

Relations of serotonin function to personality:
current views and a key methodological issue

Charles S. Carver *

Christopher J. Miller

Department of Psychology

University of Miami

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Correspondence: Charles S. Carver
Department of Psychology
University of Miami
Coral Gables, FL 33124-0751

Phone: (305) 284-2817

FAX: (305) 284-3402

E-mail: Ccarver@miami.edu

Christopher J. Miller
Department of Psychology
University of Miami
Coral Gables, FL 33124-0751

Abstract

Studies of biological underpinnings of personality suggest that serotonergic functioning relates to certain personality traits. However, how to interpret the findings depends partly on assumptions about how personality is organized. These assumptions are reflected in the assessment devices used and also in how the data are examined. Review of evidence to date appears to link serotonin function to impulsivity and, to some extent, to hostility. The relation of serotonin function to anxiety proneness is far more questionable. Indeed, when such a relation occurs, it often takes a form opposite of the direction argued by theory. It is recommended that research use measures that discriminate adequately among personality qualities reflecting incentive sensitivity, threat sensitivity, and impulsiveness. Indeed, it is highly desirable to examine facets of each of these qualities separately.

Key words: Serotonin, personality, temperament, anxiety, impulsivity, harm avoidance

The idea that specific neurotransmitters are differentially involved in particular aspects of human behavior is receiving steadily increasing research attention. For some researchers, that work is an effort to link specific disorders to specific neurotransmitters, in hope of clarifying the nature of the disorder. There is also growing interest in the idea that neurotransmitter functions relate to normal variations in personality (Depue and Collins, 1999; Zuckerman, 2005). Evidence of such associations would represent a bridge across disciplines, helping to clarify the nature of personality.

This article focuses on the effort to relate serotonin function to personality (and more briefly addresses another literature on links from personality to genetic markers of serotonin function). To study this relationship requires assessing both serotonin function and personality. In many studies on this topic, serotonin functioning is assessed by responses to a drug challenge; in other studies, serotonin function is experimentally manipulated. In assessing personality, methods have been more diverse. Indeed, the methods differ enough to create potentially serious problems in interpreting research outcomes (see also Sen et al., 2004a; Munafò et al., 2005).

We begin this article by briefly describing the core issue concerning the assessment of personality. In so doing, we distinguish between aspects of personality that often are confounded in assessment. Then we turn to recent evidence relating personality to serotonin function. We also consider more briefly the literature relating personality to serotonergic genes. We close with conclusions about the findings and recommendations for future work.

1. Conceptualizing and measuring personality

There are many ways to conceptualize personality (Carver and Scheier, 2004), but most research on the biological substrate of personality adopts some version of a trait approach. Some studies examine one trait at a time, but researchers sometimes employ broad inventories of traits. Many people regard such inventories as interchangeable, but they differ in very important ways. These differences can make it difficult to compare measures to each other, and thus to compare results from studies using different measures.

Perhaps the most influential approach to personality assessment at present is the 5-factor model (e.g., McCrae and John, 1992; Goldberg, 1993; Wiggins, 1996; McCrae and Costa, 1997).

This approach, based in factor analytic work, holds that much of the variability in personality can be captured by five broad dimensions. The first two dimensions—neuroticism and extraversion—also appear in most other trait models. The other dimensions are best known as agreeableness, conscientiousness, and openness (or intellect). Several measures of these five traits are in wide use; the one most often seen in studies of biological substrates of personality is the NEO-PI-R (Costa and McCrae, 1992). Most studies using measures from the 5-factor approach focus on the supertraits, but many measures (including the NEO-PI-R) have facet scales within each global trait for more subtle and differentiated assessment.

Two 3-factor models that are similar in some ways to the 5-factor model are also in wide use. Eysenck (1970, 1992) posited neuroticism and extraversion, plus a third trait called psychoticism. These traits are typically assessed by the Eysenck Personality Inventory (EPI; Eysenck and Eysenck, 1964) or the Eysenck Personality Questionnaire (EPQ; Eysenck and Eysenck, 1975). Tellegen (1985) recast neuroticism slightly as negative emotionality and extraversion as positive emotionality, and added a third factor called constraint. These traits are assessed by the Multidimensional Personality Questionnaire (MPQ; Tellegen, 1985). To some extent, psychoticism in Eysenck's model and constraint in Tellegen's model represent blends of agreeableness and conscientiousness.

Zuckerman and his colleagues (1993) have proposed an "alternative 5," in which sociability is generally equivalent to extraversion, aggression-hostility is similar to agreeableness (inversely), impulsive sensation seeking is similar to conscientiousness (inversely), and neuroticism-anxiety is generally the same as neuroticism (Zuckerman, 1995, 2005). These 5 factors are assessed by the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ; Zuckerman et al., 1993). An important difference between this model and the others is that Zuckerman and colleagues place hostility in a factor separate from neuroticism. There are independent reasons to believe that that placement is the more appropriate one (see Jang et al., 2002; Carver, 2004).

There is an emerging consensus among those who adopt the 5-factor models and these 3-factor models that extraversion (positive emotionality) reflects a system that regulates approach of incentives and neuroticism (negative emotionality) reflects a system that regulates avoidance

of threats (Tellegen, 1985; Fowles, 1993; Gray, 1994a; Depue, 1995; Harmon-Jones and Allen, 1997; Depue and Collins, 1999; Watson et al., 1999; Carver et al., 2000; Davidson et al., 2000; Lucas et al., 2000). Such a construal serves to link two bio-behavioral functional properties to what otherwise are only descriptive dimensions.

Another view of personality often adopted in studies of biological substrates is that of Cloninger (1987; Cloninger et al., 1993). Cloninger (1987) began with three dimensions: Novelty seeking (the tendency to seek excitement); harm avoidance (the tendency to inhibit behavior to avoid punishment); and reward dependence (the intensity of responses to social approval), measured by the Tridimensional Personality Questionnaire (TPQ). The TPQ also has facet scales. Cloninger (1987) proposed that each trait relates to the functioning of a specific neurotransmitter, linking serotonin to harm avoidance. The theory was later elaborated (Cloninger et al., 1993) to add a fourth dimension (persistence) to what was now called temperament, plus three new dimensions referred to as character. The latter are self-directedness (self-determination, purposefulness, or willpower), cooperativeness (empathy with and acceptance of other people), and self-transcendence (spirituality and absorption). With elaboration of the theory came a new measure, the Temperament and Character Inventory (TCI).

This last theoretical view obviously shares some themes with the others previously outlined. There appears at first glance to be considerable similarity between novelty seeking and extraversion, and between harm avoidance and neuroticism. However, there are also important differences. Novelty seeking incorporates a thrill-seeking, impulsive quality that is not part of extraversion. Indeed, some view this trait as closer to psychoticism or impulsive sensation seeking than to extraversion (Zuckerman, 1995). There are also differences pertaining to harm avoidance. Although being high in harm avoidance yields the inhibited apprehension that one would expect from high neuroticism, low levels of harm avoidance are said to yield sociability, which in other models relates to extraversion rather than low neuroticism. Low harm avoidance also manifests as openness to risk taking and proneness to harmful impulsive behavior such as aggression and suicide. Thus, impulsiveness is strongly implicated in both novelty seeking and harm avoidance.

1.1 Impulse and constraint

In considering evidence on how serotonin function relates to personality, the quality of impulsiveness versus constraint emerges repeatedly as important; indeed, as will be seen, there is a very good basis for arguing that this quality of behavior is the core of the relation of serotonin to personality (see also Soubrié, 1986; Depue, 1995; Depue and Collins, 1999; Manuck et al., 2003). For that reason, it is important to examine more closely how this quality is viewed in various theories, and how it is operationalized in the various measures.

The simplest dynamic behind impulse versus restraint is one in which impulsiveness and anxiety are at opposite ends of a dimension. Specifically, impulsiveness occurs when anxiety is low; on the other side, high levels of anxiety inhibit impulses (Gray, 1982, 1994a, 1994b).

It is increasingly recognized, however, that at least two different dynamics underlie displays of impulse versus restraint (Derryberry and Rothbart, 1997; Nigg, 2000; Eisenberg, 2002; Carver, 2005). One dynamic derives from anxiety about an impending threat (versus the impulse to approach an incentive). A separate dynamic concerns the choice between having a small desired outcome now versus a larger desired outcome later: the phenomenon of delay of gratification (Mischel, 1974) or the problem of intertemporal choice (Manuck et al., 2003). Some theorists see these two dynamics as underlying distinct classes of restraint phenomena. Restraint in response to threat is considered relatively involuntary, whereas planful restraint is considered effortful (Derryberry and Rothbart, 1997; Rothbart and Bates, 1998; Rothbart et al., 2000; Rothbart et al., 2004; see also Nigg, 2000; Kochanska and Knaack, 2003). Involuntary restraint involves reflexive avoidance of harm. Effortful restraint reflects attempts to optimize outcomes by selecting the best choice of available actions.

Eisenberg (2002) characterized cases of involuntary restraint (which she terms reactive inhibition) as being largely under the control of subcortical areas, and cases of effortful inhibition as depending more on executive cortical function. The sense of this characterization can also be found in statements by Cloninger et al. (1993), that qualities of temperament (including harm avoidance) depend on procedural memory and habits, whereas qualities of character depend on propositional memory and more effortful processing.

The idea that there are two distinct sources of impulse and restraint also resonates with ideas and evidence linking brain function with impulsive versus restrained behavior (see Lieberman et al., 2002; Strack and Deutsch, 2004; Carver, 2005; Bechara, 2005). Some of the conceptual models relating to this work suggest there are two modes of processing, one of which (subcortical) is quick and associative, the other (with more cortical involvement) slower, more deliberative, and symbolic (see also Epstein, 1973, 1994; Smolensky, 1988; Shastri and Ajjanagadde, 1993; Sloman, 1996; Metcalfe and Mischel, 1999; Smith and DeCoster, 2000). Evidence consistent with this view is reviewed elsewhere (Lieberman et al., 2002; Strack and Deutsch, 2004; Carver, 2005).

The 5-factor and 3-factor trait models other than Cloninger's all incorporate one or more dimension bearing specifically on impulse and restraint. In Eysenck's theory, this factor is psychoticism; in Tellegen's theory, it is constraint; in the alternative 5, it is impulsive sensation seeking; the dominant 5-factor models have two factors that are relevant, conscientiousness and agreeableness. Measures of each of these personality qualities have been linked to diverse behaviors that reflect impulsiveness versus restraint and sometimes antisociality (for review see Carver, 2005). What is particularly important at present is that *the dimensions just listed are empirically distinct from the dimensions bearing on incentive sensitivity and threat sensitivity* (Watson et al., 1994; Clark and Watson, 1999; Zelenski and Larsen, 1999).

Some versions of the 5-factor model suggest another source of at least some kinds of impulse, in the trait of neuroticism. Indeed, in the NEO-PI-R (Costa & McCrae, 1992), one neuroticism facet scale is named Impulsiveness. Inclusion of impulsiveness in neuroticism in this measure appears to reflect the fact that some impulsive acts (e.g., overindulgence, which is well represented in that facet scale) are prompted by negative feelings, which themselves are a hallmark of neuroticism. In a factor analysis of measures of diverse aspects of impulsiveness, Whiteside and Lynam (2001) found the NEO-PI-R's Impulsiveness facet scale loaded on the same factor as the Urgency subscale of their new impulsiveness measure. Two-thirds of the items of the Urgency subscale refer specifically to actions that are responses to negative feelings.

Although the NEO-PI-R does have a role for neuroticism in impulsiveness, it is important to

be very clear about what that role is. The way in which impulsive action is linked to neuroticism in this case is antithetical to the idea that restraint follows from elevated anxiety and impulse follows from absence of anxiety. Rather, impulsive action in this case stems from the *same* core quality of personality as underlies anxiety proneness. That is, the people who report often being distressed and anxious are the ones who also report overindulging and doing things on impulse that they later regret.

In contrast to measures derived from those 3-factor and 5-factor models, measures from Cloninger's approach incorporate qualities of impulse in multiple traits. As noted above, novelty seeking (which some equate with extraversion) has a thrill-seeking quality that is not part of extraversion. Indeed, Zuckerman (1995) reported that novelty seeking relates primarily to impulsive sensation seeking from his inventory. Similarly, De Fruyt et al. (2000) found that novelty seeking correlated positively with NEO-PI-R facets of impulsiveness and excitement seeking and inversely with dutifulness and deliberation. Although harm avoidance is typically interpreted in terms of anxiety proneness, it also correlates substantially with extraversion (Zuckerman, 1995; De Fruyt et al., 2000). Indeed, Zelenski and Larsen (1999) found that harm avoidance loaded almost equivalently on three factors: incentive sensitivity, threat sensitivity, and impulsivity (see also Carver and White, 1994).

The TPQ and TCI have also been criticized more generally on psychometric grounds, both with regard to failures to find the theoretical factor structure and with regard to the blending of conceptually distinct qualities within scales (Waller et al., 1991; Earleywine et al., 1992; Cannon et al., 1993; Herbst et al., 2000; see also Cloninger et al., 1991). For example, Herbst et al. (2000) factor-analyzed facet scales as data points in a sample of 946 normal participants. One emerging factor had positive loadings for all facets of harm avoidance plus inverse loadings for exploratory excitability (from novelty seeking), three facets of self-directedness (purposefulness, resourcefulness, and congruent second nature), and social acceptance (from cooperativeness). This pattern appears to suggest a key role for impulse versus constraint in the emerging factor, which is defined partly around harm avoidance.

In another study, Cannon et al. (1993) conducted an item-level analysis of TPQ data among

303 male alcoholics. They found that harm avoidance items split into a distress factor and a relaxed confidence factor (indeed, no TPQ dimension was unidimensional in that study). Of considerable interest, the relaxed confidence factor related to a variety of measures of antisocial behavior, whereas the overall harm avoidance scale related to none of them. Indeed, the relaxed confidence factor made unique contributions to the antisocial measures, even when entered along with a disinhibition factor deriving from novelty seeking.

Thus, measures from the different theories have very different ways of assessing impulse versus restraint. This is a very important difference among measures. Disregarding this difference can lead to confusion in interpreting results.

2. Serotonin functioning and personality

With these issues in mind, we turn to a consideration of evidence linking serotonin function to personality. Our coverage here is relatively selective. We focus on three groups of studies: some examined effects of experimental manipulations of serotonin function in nonclinical samples; some examined how serotonin function relates to certain kinds of disturbances in behavior; and some examined relations of naturally occurring differences in serotonin function to personality in nonclinical samples.

2.1 Serotonin manipulation in nonclinical samples

Many studies have manipulated serotonin function by SSRIs and looked for impact on personality qualities or behavior. The vast majority of these studies, however, have used patient samples under treatment. In such cases, an important question arises as to whether any change observed relates to the change in serotonin function or relates instead to other changes that follow from improved psychiatric status. Given such issues, studies examining effects of SSRIs in non-clinical samples are of particular value. Several such studies have now been published.

Knutson et al. (1998) found that 4 weeks of SSRI (paroxetine) among 26 non-clinical participants (compared to a control group of 25) led to lower self-reports of assaultiveness and irritability scores on the Buss-Durkee Hostility Inventory (BDHI, Buss and Durkee, 1957) and less overall negative affect (as an index from the Positive and Negative Affect Scales, PANAS; Watson et al., 1988). There was no change in positive affect, and no tests were reported for specific affects.

Participants with SSRI also displayed more cooperative behavior in a group task than did controls.

Another small study of non-clinical participants ($n = 11$ vs 9) examined effects of SSRI (citalopram) on personality self-reports (Tse and Bond, 2001). The outcome measure was an abbreviated version of the TCI. SSRI produced an increase on self-direction (reflecting such qualities as responsibility versus blaming, purposefulness, and resourcefulness) but no other difference. Another study by the same researchers (Tse and Bond, 2002) assessed personality by roommate ratings, and measured several qualities of behavior during a mixed-motive game with another person. Participants receiving SSRI (citalopram, $n = 10$) were rated by roommates as being less submissive compared to controls ($n = 10$). Similarly, those receiving SSRI showed more dominant eye-contact behavior during the game than controls, but they also displayed more cooperative, affiliative behavior. The latter result replicates the finding of Knutson et al. (1998).

There have also been studies in which the effect of serotonin function on personality-related behavior was examined in normal subjects by manipulation of tryptophan, a precursor to serotonin. Cleare and Bond (1995) examined samples of participants assessed as high and low in aggression. Those high in aggressive tendencies became more aggressive, hostile, and quarrelsome after tryptophan depletion, and less so after tryptophan enhancement, with no effect among those low in aggressive tendencies. This pattern suggests that variations in serotonin function are less about aggression per se and more about the restraint (or lack of restraint) of habitual tendencies to be aggressive.

A subsequent study (Bjork et al., 2000) found a similar pattern: tryptophan depletion led to greater aggressive response to provocation among men high in aggressiveness, but effects were opposite among those low in aggressiveness. Evidence of a similar pattern was subsequently found among a subset of women: increased aggression after tryptophan depletion, and decreased aggression after tryptophan enhancement (Marsh et al., 2002).

Moskowitz et al. (2001) administered tryptophan and placebo to 98 healthy subjects in a crossover design, measuring self-reports concerning social interactions during the day. Elevated tryptophan reduced self-reports of quarrelsome behavior, but only when tryptophan followed placebo. Elevated tryptophan also increased reports of dominant behavior (regardless of order). In

another study (Wingrove et al., 1999), tryptophan depletion led to more aggressiveness in evaluative messages sent to partners on a cooperative task, but only among persons who were high on a measure of motivational drive in incentive situations. Another study found that tryptophan depletion led to a more impulsive response style on a laboratory task (Walderhaug et al., 2002).

To summarize, these data appear to be relatively consistent in suggesting that experimentally elevated serotonin function caused three kinds of changes. Elevations caused decreases in aggression and increases in cooperativeness; there also were increases in what might be thought of as social potency. Reduction in serotonin function caused increases in expression of aggression and deterioration in cooperativeness, though these effects sometimes occurred only among persons who were relatively high in aggressive tendencies by disposition.

2.2 Cross-sectional studies of clinical samples

Another source of information linking serotonin function to personality is cross-sectional studies assessing some quality or qualities of personality and serotonin function. Many of these studies have focused on patient samples, typically comparing patients to controls. In some cases the personality qualities were related to serotonin function within the patient sample. Two popular groups for study in this way have been persons displaying impulsive aggression and persons with borderline personality disorder.

2.2.1 Impulsive aggression. A number of studies have related lower serotonin function to a history of fighting and assault (Coccaro et al., 1997), domestic violence (George et al., 2001), and impulsive aggression more generally, particularly among men (Cleare and Bond, 1997). There is also evidence of low serotonin function in a subset of depressed patients who had anger attacks, compared to other depressed patients (Fava et al., 2000). Indeed, low serotonin function also has long been implicated in suicidal behaviors (e.g., Ågren, 1980). One recent study found that low serotonin related (independently) to lifetime aggression and to high-lethality suicide attempts (i.e., resulting in greater medical damage), but not to low-lethality suicide attempts (Placidi et al., 2001).

Several recent studies make similar, but somewhat more differentiated points with regard to impulsive aggression. Dolan and colleagues have reported a series of studies of correlates of

serotonin function in male aggressive offenders (and the psychopathic subset of that group). Dolan et al. (2001) assessed aggressive qualities by BDHI and the interview-derived Lifetime History of Aggression (LHA, Brown et al., 1979). Impulsivity was assessed by Eysenck and Eysenck's (1978) Impulsiveness-Venturesome-Empathy (IVE) and the Barratt Impulsivity Scale (Barratt, 1985). Low serotonin function related to elevations in both impulsivity and aggression. Importantly, impulsivity and aggression both related to higher, rather than lower, anxiety. Dolan et al. 2001 pointed out specifically that the association of anxiety with measures of impulsivity argues against a simple model of impulsive aggression being attributable to low fear.

Dolan and Anderson (2004) reported that low serotonin function related to high scores on the impulsive-antisocial factor from the Psychopathy Checklist Screening Version. Dolan et al. (2002) found that impulsivity and aggressiveness both related to poorer executive (frontal lobe) function. They argued that the aggressiveness observed in their sample was likely attributable to frontal deficits rather than low serotonin functioning per se. The possibility remains, of course, that the frontal deficits and the low serotonin functioning are two sides of the same coin.

A particularly interesting study by New et al. (2002) examined 13 persons with a history of impulsive aggression and 13 controls by PET scan while undergoing serotonin challenge. Regions of interest were established in the orbitofrontal cortex (OFC) and anterior cingulate gyrus (ACG), and participants were scanned both under serotonin challenge and under placebo. Scans revealed several differences between groups in response to challenge (relative to placebo): Patients showed deactivation of ACG, whereas controls showed activation; patients showed activation in posterior cingulate, whereas controls showed deactivation. Finally, in left medial posterior OFC, patients showed lower activation than controls. New et al. (2002) interpreted the findings as indicating that impulsive aggression by these patients reflects lack of activity in the OFC, because those areas are involved in planning and long-term regulation. Consistent with these findings, the OFC has also been implicated in the control of aggressive impulses in other research (Dutton, 2002).

Another PET scan study (Frankle et al., 2005) examined 10 patients with impulsive aggression and 10 controls, but it did not incorporate a cortisol challenge. A difference between groups emerged in one region of interest. Lower serotonin availability was displayed in the ACG

among patients than controls. This difference is in the same direction as the pattern of change observed by New et al. (2002) when a serotonin challenge was introduced.

2.2.2 Borderline personality disorder. Another group of relatively frequent study in this context is persons with borderline personality disorder (BPD, e.g., Siever and Davis, 1991). Paris et al. (2004) determined that female borderline patients who were also high on impulsivity by Barratt scores ($n = 14$) showed lower serotonin function than patients low in impulsivity ($n = 13$). Within the BPD subsample, low serotonin function related to high indirect hostility from the BDHI, which tends to reflect impulsive acts such as angry outbursts and tantrums. However, effects of impulsivity were more robust than those of hostility.

In a related study, Soloff et al. (2003) found that males with BPD ($n = 20$) had lower serotonin response than controls ($n = 36$), and that this response was also predicted by impulsivity (by Barratt) and history of aggression (by LHA). When impulsivity was controlled for, the effect of BPD on serotonin was eliminated. In this study, unlike that of Paris et al. (2004), there were no effects among females. Verkes et al. (1998) found that lower serotonin function related to greater impulsiveness as reflected in the sensation seeking subscale of the EASI-III (Buss and Plomin, 1975) and in an index of harmful impulsive behaviors from a questionnaire used to diagnose borderline personality disorder ($n = 144$). Fitting this general picture, current discussions of treatment for BPD sometimes suggest the value of mindfulness training, to diminish impulsive reactions (Ryan, 2005).

2.2.3 High serotonin function in obsessive-compulsive disorder. It is also of interest that high serotonin function, rather than low, has been implicated in another type of disorder. Specifically, Insel et al. (1985) linked higher serotonin function to obsessive-compulsive disorder. Similar associations have since been reported by Fineberg et al. (1997) and Swedo et al. (1992). This pattern has been interpreted as suggesting a particularly low level of impulsivity among patients with this disorder.

To summarize, as a group the findings reviewed in this section appear to be consistent with the idea that serotonin influences a behavioral dimension that has inhibition and overcontrol at one end (obsessive-compulsive disorder) and impulsivity (and possibly aggressiveness) at the

other end (impulsive aggression, borderline personality disorder). This pattern is consistent with the view that serotonergic pathways are differentially involved in impulse control (Depue and Spoont, 1986; Soubrié, 1986; Depue, 1995; Depue and Collins, 1999; Manuck et al., 2003; Zuckerman, 2005). Further, it appears to be consistent with a view in which restraint (when it does occur) is effortful, rather than an involuntary reaction to anxiety. Although there is a good deal of evidence linking low serotonin function to hostility and aggressiveness, most of the researchers involved appear to believe that the link is more directly to impulsiveness or volatility in behavior than to hostility per se.

2.3 Cross-sectional studies of normal samples on measures of aggression-hostility

Several studies have also been conducted correlating personality qualities and serotonin function among non-clinical samples. Two relatively early studies (Depue, 1995; Cleare and Bond, 1997) fit well with the literature reviewed in the previous section, both in the measure used and in the results obtained. Specifically, both found a relation between low serotonin function and elevated aggression-hostility, as measured by the BDHI, similar to associations found with aggressive samples. Similarly, Netter et al. (1999) found a relation between low serotonin function and aggressiveness as measured by the Freiburg Personality Inventory.

The Depue (1995) article went beyond showing this relationship, in several ways. Depue found associations of low serotonin function with the control-impulsivity facet scale of the MPQ's Constraint factor, the aggression facet of the MPQ's Negative emotionality factor (but not to other facets), to two sensation seeking subscales (social disinhibition and boredom susceptibility), and to several indices of impulsiveness, including Barratt scores and psychoticism, but not risk taking or venturesomeness. Depue also reported a greater differentiation among components of BDHI hostility, with the strongest relations of low serotonin function being to subscales pertaining to impulsive, action oriented aggression, rather than to more passive, cognitive forms.

A more recent study (Hennig et al., 2005) yielded results consistent with the latter finding. Hennig et al. related serotonin function assessed by drug challenge to aspects of aggression-hostility (by BDHI) in 48 normal males. Two aspects of hostility emerged from factor analysis, a neurotic hostility component (composed of irritability, resentment, verbal hostility, and guilt) and a

component that was labeled aggressive hostility (composed of assaultiveness, negativism, and low guilt). Only the latter factor related to serotonin function (recall that Knutson et al., 1998, found SSRI treatment reduced self-reports of assaultiveness). The authors also noted that the aggressive hostility index did not relate to an independent measure of neuroticism, except for the neuroticism facet bearing on aggression. They concluded that the aggressive hostility factor probably reflects a quality similar to Eysenck's factor of psychoticism (an impulsive, socially unconnected quality), rather than neuroticism.

There have also been several other demonstrations of links between serotonin function and aspects of sensation seeking. Netter et al. (1996) related low serotonin function (by drug challenge) to the disinhibition and experience seeking subscales. They also found that the drug challenge in combination with experimental provocation produced elevated aggression only among participants high on disinhibition.

2.4 Cross-sectional studies of normal samples using omnibus measures

The research reviewed thus far focused mostly on impulsiveness and aggression. Other research on personality and serotonin function in normal samples, however, has had a broader focus. At least 7 such studies have been conducted using omnibus measures of personality, sometimes along with other measures.

One study by Manuck et al. (1998) in a community sample (N = 59 men, 60 women), used the NEO-PI-R, plus additional measures. All effects that emerged did so among men only. Low serotonin function related to greater life history of aggression (by LGA) and impulsiveness (by Barratt), consistent with previous results. Low serotonin function also related to higher neuroticism (from the NEO-PI-R), and the neuroticism facet scale angry hostility (other facets were not tested). High serotonin response related to higher conscientiousness (from the NEO-PI-R). The relation of neuroticism to low serotonin function was later replicated in a larger sample by the same research group (Flory et al., 2004), but they did not report a test for any facet scale, nor a test for conscientiousness.

At least four studies have related serotonin response to the TPQ in normal samples. Hansenne and Ansseau (1999) found a significant relation between low levels of TPQ harm avoidance and

low serotonin response to drug challenge in 23 normal subjects. Gerra et al. (2000) found a similar relation in 22 normal males. Hennig et al. (2000) found the opposite in a sample of 16 males. Evans et al. (2000) selected extremes on Eysenck and Eysenck's (1964) index of impulsivity, and found evidence of a lower serotonin response among the more impulsive ($n = 14$) than the less impulsive ($n = 14$), but no association of serotonin response with any TPQ scale.

At least two studies have also related the TCI in normal samples to serotonin receptor sensitivity, rather than response to drug challenge. Peirson et al. (1999) found that greater harm avoidance related to greater receptor sensitivity in a sample of 49. This finding appears to be opposite to those described in the previous paragraph (greater receptor sensitivity implies lower serotonin function), though Peirson et al. (1999) interpreted it as being consistent with Cloninger's theory. This study also found associations with lower receptor sensitivity for TCI self-directedness and the self-directedness facets of responsibility and resourcefulness. These links seem consistent with links between high serotonin function and conscientiousness (Manuck et al., 1998).

Kusumi et al. (2002) also tested serotonin receptor sensitivity in 133 normal participants. They found a tendency ($P < 0.07$) toward an association of greater receptor sensitivity (reflected in greater Ca levels to a uniform serotonin dose) with lower harm avoidance, consistent with the picture of lower harm avoidance relating to lower serotonin function. Four facets scales significantly related to Ca: shyness (from harm avoidance) and pure-hearted principles (from cooperativeness) related to higher Ca; persistence (from reward dependence) and purposeful (from self-directedness) related to lower Ca. The latter appear consistent with the link of high serotonin function to conscientiousness (Manuck et al., 1998).

Moresco et al. (2002) conducted PET scans to assess the binding of cortical serotonin receptors in 11 normal participants, and related those results to TPQ scores. Harm avoidance had a substantial inverse relationship to receptor binding, particularly in the frontal and left parietal areas. The authors noted, however, that the biological meaning of the association is uncertain: it may indicate higher or lower levels of serotonin activity relate to high harm avoidance.

Thus, 2 of 4 studies of normal samples using the TPQ found an association between greater harm avoidance and higher serotonin function, with one study being ambiguous about the

direction of the association. Two studies using the TCI appear to have had conflicting results, with one relating greater harm avoidance to greater receptor sensitivity and the other to lower receptor sensitivity. The latter two studies also found partial support for the idea that high serotonin response relates to qualities reflecting focused concentration and deliberation.

2.5 Role of anxiety-proneness

An early view of serotonin related it to the experience of anxiety (Handley, 1995). It is clear from the evidence reviewed above that the majority of findings in humans relate serotonin function to impulsiveness rather than anxiety. Nonetheless, it remains quite common to refer to anxiety-related traits in discussing this literature (e.g., Lesch and Mössner, 1998; Mazzanti et al., 1998; Katsuragi et al., 1999; Hennig et al., 2000; George et al., 2001; Murphy et al., 2001; Schinka et al., 2004; Munafò et al., 2005; Schinka, 2005). To some degree, this appears to reflect associations of serotonin function with harm avoidance from the TPQ and TCI, and the further assumption that the harm avoidance scale measures anxiety proneness. There is good reason to suggest, however, that what is relevant to serotonin function about the harm avoidance scale is not its assessment of anxiety proneness, but rather its assessment of impulsiveness.

A slightly different but related issue can be raised about studies examining the broad factor of neuroticism as the operationalization of anxiety proneness. The view that anxiety proneness is the core of neuroticism may well be correct. However, broad-scope measures of neuroticism such as the NEO-PI incorporate other qualities as well. When the facets are examined separately, which is not commonly done, the weight of the effect appears to be carried by angry hostility (e.g., Manuck et al., 1998).

Finally, it should also be noted that associations of low serotonin function with high anxiety proneness, rather than low, completely contradict the idea that the absence of anxiety is what results in the impulsive behavior. Support for the latter idea is almost wholly lacking in this literature.

3. Genotype research

We should also consider the literature that links serotonin genotype to personality, though we will do so more briefly. This literature began with several large scale studies in which the data

were examined quite thoroughly. Lesch et al. (1996) related variations in the 5-HTTLPR gene to personality in a sample of 505 normal participants, mostly male. They found a relation between neuroticism and the genotype that relates to low serotonin function. Of particular interest, however, analysis of facet scales revealed that the strongest associations were with angry hostility, depression, and impulsiveness, with anxiety being barely significant and vulnerability nonsignificant. There was also an association with low scores on the trait of agreeableness.

Greenberg et al. (2000) conducted a similar analysis of 397 participants, mostly female. Again, there was an association of genotype with both neuroticism and agreeableness. Again analysis of facets of neuroticism revealed that the strongest relations were with angry hostility and depression. Anxiety, impulsiveness, and vulnerability were all nonsignificant in this study.

A third large-scale study was reported by Sen et al., (2004b). This sample of 419 participants in a blood pressure study yielded an association of genotype with NEO-PI neuroticism and a weaker, though significant association with agreeableness. As in the previous studies, the strongest facet scale association was depression. Anxiety and self-consciousness were significant in this sample, hostility only marginal ($P = .052$), and impulsiveness and vulnerability not significant.

A relatively large number of smaller-scale studies have been conducted on this topic, including failures to find an association (e.g., Willis-Owen et al., 2005) and the occasional reverse finding (e.g., Brummett et al., 2003). By this point in the evolution of this literature, there have now been several meta-analyses to assess the strength of the relationship. These meta-analyses however, themselves raise important issues that have generally been disregarded.

Sen et al. (2004a) conducted a meta-analysis of studies relating 5-HTTLPR genotype with neuroticism. They reported that when all studies were combined, there was not a significant association. When the studies were separated by personality measure, however, there was an association of genotype with NEO-PI-R, but not with TCI/TPQ harm avoidance. Schinka et al. (2004) reached a similar conclusion from their meta-analysis. Munafò et al. (2005) found exactly the opposite: a significant relation of genotype with TPQ/TCI harm avoidance, but no relation of NEO-PI neuroticism.

One more meta-analysis is worth noting, because it examined three broad aspects of

personality rather than just one (Munafò et al., 2003). The authors concluded that serotonin genotype related to avoidance traits (broadly defined) and also aggressive traits (broadly defined). There was no test of the moderating role of the measure of avoidance traits, however, and the operationalization of aggressive traits across the meta-analysis was quite diverse. Given that diversity, those results are hard to evaluate.

Unfortunately, all of these meta-analyses but the last one disregarded traits other than neuroticism. Thus, there was no test of a potential link from genotype to agreeableness, as the earlier large-scale studies had found (Lesch et al., 1996; Greenberg et al., 2000). Similarly, in no case did the meta-analysis examine facets of neuroticism. Because facet analyses had been very informative in the earlier large-scale studies, this appears a very important omission. We would argue that these meta-analyses serve more to muddy the waters than to clarify them. Indeed, by ignoring facet scales and emphasizing overall neuroticism (which they often label trait anxiety, e.g., Schinka, 2005), the authors of those articles may unwittingly be misleading the field.

4. Conclusions and recommendations

The evidence reviewed here leads us to a conclusion about the role of serotonin in personality that is not so different from the one that was reached earlier by Soubrié (1986), Depue (1995), and Zuckerman (2005), though the evidence leading us to this conclusion differs somewhat from what was reviewed by those authors. We should be explicit in pointing out, as did those authors, that an attempt to link any given neurotransmitter to the operation of a single behavioral system may be a great oversimplification. There is a good basis for arguing that some of the effects attributable to one neurotransmitter may depend on the person's level of another neurotransmitter (Depue, 1995; Zuckerman, 2005). Despite these cautions, however, some consistency does seem to emerge from the findings.

Serotonin function appears to relate far more reliably to impulsiveness, volatility, and aggressiveness than it relates to anxiety proneness. To the extent that serotonin function does relate to anxiety proneness, the direction of the relation contradicts the assumption that anxiety traits and impulse traits oppose each other. When relations do emerge in the data, they tend to link high anxiety proneness to low serotonin function, the very pattern that relates to high

impulsiveness.

What is the meaning of the link between low serotonin function and volatility in behavior? If the impulsiveness is not a reflection of low anxiety, what does it reflect? Following the lead of others (Derryberry and Rothbart, 1997; Rothbart and Bates, 1998; Nigg, 2000; Rothbart et al., 2000; Eisenberg, 2002; Kochanska and Knaack, 2003; Rothbart et al., 2003), we argued earlier in the article that there are two potential routes to behavioral constraint (see also McClure et al., 2004). In one route, a threat response opposes and inhibits an incentive response. That route is not supported in the data on serotonin. In the other route, constraint reflects greater deliberative planfulness and executive control. A relative deficit in this path to constraint strongly resembles an aspect of Depue's (1995) characterization of low serotonin effects: that low serotonin function creates enhanced responsiveness to current reward stimuli rather than to cues of longer-term outcomes (thus an inability to delay gratification). We also sketched earlier in the article a depiction, deriving from theory and evidence from other sources, suggesting an important role for frontal cortical involvement in that quality of planfulness (see also Clarke et al., 2004).

In light of that picture, it may be noteworthy that some of the studies reviewed here raised the tantalizing possibility that the volatility linked to low serotonin function may represent a deficit in frontal cortical control over behavior. Dolan et al. (2002) found that impulsivity and aggressiveness both related to poorer frontal lobe function. New et al. (2002) found that persons with a history of impulsive aggression had PET scan patterns under serotonin challenge indicating a deactivation of the ACG and the left medial posterior OFC. Frankle et al. (2005) found that patients with impulsive aggression had lower serotonin availability in the ACG than controls, without a drug challenge. Moresco et al. (2002) found greater binding of cortical serotonin receptors in normal participants with elevated harm avoidance scores, particularly in the frontal and left parietal areas. This general line of inquiry certainly deserves further scrutiny.

4.1 What traits should be measured?

We believe it is important for researchers who take up this topic to avoid the automatic mental link between serotonin and "anxiety-related traits." This link remains very much alive in many minds, despite an announcement of its burial twenty years ago (Panksepp & Cox, 1986).

This automatic association leads researchers to be far more limited in their approach to trait assessment than they should be. Studies should examine associations for a broader range of traits whenever they are available—for example, in cases in which the full NEO-PI is used. Only in that way can a pattern of associations with traits other than anxiety-proneness become visible. Although we are discussing this issue with respect to serotonin function, it obviously applies as well to research linking personality to other neurotransmitters, or to genetic polymorphism.

We believe that studies relating serotonin function to personality should use a measure of personality that isolates separate traits pertaining to approach, avoidance, and constraint. Unless the qualities are assessed separately, one cannot know which quality or qualities relate to serotonin function. It is important to keep in mind that what a scale is assessing is not always clear from its label. The scales in the TPQ and TCI, which have been used in a good deal of research in this area, blend together qualities that other measures differentiate (see, e.g., Waller et al., 1991). If the tendencies are not differentiated, their separate roles can not be determined (Clark and Watson, 1999). For this reason, we recommend against the use of these two measures.

With measures such as the NEO-PI, the MPQ, the ZKPQ, or the BIS/BAS scales of Carver and White (1994), the two routes to constraint can be examined separately. The anxiety-proneness versus reward-seeking route can be examined by looking separately (or jointly) at involvement of incentive sensitivity and threat sensitivity. If the hypothesis concerns a highly reactive incentive system, that sensitivity can be assessed by scales for extraversion or positive emotionality or two of the BAS scales. If the hypothesis concerns a highly reactive threat system, that sensitivity can be assessed by scales for neuroticism or negative emotionality or the BIS scale; if the hypothesis is that the balance between these two is crucial, that balance can be computed. The second source of impulse can and should be assessed separately, by measures organized explicitly around the construct of deliberative restraint: measures of constraint (Tellegen, 1985; Watson and Clark, 1993), psychoticism (Eysenck, 1970), impulsive sensation seeking (Zuckerman, 1995), impulsiveness (Barratt, 1985; Whiteside and Lynam, 2001), or fun seeking (Carver and White, 1994).

We should also emphasize, however, that each of these broad constructs can be manifested

in diverse ways. For example, many people would regard it reasonable to use neuroticism as the equivalent of anxiety proneness. As noted earlier, anxiety proneness may well be the core of neuroticism. However, broad-scope measures of neuroticism (such as the NEO-PI) incorporate other qualities as well. When the facets are examined separately as correlates of serotonin function, which is not commonly done, the weight of the effect often appears to be carried by facets other than anxiety proneness. Accordingly, we very strongly recommend systematically examining facet scales separately. Indeed, we are not alone in this preference: Hennig (2004) has gone so far as to advocate examining individual items separately.

The same issue exists for the other traits under discussion. Impulsiveness is represented in a very wide range of ways, which are not that closely related to each other. Impulsiveness can be cognitive or behavioral (White et al., 1994). It can reflect variations in attentional management (Stanford and Barratt, 1992); it can reflect an inability to persevere, or distractibility, or the lack of planning and forethought (Whiteside and Lynam, 2001). These qualities need to be examined separately from each other, to assess which among them relate to serotonin function. The evidence thus far appears to suggest that planfulness and foresight are key, but the evidence at this point is quite sketchy.

The empirical strategy we recommend is very much that of the “splitter” rather than the “lumper.” By splitting broad constructs into their constituent facets, researchers can evaluate the generality of effects across the facets. They can thereby create the potential of realizing that there are patterns of facet associations that do not fit the overall picture they had expected. Indeed, that strategy can lead to conceptual advances, by allowing researchers to use emergent patterns of facets to create “recombinant” constructs that better reflect the nature of the patterns.

5. Serotonin function and emotion

Our focus here has been on serotonin function and personality. Some studies in this general area (albeit fewer in number) focus on emotions, rather than personality. An issue analogous to the one addressed in this article awaits in that research as well. Specifically, just as less than complete consensus exists about how to parse personality, there is less than complete consensus on how to parse affect. One widely known approach groups affects by valence, into those that are positive

and those that are negative (e.g., Watson and Tellegen, 1985; Lang et al., 1998; Cacioppo et al., 1999; Watson et al., 1999). Many who adopt this view would argue that it is more effective to aggregate into these positive and negative affect groups than to make fine distinctions within each group. Because this argument has many adherents, a good deal of research does not distinguish, for example, among anger, depression, and anxiety, but rather blends them into overall negative affect.

Whether this is a good strategy is highly questionable. Although these negative feelings do correlate, there is also evidence that they relate to the actions of different biological systems. In particular, although there is consensus that anxiety relates to the functioning of a threat-avoidance system, there is evidence that anger and at least some cases of sadness relate to the functioning of an incentive-approach system (for review see Carver, 2004).

This appears to constitute an important basis for arguing that different affects should be examined separately, even if they share a common valence, at least at this relatively early stage of investigation. If serotonin function were to prove over replications to relate more robustly to anger than to anxiety, that would be an important finding with implications for many areas of theory. If serotonin function proved to relate equivalently to a wide range of affects, it would similarly have important implications. This question cannot be asked, however, unless the affects are examined separately. We recommend that this be done as a matter of course.

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Communication concerning the article should be sent to Charles S. Carver, Department of Psychology, University of Miami, Coral Gables, FL 33124-0751. E-mail: Ccarver@miami.edu

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