatments. In addition, we examine the relationship between the NAQ subscales and normal and abnormal personality characteristics.

Method

Participants. This online study included 901 participants (76.5% women, 23.4% men) solicited through notices, word of mouth, or through emails posted on academic and other listservs, as well as advertisements in the "Volunteer" section of the online craigslist in a variety of cities in the United States. Participants were invited to our lab's (Emotion, Personality, & Altruism Research Group) web page (http://www.eparg.org) to the study "Emotions and Personality." Participation was anonymous. Participants' ages ranged from 18 to 84 years, with the mean at 34.4 (*SD* = 12.1). The majority (about 89%) were from the United States. About 80% were of European decent, 4.2% were Asian/Asian American, 2.1% were Latin/Latin American, and 1.8% African/African American. Education varied from high school or less (5.3%) to doctoral or law degrees (16.1%). In all, 4% had attained an associates degree, 18.8% a bachelors degree, and 18.1% a masters degree. An additional 20% had some undergraduate education and 13.5% some graduate education. A total of 1% did not disclose their education level, and 2.3% indicated other educational achievements. Participants also indicated history of psychiatric diagnoses and current medications (see Tables 1 and 2).

Instruments. A variety of instruments were used to assess the validity of the two subscales of the NAQ (O'Connor, Lewis, Berry, Yi, & Crisostomo, 2005) including measures of

Table 1. Frequency of Self-Reported Diagnoses.

Self-reported diagnosis	Frequency	%
Depression	146	16.2
Anxiety	34	3.8
Bipolar disorder	19	2.1
ADHD	12	1.3
Insomnia	10	1.1
OCD	7	0.8
Addiction	2	0.2
Epilepsy	2	0.2
Pain	3	0.3
None	666	73.9

Table 2. Most Frequently Used Psychoactive Medications.

Medication	Frequency	%
Wellbutrin	28	4.5
Tricyclic antidepressants	14	2.3
Stimulant	8	1.3
Selective serotonin reuptake inhibitor	115	18.5
Provigil	2	0.2
Mood stabilizer	17	2.7
Benzodiazapine (valium, klonipin, etc.)	43	6.9
Antipsychotic	16	2.6
Ambien/sonata	6	1

psychopathology known to be associated with either low dopaminergic tone (i.e., often treated with a dopamine agonist) or low serotoninergic tone (i.e., often treated with a serotonin agonist). We also included measures of the Big Five personality factors, as a beginning exploration of personality dimensions from the perspective of the circuit model of neurotransmitters.

The NAQ is a 46-item questionnaire with responses indicated on a Likert-type scale of 1 to 5. The instrument was derived from a list of questions generated by a psychiatrist, specializing in psychopharmacology, which he typically asks before determining what medication(s) might be most effective, and to evaluate response to treatment. Item content validity was subsequently assessed by other practicing psychiatrists. The NAQ was piloted in a study at a major research university, and then revised for clarity and reliability. The S-scale consists of 27 items, derived from the low-serotonin questions, and the D-scale consists of 19 items from the low-dopamine questions. Procedures for generating items, evaluating content validity, and assessing the psychometric functioning of item and scale characteristics are described in detail below.

The Interpersonal Guilt Questionnaire-67 (IGQ-67; O'Connor, Berry, Weiss, Bush, & Sampson, 1997) is a 67-item, self-report questionnaire, with responses indicated on a Likert-type scale ranging from 1 to 5. The IGQ-67 was

designed to assess guilt related to the fear of harming others, and includes four subscales: Survivor Guilt, Separation Guilt, Omnipotent Responsibility Guilt, and Self-Hate. Reliabilities of all subscales ranged from .75 to .88. The IGQ-67 subscales are significantly correlated with psychopathology across cultures; the two subscales most significantly associated with psychopathology, Survivor Guilt, and Omnipotent Responsibility Guilt, were included in this study. Survivor guilt is characterized by the belief that pursuing normal goals and achieving happiness or well-being will cause others, loved ones and strangers, to suffer. Omnipotent responsibility guilt is characterized by the belief that one has omnipotent responsibility for the happiness and well-being of others.

The Center for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977) is a widely used 20-item self-report instrument, with responses on a Likert-type scale, ranging from 0 to 3, and total scores ranging from 0 to 60. The cut-off score for depression is equal to or greater than 16, which indicates at least a mild depression, although many clinicians mark a mild depression starting well below 16.

Generalized Anxious Temperament (GAT; H. S. Akiskal, 1998) is a 26-item instrument with responses indicated on a Likert-type scale from 1 to 5. Participants are asked to describe themselves "through most of your life." Along with a total GAT score, there are two subscales, the GAT-Self, with items related to self-worry, and the GAT-Other, with items reflecting worry about others. Theoretically, the GAT was developed by placing anxious, worrying, temperaments in the context of evolutionary adaptations, in which members of the population who are high in this trait are those on the outlook for danger not only for themselves, but for the good of their families and groups.

The Jasper−Goldberg Adult ADD Screening Examination is a 24-item screening device, rated on a Likert-type scale from 0 (*not at all*) to 5 (*very much*), indicating how they have felt "most of your adult life." Scoring 70 or above is considered suggestive of an attention deficit disorder (ADD) diagnosis. Most people who score at this level have been eventually diagnosed with ADD although other psychiatric problem such as bipolar disorder may be present and account for the high score.

The Obsessive Compulsive Inventory-R is derived from the Obsessive-Compulsive Symptoms Scale from the International Personality Item Pool (Foa, Kozak, Salkovskis, Coles, & Amir, 1998). This 20-item self-report instrument assesses perfectionism, intrusive thoughts, and the need for order and cleanliness.

Brief Big Five Inventory (BFI; John, 1990) is a 44-item self-report inventory for assessing five personality traits: openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism.

Procedure. Participants volunteered anonymously, indicating informed consent by clicking an appropriate button, before proceeding. Data entered our server through FileMaker Pro, was transferred to Microsoft Excel, and then to SPSS for analysis.

Data analysis strategy. An initial item pool for the NAQ scales was generated by a psychiatrist, specializing in psychopharmacology. Each item was classified as reflecting traits associated with either serotonin or dopamine systems. To assess content validity of the items in each subscale, judgments were obtained from three other practicing psychiatrists who frequently evaluate patients' probable responses to medications (see below). Overall NAQ scale reliabilities, individual-item performance, scale dimensionality, and potential item bias (by gender) were assessed using a Rasch model for rating scales (O'Connor et al., 2005). Convergent and discriminant validity were assessed using correlations with standardized measures of psychopathology and personality, and by comparisons of groups distinguished by self-reported psychiatric diagnoses.

Results

NAQ Content Validity Assessment

Three independent psychiatrists rated each item of the NAQ item pool on two separate Likert-type scales (from 1 = *not at all* to 5 = *a great deal*) indicating the degree to which items reflect characteristics associated with dopamine and serotonin systems. We assessed interrater agreement using intraclass correlations (ICC) based on fixed effects analysis of variance. The ICC for the serotonin ratings was .79 and for the dopamine ratings was .81. Rater averages on each were calculated. Items were then classified as either dopamine or serotonin-related, depending on the higher of the two scale averages. These classifications were then compared with the initial classifications obtained from the psychiatrist who generated the items. All but one item ("I lose my temper easily") obtained the same classification from the two sources. This ambiguous item was removed from the item pool, leaving 19 items in the S-scale and 27 items in the D-scale. Items were subsequently assessed for reliability and validity using data from the online sample.

Reliabilities and Item Analyses of NAQ scales

To assess psychometric characteristics of the S and D scales, we fit the items of each to a rating scale extension of the Rasch model (Andrich, 1978). The Rasch model for dichotomous items posits that any individual's score on a given item is a function of two parameters: a parameter representing the difficulty (or endorsability) of the item, and a parameter representing the individual's standing on the latent construct being measured. The rating scale extension of the Rasch model also includes a threshold parameter for each response category in polytomous items. Item difficulties and person measures are on a common logit scale. In Rasch analysis, ordinal raw scores (the sum of items in the scale) are

Table 3. Item Statistics for the S-Scale.

Order		*d*	MS Fit
15	I get migraine headaches.	56.68	1.19
18	I have irregular bowel movements.	55.54	1.03
31	I'm the sort of person who gets lonely pretty quickly if I'm not around other people.	54.44	1.05
23	When away from home, I can easily get a feeling of homesickness.	54.36	1.02
10R	My thoughts are organized.	53.21	1.02
29	I'm the sort of person who holds a grudge.	53.01	0.99
11	I often feel intimidated when I'm faced with people in authority—judges, police officers, supervisors, etc.	52.73	1.03
3	My mood tends to decline noticeably in the winter months.	52.03	0.91
5	I tend to be a light sleeper.	51.46	1.24
38	I have had at least one anxiety attack in my life.	50.92	1.01
20	In the winter, I find it a lot harder to get up in the morning.	49.96	0.98
46	If female: I have moodiness, depression, or irritability just before my period starts. If male: I tend to ejaculate within just a few minutes of starting sex.	49.91	0.95
1	I am a moody person.	49.35	0.85
7	I think of myself as an anxious person or as a worrier.	48.90	0.80
33	I tend to second guess myself.	47.27	0.84
25	When a relationship ends, I often feel acutely anguished or distraught.	47.16	0.94
36	I often go back and check my work when it's done, just to be sure I did it correctly.	47.12	1.25
27	When I have an unpleasant feeling like anger or anxiety, it tends to linger in my mind.	44.33	0.76
41	If I'm going somewhere and I've never been there before, I often consult a map.	42.26	1.30

Note. Order = order of item in test administration; *d* = item difficulty estimates in logits; MS Fit = mean-square fit statistics; R = reverse scored item.

transformed into interval-level logit measures. For the D and S scales, we transformed the scales such that the lowest possible raw score was associated with a Rasch measure of 0 and the highest raw score was associated with a Rasch measure of 100. Rasch measures were used in all subsequent validity analyses. (Tables for converting raw score sums to Rasch interval measures are available on request from the authors.)

To assess overall scale characteristics, we examined item and person separation reliabilities. Item separation indicates the degree to which items are sufficiently separated in difficulties to form a useful measurement continuum (values greater than .90 are acceptable). Person separation indicates the degree of error-free variability among respondents on the measured construct. It is generally interpreted by the same standards as Cronbach's alpha coefficient. The fit of individual items to the Rasch model was assessed using information-weighted mean-square fit statistics. These fit statistics have an expected value of 1. Items with fit statistics less than 1.5 contribute effectively to a measurement system (Linacre, 2007).

Psychometric functioning of the S-scale. For the 19-item S-scale, the Rasch item separation reliability was .99, indicating adequate spread of item difficulties. The person separation reliability was .80 (.70 is a conventional cut-off). In Table 3, we present the item difficulty estimates and the mean-square fit statistics for each item of the S-scale. Items are displayed from highest to lowest item difficulties. Lower values of item difficulties indicate "easier-to-endorse" items. All items fit the model successfully, with fit statistics ranging from 0.76 to 1.30. We examined potential differential

item functioning (DIF) by gender. To test for DIF using Rasch methods, items are calibrated separately for all subgroups (equated onto a common scale) and item difficulties are compared between subgroups (Draba, 1977). Gender differences in item difficulties ranged from −.49 to .26 logits. Differences of less than half a logit suggest no serious item bias for most testing situations (Wright & Douglas, 1975).

Psychometric functioning of the D-scale. For the 27 items of the D-scale, the item separation reliability was .99 and the person separation reliability was .85. Table 4 displays the item difficulty estimates and the mean-square fit statistics for each item. Item fit statistics ranged from 0.79 to 1.53. We also examined potential DIF by gender on the D-scale items. Gender differences in item difficulties ranged from −.27 to .29 logits, suggesting no serious item bias by gender.

Associations of NAQ Scales With Psychopathology and Personality

Table 5 presents correlations of the NAQ scales with continuous measures of psychological symptoms and with personality factors. Means and standard deviations for all scales are displayed. Among zero-order correlations, most were statistically significant at the .001 level, and correlations were moderately high except for Extraversion and Openness to Experience, which had meager correlations with both NAQ subscales. Figure 1 displays the correlations between NAQ scales and standardized measures of psychopathology. Correlations were stronger with the S-scale for all measures

Table 4. Item Statistics for the D-Scale.

Order		d	MS Fit
14	I get more parking tickets than most people.	61.37	1.12
21	I have had a problem with drinking too much.	56.76	1.19
24	I pace back and forth often.	56.46	1.00
22	People complain that I interrupt them.	56.01	1.06
4	I tend to blurt things out and later regret having said them.	53.61	0.94
30	I drink more caffeine (tea, coffee, cola, energy drinks, etc.) than most people.	53.56	1.23
44	When I'm starting a project that has a number of sub-tasks associated with it, it's hard for me to know how to prioritize or rank-order them in terms of importance.	53.45	0.83
28	I find that I'm late for a lot of appointments.	53.33	1.01
43	I often get a feeling of being defeated before even starting a project.	53.21	0.80
32	At times, I've gotten so mad in the car that I've yelled out loud or pounded on the steering wheel.	52.18	1.14
39	I'm naturally athletic and coordinated.	51.09	1.53
6	I often stop working on a task or project before finishing it.	50.52	0.85
34	I am a messy person.	50.46	0.93
9	It is hard for me to sit at a desk and work without getting up and moving around.	50.33	0.96
40	I have a hard time getting started on projects.	50.31	0.84
17	It is difficult to stay with one thought or idea without being interrupted by other thoughts that lead to still more thoughts or ideas that are not related to the thought or idea I began with.	50.06	0.80
37	I get frustrated pretty easily.	49.92	0.85
19	Waiting in lines really bothers me.	49.52	1.01
13	In conversations, my mind tends to wander away from what the other person is saying.	49.29	0.82
45	I spend a lot of time doing tasks that aren't very important, even if there are tasks that are much more important that I should be working on.	49.09	0.83
26	I tend to fidget.	48.89	0.93
2	Being stuck in traffic really bothers me.	48.11	1.03
8R	I balance my checkbook regularly.	47.34	1.17
42	I tend to procrastinate, and then try to do the majority of my work right before it absolutely has to be done.	47.25	0.81
12	When I try to go to sleep at night, I often find that my mind doesn't shut off.	47.16	1.08
35	It is hard for me to read things that don't really interest me.	44.39	0.98
16	I really enjoy being outdoors in nature.	41.97	1.36

Note. Order = order of item in test administration; d = item difficulty estimates in logits; MS fit = mean square fit statistics; R = reverse scored item.

Table 5. Descriptive Statistics and Correlations Between NAQ Scales and Measures of Psychopathology and Personality in the Whole Sample.

	Zero-order correlations		Partial correlations		
	D-Scale	S-Scale	D-Scale	S-Scale	M (SD)
Depression (CESD)	.49*	.61*	.19*	.43*	16.9 (12.5)
Anxiety (GAT)	.52*	.76*	.09	.65*	67.3 (21.6)
Attention disorder (ADHD)	.77*	.67*	.63*	.36*	62.7 (23.2)
OCD (OCI-R)	.24*	.48*	−.09	.43*	58.9 (9.8)
Survivor guilt	.37*	.47*	.11	.33*	33.1 (8.8)
Omnipotent guilt	.32*	.45*	.06	.33*	33.7 (6.9)
Personality (BBF-44)					
Extraversion	−.08	−.18	.05	−.17*	25.3 (7.6)
Neuroticism	.47*	.75*	−.01	.66*	24.2 (7.2)
Conscientiousness	−.66*	−.39*	−.59*	.05	31.8 (6.9)
Agreeableness	−.31*	−.31*	−.17*	−.15*	33.4 (6.0)
Openness	−.03	−.12	.06	−.13*	39.2 (6.8)
M (SD)	50.1 (4.26)	50.6 (4.80)			

Note. NAQ = Neurotransmitter Attributes Questionnaire; CESD = Center for Epidemiologic Studies Depression Scale; GAT = generalized anxious temperament; OCI-R = Obsessive-Compulsive Inventory–Revised; BFI-44 = The Brief Big Five Personality Inventory, *V44* (John, Donahue, &Kentle, 1991).
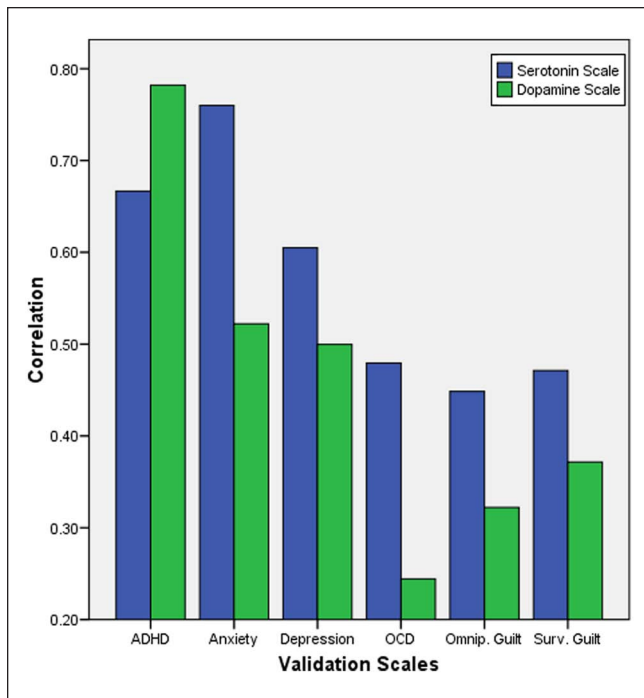*$p < .001$.

Figure 1. Correlations between NAQ scales and validation scales.
Note. NAQ = Neurotransmitter Attributes Questionnaire.

Table 6. Correlations Between NAQ Scales and Measures of Psychopathology and Personality by Gender.

	D-Scale		S-Scale	
	Men	Women	Men	Women
Depression (CESD)	.63*	.45*	.67*	.59*
Anxiety (GAT)	.59*	.49*	.77*	.74*
Attention disorder (ADHD)	.82*	.76*	.64*	.68*
OCD (OCI-R)	.37*	.23*	.49*	.48*
Survivor guilt	.48*	.34*	.57*	.43*
Omnipotent guilt	.44*	.28*	.47*	.42*
Personality (BBF-44)				
Extraversion	−.19	−.05	−.28*	−.05
Neuroticism	.54*	.45*	.75*	.74*
Conscientiousness	−.69*	−.65*	−.43*	−.40*
Agreeableness	−.33*	−.31*	−.32*	−.34*
Openness	−.13	0	−.20	−.07

Note. NAQ = Neurotransmitter Attributes Questionnaire; CESD = Center for Epidemiologic Studies Depression Scale; GAT = generalized anxious temperament; OCI-R = Obsessive-Compulsive Inventory–Revised; BFI-44 = The Brief Big Five Personality Inventory, *V44* (John, Donahue, & Kentle, 1992).
*$*p < .001$.

except the ADHD measure, which had a stronger relationship with the D-scale.

Because NAQ scales were moderately correlated with each other ($r = .60$), we also calculated partial correlations of the NAQ subscales (each controlling for the other) with the measures of symptoms and personality (see Table 5). These results reflect the independent contribution of each NAQ subscale to predicting the validity measures, and better highlight the discriminant validity of the D- and S-scales.

Table 6 presents the same correlations obtained among the male and female participants separately. Independent-samples *t*-tests determined whether males and females differed in mean scores on the NAQ scales. On the D-scale, there was no significant difference between males ($M = 49.8$, $SD = 4.49$) and females ($M = 50.2$, $SD = 4.21$), $t(894) = −1.23$, $p = .22$. There was, however, a significant difference on the S-scale, with females ($M = 51.2$, $SD = 4.73$) higher than males ($M = 48.5$, $SD = 4.52$), $t(894) = −6.98$, $p < .001$.

NAQ Scales and Self-Reported Diagnoses

One-way analyses of variance were used to predict NAQ scale scores from self-reported diagnoses. Diagnoses of epilepsy, pain, and addiction were excluded because of inadequate sample sizes. Table 7 displays the means and standard deviations for each diagnostic category. The overall *F*-tests for both scales were statistically significant. Dunnett's post hoc tests (two-sided, $\alpha = .05$) were used to compare each diagnostic group with the group that reported no diagnosis. For the

D-scale, three diagnostic groups were significantly higher than the no-diagnosis group: ADHD, depression, and bipolar. Figure 2 shows Cohen's d effect size estimates for the S-scale, based on the mean and standard deviation of the no-diagnosis group. For the S-scale, the depression, anxiety, bipolar and OCD groups were significantly higher than the no-diagnosis group. All of these diagnostic groups had effect sizes greater than .50—at least half a standard deviation above the mean of the no-diagnosis group. Only the OCD and bipolar groups had effect sizes greater than 1.0. For the D-scale, three diagnostic groups were significantly higher than the no-diagnosis group, ADHD, depression, and bipolar disorder. Figure 3 presents effect sizes for the diagnostic groups on the D-scale. Only the ADHD group had an effect size greater than 1.0, with the bipolar group approaching this level.
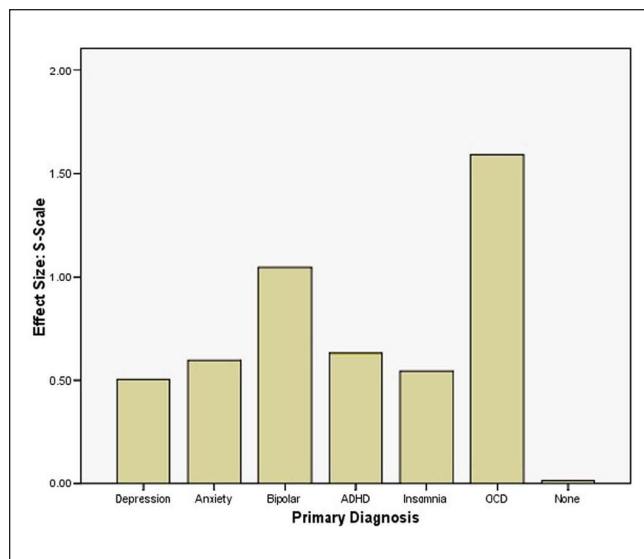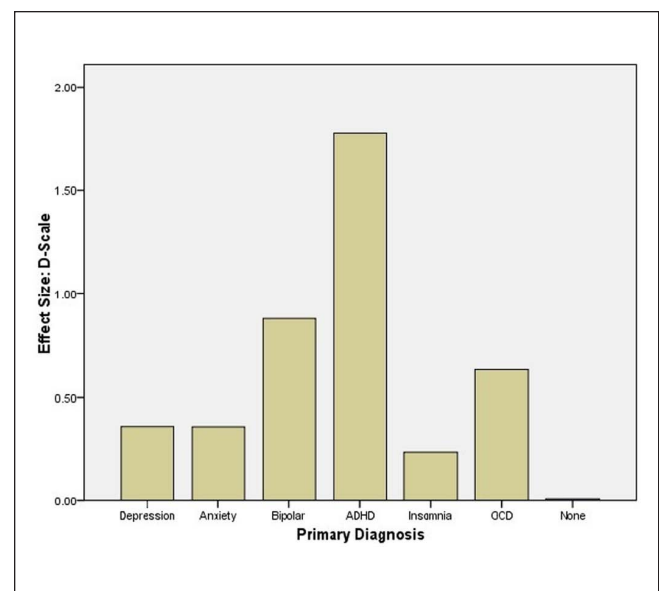
Discussion

This study supports the psychometric strength of a new clinical screening tool and demonstrates the potential value of posing questions captured in the NAQ when physicians are prescribing medications for patients presenting with psychological problems. While these complaints may be regarded as unusual, idiosyncratic, or even disagreeable personality variations rather than signs of discrete disorders, they may be treatable by psychotropic medications or psychosocial strategies. The NAQ subscales appear to confirm common clinical observations; disorders known to be treated best with particular medications are found to be elevated on subscales as would be predicted. For example, subjects who score high on a well-used screening measure of attention deficit and hyperactivity disorder also show evidence of dysfunction on the

Table 7. Comparison of Primary Diagnostic Groups on the NAQ Scales.

	Depression	Anxiety	Bipolar	ADHD	Insomnia	OCD	None	*F*
D-scale								
M	50.9	50.8	53	56.5	50.5	52.1	49.6	9.26*
SD	−4.75	−3.93	−4.42	−7.42	−5.99	−4.39	−4.39	
S-scale								
M	52.1	52.5	54.6	52.7	52.3	57.1	49.8	11.38*
SD	−5.11	−3.73	−3.88	−5.21	−5.14	−4.64	−4.58	

Note. NAQ = Neurotransmitter Attributes Questionnaire.
*$p < .001$.

Figure 2. S-scale score effect size estimates for diagnostic groups relative to group reporting no diagnosis.

Figure 3. D-scale score effect size estimates for diagnostic groups relative to group reporting no diagnosis.

dopaminergic subscale of the NAQ, and this corresponds to the common treatment of ADHD with a dopaminergic agonist. Likewise, patients who demonstrate elevations in a screening tool for OCD appear to have greater dysfunction in the serotonergic circuit, corresponding to the well-known efficacy of serotonergic medications in the treatment of OCD. These findings most succinctly validate the subscales of the NAQ. In depression, data from the NAQ suggests that the disorder may represent dysfunction of either or both circuits, and this too corresponds to the experience of psychopharmacologists and other physicians treating depression. This includes internists and other nonpsychiatric specialists along with prescribing treatment providers with other licenses, such as supervised nurse practitioners and physician assistants.

Psychiatric lore suggests that depressed women respond to monotherapy with a serotonin agonist more often than do men. The NAQ subscales contribute to a growing body of evidence confirming the psychiatric impression that women and men differ in their predisposition to serotonin-associated

psychiatric disorders (Jovanovic et al., 2006). The results of this study demonstrate that many depressed men may suffer from a dopaminergic and serotonergic dysfunction, while women are more likely to be experiencing a serotonergic problem. Subtleties found by the NAQ support the commonly held experience that individual differences may be important in the treatment of depression and the questions commonly asked by specialists in psychopharmacology should be moved into the internist's office. All patients may need a case-specific approach to effective treatment design.

The effective use of a neurotransmitter-focused screening and assessment tool before deciding on specific psychopharmacological treatments and even, perhaps, behavioral treatment is one of the recommendations suggested by this study, warranting future research. Assessing a patient's serotonergic and dopaminergic tone using the NAQ might allow clinicians treating depression and anxiety disorders—often confusing and intermixed in presentation—to better predict the medication most likely to be effective, that is, a serotonergic agonist such as

citalopram (Celexa) or a dopaminergic agonist such as bupropion (Wellbutrin), or in some cases both. Assessing patients and tailoring medication approaches before treatment might yield improved compliance and subsequence remission rates, particularly when the first agent or agents used are effective. When initial trials fail to provide relief from symptoms, patients are likely to drop out of treatment, instead of hanging in while the prescribing professional initiates second or third trials.

The potential research applications in social cognitive neuroscience and psychopathology might increase our understanding of the mechanisms underlying many psychological problems. In addition, current clinical trials comparing medication and psychotherapy only become specific in terms of what kind of psychotherapy is used in a study. So for example, a CBT for depression is compared with a pharmacological treatment. However, all patients in such a study are treated with one medication, most often a SSRI, a serotonin agonist, helpful for the depressed person who suffers from poor serotonergic tone. However, the medication may fail to help the patient who needs a dopaminergic agonist. The lack of case-specificity in psychopharmacological agents used in studies comparing CBT with treatment with medication for depression may be producing erroneous results. Studies comparing psychotherapy with medication might yield an entirely different picture, if the appropriate class of medication were used for each patient in a case-specific manner (Cuijpers et al., 2012).

While beginning with clinical observations, we suggest that the circuit model of psychopathology extends to normal personality within an evolutionary framework. The circuit model might provide personality researchers with new insights into fundamental biological systems that underlie many commonplace individual differences. For example, it would be reasonable to expect that many underachieving individuals, who seemingly fail to pursue socially valued goals, might be characterized as having low levels of appetitive motivation, assertiveness, and reward dependence, that is, traits linked to dopaminergic systems. This initial expectation, however, might be unjustified in some cases. In previous research, submissive behavior, low social ranking, and depressive symptomatology have been linked to elevated levels of empathy-based survivor guilt (O'Connor, Berry, Weiss, Schweitzer, & Sevier, 2000; O'Connor et al,, 2002). In the present study, survivor guilt (and the closely related omnipotent responsibility, also based on empathy) was more strongly correlated with the S-scale of the NAQ than with the D-scale. One implication of these results is that what might appear at first to be low dominance and achievement motivation (low anger/BAS) might instead be a consequence of fearful, anxious, and inhibitory traits (high fear/BIS) related to concerns about the safety and well-being of others (H. S. Akiskal, 1998).

There are obvious limitations to this study. To date, it is still impossible to provide direct biological evidence linking the hypothesis that subscales of the NAQ are associated with dysfunctions in dopaminergic or serotonergic circuits. We are still unable to measure brain levels of serotonin or dopamine, from blood or urine samples. Furthermore, even if such a technological advance were to be made, and it became easy to empirically measure these neurotransmitters, it is not clear that direct correlations between dysfunctions in the dopaminergic or serotonergic circuits and personality traits associated with particular disorders would necessarily correlate with overall levels of the respective neurotransmitter levels. There are also differences in the manner in which brain circuits respond in terms of their regulation in various psychiatric disorders and in different parts of the brain. Therefore, the knowledge of measured neurotransmitter levels might be of limited use in linking clinical data and personality traits to the treatment plans. Furthermore, assessments are based on self-reports, which might have resulted in bias due to shared method variance. These issues must be considered in future research before further conclusions can be drawn about the clinical validity and utility of the NAQ.

The development and validation of the NAQ is a good first step in trying to provide a systematic measure that links personality traits and clinical data to pharmacological treatment approaches. With few exceptions, scholars, clinicians, and researchers fail to link personality and temperament traits with psychiatric treatment and there has largely been an absence of efforts to point out obvious connections. The NAQ attempts to fill that void with a relatively accessible instrument needed at least until there are more sophisticated methods by which to determine biological indicators of specific dysfunction of neurotransmitter circuits. Future research in clinical populations may find the NAQ useful to prescribing treatment providers in making medication decisions. If prescribers are more quickly and reliably able to determine the medications most likely to be successful in providing relief from symptoms by even a few weeks, there will inevitably be better patient compliance and treatment outcome. The subscales of the NAQ may be used to improve the validity of outcome studies. Instead of using the same medication for all depressed patients in an outcome study comparing psychopharmacological with cognitive behavioral and/or other psychosocial treatments, classes of medications might be selected on a case-specific basis. In this era of evidence-based medicine, the use of instruments designed to consider individuals in a case-specific manner is increasingly called for, and the NAQ is a step in that direction.

Acknowledgment

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