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Revisiting the Serotonin-Aggression Relation in Humans: A Meta-analysis

Aaron A. Duke,

University Pierre Mendès-France, Grenoble and University of Kentucky

Laurent Bègue,

University Pierre Mendès-France, Grenoble

Rob Bell, and

Queen's University Belfast

Tory Eisenlohr-Moul

University of Kentucky

Abstract

The inverse relation between serotonin and human aggression is often portrayed as “reliable,” “strong,” and “well-established” despite decades of conflicting reports and widely recognized methodological limitations. In this systematic review and meta-analysis we evaluate the evidence for and against the serotonin deficiency hypothesis of human aggression across four methods of assessing serotonin: (a) cerebrospinal fluid levels of 5-hydroxyindoleacetic acid (CSF 5-HIAA), (b) acute tryptophan depletion, (c) pharmacological challenge, and (d) endocrine challenge. Results across 175 independent samples and over 6,500 total participants were heterogeneous, but, in aggregate, revealed a small, inverse correlation between central serotonin functioning and aggression, anger, and hostility, $r = -.12$. Pharmacological challenge studies had the largest mean weighted effect size, $r = -.21$, and CSF 5-HIAA studies had the smallest, $r = -.06$, $p = .21$. Potential methodological and demographic moderators largely failed to account for variability in study outcomes. Notable exceptions included year of publication (effect sizes tended to diminish with time) and self-versus other-reported aggression (other-reported aggression was *positively* correlated to serotonin functioning). We discuss four possible explanations for the pattern of findings: unreliable measures, ambient correlational noise, an unidentified higher-order interaction, and a selective serotonergic effect. Finally, we provide four recommendations for bringing much needed clarity to this important area of research: acknowledge contradictory findings and avoid selective reporting practices; focus on improving the reliability and validity of serotonin and aggression measures; test for interactions involving personality and/or environmental moderators; and revise the serotonin deficiency hypothesis to account for serotonin's functional complexity.

Keywords

serotonin; 5-HT; aggression; anger; hostility

Correspondence concerning this article should be addressed to Aaron A. Duke, Department of Psychology, University of Kentucky, Lexington, KY 40506. dukuru@gmail.com.

Author Note Aaron A. Duke, University Pierre Mendès-France, Grenoble and Department of Psychology, University of Kentucky; Laurent Bègue, University Pierre Mendès-France, Grenoble; Rob Bell, School of Psychology, Queen's University Belfast; Tory Eisenlohr-Moul, Department of Psychology, University of Kentucky.

“The greatest enemy of knowledge is not ignorance, it is the illusion of knowledge.” — Stephen Hawking

Considerable research has been dedicated to elucidating the neurochemical basis of human aggression ever since Brown and colleagues' original finding that cerebrospinal fluid (CSF) levels of the principle serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), “accounted for 80% of the variance in aggression scores” among a group of military men diagnosed with personality disorders (Brown, Goodwin, Ballenger, Goyer, & Major, 1979, p. 133). These results were interpreted to suggest that a deficiency in serotonin was largely responsible for these men's aggressive behavior. This *serotonin deficiency hypothesis* of human aggression has been tested hundreds of times over the past several decades and remains the most common hypothesis of serotonin's role in pathological aggression (e.g., Montoya, Terburg, Bos, & van Honk, 2012; Passamonti et al., 2012; Raine, 2008; Stadler et al., 2007; Steiger et al., 2004; Yanowitch & Coccaro, 2011). One widely cited author called the inverse relationship between serotonin activity and aggression “perhaps the most reliable finding in the history of psychiatry” (Fishbein, 2001, p. 15). Glancing through several recently published psychology and psychiatry textbooks reveals a concordant lack of controversy—no mention of contradictory findings (e.g., Bushman & Bartholow, 2010; Carlson, 2010; Higley & Barr, 2007; Hollander & Berlin, 2008).

One *sine qua non* of science is a healthy skepticism, and with a little bit of effort one can find numerous examples of studies finding no relation, or a positive relation between serotonin and human aggression (e.g., Booij, Tremblay, et al., 2010; Castellanos et al., 1994; Gardner, Lucas, & Cowdry, 1990; Germine, Goddard, Woods, Charney, & Heninger, 1992; Handelsman et al., 1998; Koszycki, Zacharko, Le Melleo, Young, & Bradwejn, 1996; Lopez et al., 1996; Tuinier, Verhoeven, & van Praag, 1996; Wood, Rilling, Sanfey, Bhagwagar, & Rogers, 2006). Understanding of the relation between serotonin and human aggression will be advanced by revisiting this “most reliable finding” in a more inclusive and objective light. We begin this review by critically evaluating the evidence for the serotonin deficiency hypothesis across four methods of assessing serotonin: CSF 5-HIAA, acute tryptophan depletion, pharmacological challenge, and endocrine challenge. We then introduce a comprehensive meta-analysis designed to test whether divergent findings in the literature can be explained by taking into account a variety of methodological and sample-level moderators.

CSF 5-HIAA

There is too much overlap between the mean 5-HIAA levels of “normal” and “affected” populations for the term “low 5-HIAA levels” to have a scientifically legitimate meaning ... Thus, low 5-HIAA levels are inappropriate markers for increased “risk” for any specific psychiatric condition or behavior in the general population or in comparison among individuals. (Balaban, Alper, & Kasamon, 1996, p. 29).

Several reviews have been published examining the relation between 5-HIAA and aggressive, disruptive, or antisocial behaviors (e.g., Åsberg, 1994; Balaban et al., 1996; Moore, Scarpa, & Raine, 2002; Tuinier, Verhoeven, & van Praag, 1995, 1996). The results from these reviews have been equivocal. The quotation at the beginning of this section was taken from an early meta-analysis (Balaban et al., 1996), which found that 5-HIAA levels did not differ significantly between aggressive and unaggressive clinical groups and that both aggressive and unaggressive clinical groups had a small, but significant reduction in 5-HIAA levels when compared to nonclinical controls. Another early review (Tuinier et al., 1996) concluded that only 8 out of 23 studies published at the time on 5-HIAA and aggression provided support for an inverse relation. Furthermore, these 8 studies were

almost entirely restricted to personality-disordered young adult males such as those in Brown and colleague's original study (Brown et al., 1979). A 2002 meta-analysis of 16 studies looking at 5-HIAA and adult antisocial behavior (Moore et al., 2002) revealed a "medium" (Cohen, 1988, p. 157) mean weighted effect size of $d = -0.45$. Results revealed no significant effects of gender, alcoholism, suicidality, or whether violence was against persons or property. Age, however, was found to significantly moderate the relation between 5-HIAA and aggression such that studies with young adult, antisocial individuals exhibited a much larger effect than studies with older antisocial individuals. There are a number of limitations in the two meta-analyses just mentioned that require further qualification. Both Balaban et al. (1996) and Moore et al. (2002) failed to account for study quality, excluded studies with limited statistical information (e.g., studies reporting only that findings were "non-significant"), and did not test, or attempt to account for, publication bias. Thus, there is reason to believe that these meta-analyses may have included a sample of studies biased towards finding statistically significant results.

The failure to clarify the ambiguous relation between 5-HIAA and aggression may be in part due to difficulties in establishing reference levels of CSF 5-HIAA. CSF 5-HIAA has been shown to be moderated by age (e.g., Hedner, Lundell, Breese, Mueller, & Hedner, 1986; Seifert, Foxx, & Butler, 1980; Takeuchi et al., 2000), gender (e.g., Blennow et al., 1993; Hagenfeldt, Bjerkenstedt, Edman, Sedvall, & Wiesel, 1984), height and weight (e.g., Blennow et al., 1993; Hartikainen et al., 1991; Strömbom et al., 1996), physical activity (Eklundh, Gunnarsson, & Nordin, 2001; Nordin, Lindström, & Wieselgren, 1996), season (e.g., Brewerton, Berrettini, Nurnberger, & Linnoila, 1988; Hartikainen et al., 1991), atmospheric pressure (Eklundh, Fernström, & Nordin, 1994; Nordin, Swedin, & Zachau, 1992), and intra-spinal pressure (Eklundh & Nordin, 2001) along with several psychiatric and neurological conditions (for a review of CSF 5-HIAA moderators see Dhondt, 2004). One of the most serious confounding influences associated with measuring CSF 5-HIAA may be an inverse relation between CSF5-HIAA levels and stress associated with the lumbar puncture procedure itself (Hill et al., 1999). Despite CSF 5-HIAA's important historical role as the first biomarker used to support the serotonin deficiency hypothesis in humans, there remain doubts about the reliability and validity of using CSF 5-HIAA as an index of central serotonergic functioning (e.g., Balaban et al., 1996; Hyland, 2008; van der Vegt, Lieuwes, Cremers, de Boer, & Koolhaas, 2003).

Acute Tryptophan Depletion (ATD)

Although ATD ... [is] important in the investigation of the monoamine systems, monoamine depletion does not directly decrease mood. (Ruhé, Mason, & Schene, 2007).

Acute tryptophan depletion represented the first broad attempt at experimentally manipulating central serotonin levels in humans (Young, Smith, Pihl, & Ervin, 1985). Acute tryptophan depletion relies on the assumption that modifying plasma levels of L-tryptophan, the primary precursor of serotonin, will lead to corresponding modifications in levels of brain serotonin (Hood, Bell, & Nutt, 2005). Because the blood brain barrier prevents peripheral serotonin from entering directly into the central nervous system, serotonin in the brain must be synthesized locally from its precursor tryptophan. Humans receive all of their tryptophan from dietary sources (Moore et al., 2000), and therefore, dietary tryptophan intake can be experimentally manipulated to influence central serotonin availability. However, free plasma levels of tryptophan are relatively resilient to short periods of tryptophan-free dieting with a typical reduction in only about 15–20% of central serotonin availability (Delgado, Charney, Price, Landis, & Heninger, 1989). Thus, while often used as an experimental control, tryptophan-free diets are less effective at reducing serotonin availability than acute tryptophan depletion. Acute tryptophan depletion relies on two

additional physiological processes in order to reduce central serotonin availability (for an overview of the rationale and methodology of acute tryptophan depletion, see Hood et al., 2005). First, tryptophan must compete with five other large neutral amino acids (LNAA) for active-transport across the blood brain barrier; therefore, the ratio of free plasma tryptophan to other LNAAs determines the rate by which tryptophan can cross the blood brain barrier and be synthesized into serotonin. The tryptophan/LNAA ratio can be augmented by increasing available tryptophan relative to other LNAAs (e.g., through direct administration of tryptophan supplements), and can be attenuated (i.e., in acute tryptophan depletion) by increasing the availability of other LNAAs relative to tryptophan (e.g., through administration of non-tryptophan supplements including other LNAAs). The second process has to do with synthesis of proteins in the liver. When there is a dietary influx of amino acids, the liver will begin to synthesize various new proteins, many of which require tryptophan. If an amino-acid mixture (containing both LNAAs and non-LNAAs) is administered without any tryptophan included, the liver will use existing plasma tryptophan for protein-synthesis, thereby further reducing tryptophan's ability to be synthesized into serotonin.

While a variety of different amino acid mixtures have been utilized in acute tryptophan depletion studies, they can be roughly divided into three categories: tryptophan-free (T-) amino acid mixtures, balanced (B) amino acid mixtures, and tryptophan-enhanced (T+) mixtures. Young, as the first to use acute tryptophan depletion in humans, standardized the 100 gram T-amino mixture with 15 amino acids in the proportion that are found in human breast milk minus the tryptophan (Young et al., 1985). Young's balanced mixture consisted of adding 2.3 grams of tryptophan to the 100 gram mixture while the T+ mixture included 10.3 grams of tryptophan (i.e., a higher than normal ratio of tryptophan compared to the other amino acids). In these mixtures, the amino acids aspartic acid and glutamic acid are typically excluded due to concerns about toxicity (Hood et al., 2005). Further, these amino acid mixtures are renowned for having a very "unpalatable" taste to them—an issue that has been addressed differently by different researchers. Often something is added to the mixture to improve its taste (e.g., chocolate syrup). Also, researchers began administering amino acids containing sulfur separately from the rest of the mixture in the form of capsules, as these amino acids (methionine, cystine, and arginine) are considered the most unpalatable.

Similar amino-acid depletion techniques have been adopted for other monoamines and a number of reviews have been conducted examining the effects of monoamine depletion on mood (Ruhé et al., 2007; van der Does, 2001), anxiety (Anderson & Mortimore, 1999), psychiatric disorders (Bell, Hood, & Nutt, 2005; Booij, Van der Does, & Riedel, 2003; Moore et al., 2002; Reilly, McTavish, & Young, 1997; Sobczak, Honig, Duinen, & Riedel, 2002), neural activation (Fusar-Poli et al., 2006), memory (Sambeth et al., 2007), executive functioning (Mendelsohn, Riedel, & Sambeth, 2009), and cognitive flexibility (Evers, van der Veen, Fekkes, & Jolles, 2007). Booij, Van der Does, and Riedel analyzed the literature on acute tryptophan depletion and aggression and found several contradictory findings. These authors concluded that there was evidence for acute tryptophan depletion increasing aggression in individuals predisposed to act aggressively, but not in individuals with low trait levels of aggression. A recent systematic review of acute tryptophan depletion's effects on executive functioning concluded that the majority of findings indicate that acute tryptophan depletion does *not* impair key executive functioning processes including response inhibition, decision making, planning, sustained attention, and set shifting (Mendelsohn et al., 2009). It should be noted that impaired executive functioning has been argued to be important in predicting many forms of impulsive aggression (e.g., Hancock, Tapscott, & Hoaken, 2010). In the only relevant meta-analysis conducted on monoamine depletion studies, acute tryptophan depletion was found to have no effect on mood in healthy individuals, but to moderately decrease mood in individuals with a history of

depression (Ruhé et al., 2007). Finally, findings from a recent review of an alternate, but much less common approach to serotonin manipulation—tryptophan augmentation—have suggested similarly equivocal results with respect to mood and similarly negative results with respect to executive functioning (Silber & Schmitt, 2010).

Pharmacological/Endocrine Challenge

Caution seems to be indicated in drawing inferences about the functional status of central serotonergic neurotransmission from neuroendocrine responses elicited by challenge studies using serotonergic agents. (Murphy, Aulakh, Mazzola-Pomietto, & Briggs, 1996, p. 213).

Coinciding with the increase in availability of drugs that more selectively target various serotonergic receptors, acute pharmacological challenge tests began to be applied to the study of human aggression in the late 1980s. In these studies, a serotonergic agent is administered and acute changes in aggression and related constructs are measured over the course of several hours. Similar to acute tryptophan depletion, pharmacological challenge studies allow for experimental manipulation of central serotonin levels and typically involve comparing mean responses across different drug dosage conditions. However, group level data derived from pharmacological challenge studies does not allow for measurement of individual differences in responsivity to manipulation of central serotonin levels.

The endocrine challenge paradigm, on the other hand, provides a putative index of individual responsivity to serotonergic agents. Evidence indicating increased hypothalamus-pituitary-adrenal activity following serotonergic pharmacological challenges led to the use of pituitary hormones (e.g., prolactin, adrenocorticotrophic hormone, growth hormone) and adrenal hormones (e.g., cortisol) as indices of individual serotonergic functioning (Cowen, Anderson, & Gartside, 1990). Thus, endocrine challenge studies are pharmacological challenge studies in which hormonal endpoints are used as an index of central serotonergic functioning. Some concerns have been raised concerning the implications of differential hormonal responses following serotonergic challenges. For example, the quotation above was taken from Murphy et al. (1996) in a review of “neuroendocrine responses to serotonergic agonists as indices of the functional status of central serotonin neurotransmission in humans,” in which a high level of discordance was found between different endocrine endpoints (e.g., prolactin and cortisol), temperature, and behavioral measures. Despite the popularity of endocrine challenge studies, information concerning their validity remains somewhat sparse.

A number of different pharmacological agents have been used in challenge studies, though the most popular choice has been d,l-fenfluramine (d,l-FEN), the racemic mixture of two enantiomers, dextrofenfluramine (d-FEN) and levofenfluramine (l-FEN). The denantiomer (d-FEN) has also been used extensively in endocrine challenge studies. Some researchers (e.g., Coccaro, Lee, & Kavoussi, 2010) have noted that the l-isomer in d,l-FEN is problematic because it has been shown to have antagonistic effects on the dopaminergic system that can influence prolactin release (see Ben-Jonathan, Arbogast, & Hyde, 1989; Coccaro & Kavoussi, 1994; Crunelli, Bernasconi, & Samanin, 1980); however, the hormonal response to both d-FEN and d,l-FEN is thought to be “very similar” (Coccaro, Lee, & Kavoussi, 2010, p. 436). Both d-FEN and d,l-FEN are thought to increase synaptic serotonin levels by increasing serotonin release from nerve terminals and by inhibiting its reuptake (Pine et al., 1997).

Meta-chlorophenylpiperazine (*m*CPP) was another early drug to receive widespread use in endocrine challenge tests. Similar to fenfluramine, *m*CPP has been shown both to increase serotonin terminal release as well as block its reuptake (Pettibone & Williams, 1984). Drug

discrimination studies have found that the stimulus effects of *m*CPP are primarily mediated by 5-HT_{2C} receptors and to a lesser extent, 5-HT_{1B} receptors (Callahan & Cunningham, 1994; Gatch, 2003; Gommans, Hijzen, Maes, & Olivier, 1998). The discriminative effects of *m*CPP have also been shown to mimic those of d,l-FEN (Callahan & Cunningham, 1994). Another phenylpiperazine, eltoprazine, which has been used in at least one pharmacological challenge study (Cherek, Spiga, & Creson, 1995), acts as a 5-HT_{1A} and 5-HT_{1B} receptor agonist and a 5-HT_{2C} receptor antagonist (Schipper, Tulp, & Sijbesma, 1990).

Two azapirone class selective partial 5-HT_{1A} receptor agonists, ipsapirone and buspirone, have been used by several serotonin challenge studies. Ipsapirone's affinity for the 5-HT_{1A} receptor is thought to be 1000 fold greater than for the 5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2C} receptors (Hamon et al., 1988) and is thought to act as a full agonist at somatodendritic 5-HT_{1A} autoreceptors and a partial agonist at post-synaptic 5-HT_{1A} receptors (Almeida, Lee, & Coccaro, 2010). Buspirone has been used less often than ipsapirone in challenge studies probably because it has a less selective pharmacological profile (e.g., Moser et al., 1990). Other drugs that have been used include the racemic selective-serotonin reuptake inhibitor (SSRI) citalopram and its s-enantiomer escitalopram, the SSRIs paroxetine, fluvoxamine, fluoxetine, and zolmitriptan, as well as the amino acid tryptophan (see acute tryptophan depletion section above).

While a diverse group of drugs have been used, the underlying principle behind pharmacological and endocrine challenge tests utilizing these drugs appears to be the same. These drugs are thought to lead to a relatively rapid increase in serotonin concentrations in the serotonergic synapses, which, in turn, is thought to activate the hypothalamus-pituitary-adrenal pathway (Berman, McCloskey, Fanning, Schumacher, & Coccaro, 2009; Kojima et al., 2003). However, these drugs are clearly dissimilar along a number of important dimensions such as their specific affinities for different receptor types. This is problematic for a number of reasons, most notably being that different serotonin receptors do not influence behavior in the same way (Quadros, Takahashi, & Miczek, 2009).

Current Study

The current meta-analytic investigation was designed to evaluate the evidence for the serotonin deficiency hypothesis of aggression in humans from the perspective of four major serotonin assessment methods. Reviewing the literature on these methods leads us to believe that there are limitations inherent in each method, particularly in CSF measurement of 5-HIAA, which may hinder the ability to draw consistent conclusions concerning the relation between serotonin and aggression. These methodological limitations are compounded by the complex, multi-faceted, and interactive nature of neural serotonergic systems (Kerman et al., 2011; Murphy et al., 1996; Tuinier et al., 1996) and the less-than-ideal reliability and validity of most aggression measures (see Ferguson & Savage, 2012).

These concerns lead us to predict that, overall, we will find a limited (i.e., “small”) relation between serotonin and aggression in spite of the large effect sizes found by early, small-*n* studies (e.g., Brown et al., 1979). In order to make our primary hypothesis explicit, we define a “small” relation in the present context according to the conventions outlined by Cohen for correlation coefficient effect sizes (1992).¹ Liberally, we will interpret any statistically significant effect less than $r = .3$ as consistent with our primary hypothesis. Note that because correlation coefficients are signed and an *inverse* correlation is expected, our actual hypothesis is that, overall, $r > -.3$ and $r < 0$.

¹Cohen identified $r = .1$ as a “small” effect, $r = .3$ as a “medium” effect, and $r = .5$ as a “large” effect (1992, p. 157).

We do not expect findings on the relation between serotonin and aggression to be homogeneous either *within* or *between* methodologies used to assess serotonergic functioning. We hypothesize that inconsistent findings may be partially attributable to differences in study methodology and sample characteristics. Across methodologies, we expect the findings from CSF 5-HIAA studies to be the most inconsistent given the profound methodological concerns mentioned above; however, we do not have specific predictions on which methods will differ in which ways. Many researchers have argued that the serotonin deficiency hypothesis only holds for certain individuals, therefore, we propose to test the following additional hypotheses related to potential demographic moderators: (a) serotonin and aggression are inversely correlated in clinical samples more so than in healthy samples, (b) serotonin and aggression are inversely correlated primarily in individuals with histories of aggression (see Booij, Van der Does, & Riedel, 2003), (c) serotonin and aggression are inversely correlated in males more so than in females (e.g., Tuinier et al., 1996), and (d) serotonin and aggression are inversely correlated in younger adults more so than in older adults (Moore et al., 2002).

Methods

Inclusion and Exclusion Criteria

To be included studies needed to directly assess human aggression (or the related constructs of anger and hostility) along with serotonergic functioning using one of the four methodologies reviewed above (i.e., CSF 5-HIAA, acute tryptophan depletion, pharmacological challenge, or endocrine challenge). This review focused solely on other-directed aggression; therefore, studies that included only measures of self-directed harm were excluded.² To this point we have not carefully distinguished between aggression, anger, and hostility. There are compelling conceptual reasons to treat anger, aggression, and hostility as a set of inter-related constructs respectively representing the *affective*, *behavioral*, and *cognitive* aspects of the same underlying antagonism domain (see Martin, Watson, & Wan, 2000). In practice, these constructs are hopelessly confounded in many aggression measures,³ and for the sake of parsimony, we often use ‘aggression’ to refer to aggression and the related constructs of hostility and anger.

Search Strategy

A comprehensive literature search was conducted for empirical studies of serotonin and aggression, anger, or hostility in humans across the following sources: PsycINFO, MEDLINE, CINAHL, System for Information for Grey Literature, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. In each of these databases, study titles, abstracts, subjects, and keywords were searched from inception through December, 2011 using the following terms: (AGGRESS* OR VIOLEN * OR ANGER OR ANGRY OR HOSTIL *) AND (((“5-HYDROXYINDOLEACETIC ACID” OR 5-HIAA OR 5HIAA OR “MONOAMINE METABOLITE *”) AND (“CEREBROSPINAL FLUID ” OR CSF)) OR (“*TRYPTOPHAN DEPLET *” OR ATD OR RTD OR “MONOAMINE DEPLET *”) OR (“SEROTONIN REUPTAKE INHIBITOR ” OR SSRI OR “ENDOCRINE CHALLENGE ” OR

²For readers interested in serotonin’s putative role in self-harm behaviors, including suicide, there are several excellent reviews and treatments of this topic (e.g., Desmyter, van Heeringen, & Audenaert, 2011; Lester, 1995; Müller-Oerlinghausen, Roggenbach, & Franke, 2004).

³The *jingle fallacy* (applying the same label to different constructs; Thorndike, 1903) and the *jangle fallacy* (applying different labels to the same construct; Kelley, 1927) are rampant in aggression research. For example, the distinctions between subscales labeled “extrapunitive hostility,” “angry hostility,” and “anger expression” are not discernible from their titles alone. One researcher’s “hostility” is another’s “aggression” or “anger” (e.g., Buchanan, 1999; Bushman & Anderson, 2001; Tremblay, 1991). Manuscript titles such as “Aggression Questionnaire hostility scale predicts anger in response to mistreatment” can leave the uninitiated feeling slightly dizzy (Felsten & Hill, 1999).

"PHARMACOLOGICAL CHALLENGE " OR *CHLOROPHENYLPIPERAZINE OR MCPP OR M-CPP OR *PAROXETINE * OR *FENFLURAMINE * OR *IPSAPIRONE* OR *CITALOPRAM * OR *ZOLMITRIPTAN * OR *ELTOPRAZINE* OR *FLUVOXAMINE * OR *ESCITALOPRAM * OR *FLUOXETINE *).

Note that an asterisk here represents a wild card character utilized in many scholarly databases that will match with any number of letters, typically placed at the end of a word to allow for variations in word endings. For example, "aggress*" matches "aggression," "aggressive," "aggressor," or any other word that began with the letters "aggress." A number of limiters were used to narrow the search results from PsycINFO, MEDLINE, and CINAHL. Specifically, results from these sources were filtered to include only empirical studies with human participants. Citations and reference sections were reviewed in articles selected for inclusion. The *curricula vitae* of authors with more than one included study were obtained and reviewed for additional relevant studies when possible. Additionally, multiple requests for unpublished studies were made over relevant academic channels, including directly contacting numerous primary authors of serotonin and aggression studies.

Effect Sizes

All effect sizes were converted to correlation coefficients (Borenstein, 2009). All *r*s were signed so that positive correlations indicate a positive relation between serotonergic functioning and aggression while negative correlations represent an inverse relation between serotonin and aggression. In order to account for dependencies introduced by studies with multiple-endpoints, *r*s were aggregated according to procedures outlined by Gleser and Olkin (2009), which take into account the correlation between the multiple measures. When the correlation between measures was not available, a default correlation of .5 was used to aggregate within-study effects (Wampold, Moody, Stich, Benson, & Ahn, 1997). Prior to the analyses, all *r*s underwent Fisher's variance stabilizing and normalizing transformation *r*-to-*z* (Fisher, 1921). Results were subsequently transformed back to *r* prior to interpretation.

Given a high prevalence of findings with insufficient data necessary to calculate an effect size, and concerns about publication bias, effect size estimates for studies which reported only the direction and/or significance were calculated using maximum likelihood estimation (MLE) as outlined by Bushman and Wang (2009). This technique allows for an overall effect size estimate based upon observed significant differences ($\alpha = 0.05$) or observed differences where significance levels are not reported ($\alpha = 0.5$). In cases where detailed statistics were reported for statistically significant findings, but not for non-significant findings, the MLE-derived estimate was used when calculating aggregate study effects.

Following the recommendation of Orwin and Cordray (1985), confidence ratings were coded for study effect size statistics. Studies which reported raw data, bivariate correlation coefficients, means and standard deviations, mean standardized differences, or other effect size statistics from which an effect size can be accurately derived were coded as involving "minimal estimation." Complex, but complete statistics (e.g., partial correlation coefficients) or statistics where some uncertainty existed were coded as including "moderate estimation." Finally, results derived from vote-counting procedures were coded as "highly estimated."

Analyses

Studies were weighted by the inverse of their variance (Shadish & Haddock, 2009). Mean weighted effect sizes are presented for both fixed-effects and random-effects models with estimates of heterogeneity (*Q* and *I*² statistics) derived from the fixed-effects model. Moderator analyses were conducted using a mixed-effects model when significant heterogeneity was evinced in the combined estimate (see Lipsey & Wilson, 2001). Random-

effects and mixed-effects models were estimated using restricted maximum-likelihood estimation (REML) along with the Knapp and Hartung (2003) adjustment to account for uncertainty in the amount of residual heterogeneity. All analyses were conducted in R using the metafor package (Viechtbauer, 2010).

Analyses were conducted to assess whether potential methodological and/or sample-level variables explained a significant amount of the variance in study outcomes. Methodological variables of interest included experimental design, sample size, quality of reported effect size, drug, dose, hormone, comparison group, control condition, and assessment instrument. Aggression measures were analyzed along four general dimensions: construct (anger, aggression, or hostility), source (self or other), modality (questionnaire, clinical interview, laboratory, criminal record, or observation), and temporal scope (state or trait). The following sample-level variables were also coded for moderator analyses: mean age, percent female, race/ethnicity, history of aggression, and presence of psychopathology. Methodological and demographic variables were not included in moderator analyses if reported in fewer than 50% of studies. For the remaining potential moderator variables, multiple-imputation (Pigott, 2009) was used to estimate missing values using the mi package for R (Su, Gelman, Hill, & Yajima, 2011).

The well-documented tendency for significant research findings to be published more often than non-significant findings has been highlighted as a problem in meta-analyses since its inception (see Sutton, 2009). Fortunately, a variety of techniques have been developed to estimate the degree to which the “file drawer problem” (Rosenthal, 1979, p. 638) is distorting meta-analytic findings. One method relies on a visual inspection of the symmetry of a “funnel plot” where effect sizes are plotted against their variance or sample size. Because studies using larger sample sizes typically have less variance, their estimates of the population effect size should be more accurate than studies with smaller sample sizes or with larger variance in their findings. Hence, in the measurement of a single population effect, one would expect multiple studies to form a “funnel” shape with less-accurate studies forming a broad, symmetrical distribution around the population effect and more-accurate studies forming a much tighter, symmetrical distribution around the population effect size. If this pattern is not evidenced, particularly with respect to small-*n* studies, there may be reason to believe that publication bias is significantly distorting one’s findings. It is important to note that there are other possible explanations of small-study bias and therefore asymmetrical funnel plots should not be interpreted as providing conclusive evidence of publication bias. In order to assess for small-study bias in the present review, a series of funnel plots were created for each methodology used to assess 5-HT functioning. These plots were analyzed both visually and, when appropriate, statistically using Egger’s regression test (Egger, Smith, Schneider, & Minder, 1997). Asymmetry tests are most appropriate when effect sizes are not significantly heterogeneous, there are at least 10 studies, the ratio of extreme variances is greater than 4, and at least some of the findings are statistically significant (Ioannidis & Trikalinos, 2007).

Results

Search Results

Comprehensive literature searches including calls for unpublished studies revealed 1738 initial results, of which, 976 were duplicates, leaving 762 potentially relevant studies (see Figure 1). Title and abstract review revealed 376 results that were either not relevant or clearly did not meet inclusion/exclusion criteria. After obtaining the full text for the remaining 386 results, 215 additional reports were excluded because they did not meet inclusion and/or exclusion requirements. Out of the subsequent 171 items which were coded for inclusion in the meta-analysis, 27 reports were identified as reporting duplicate data and

were also excluded. In total, the meta-analysis included 144 published and unpublished reports consisting of 354 effect sizes across 175 independent samples.

The combined sample included 6,567 individuals (2,004 women and 4,563 men). The mean sample size was 46 ($SD = 39$) with 30% ($SD = 35$) female participants. The mean age of participants was 30.9 ($SD = 10.6$). Ethnicity was not included as a demographic moderator because it was reported in only 23.6% of studies. In contrast, both age and gender were reported in almost all studies with reporting rates of 98.7% and 96.8% respectively. Studies included clinical (36.6%) and healthy (35.7%) populations at about the same rate with 27.7% of samples including a clinical group and healthy control. Given a large number of different measures used to assess aggression, anger, and hostility, aggression instrument moderator analyses were conducted only for the combined methods sample in order to ensure adequate power.

CSF 5-HIAA

Our literature review revealed 35 studies that measured the relation between CSF 5-HIAA and aggression yielding a total of 68 effect sizes with a combined sample size of $N = 1840$ (see Figure 2). The weighted mean effect size was $r = -0.066$ for the fixed effects model, 95% $CI[-0.11, -0.02]$, $p < .01$, and $r = -0.057$ for the random effects model, 95% $CI[-0.15, 0.03]$, $p = 0.21$. The random effects model was not significantly different from zero. The funnel plot is presented in Figure 3; however, criteria were not met for conducting a statistical test of funnel plot symmetry. Effect sizes exhibited significant heterogeneity across studies, $Q(34) = 98.01$, $p < .001$, $I^2 = 65.31$, indicating the need for additional moderator analyses.

A series of univariate and multivariate meta-regression analyses were conducted in order to assess for methodological and population moderators. The first multivariate model (see the top of Table 1) examined methodological variables including sample size, year of publication, experimental design, and quality of information used to calculate the effect size. This model accounted for a significant amount of variance in study effect sizes, $Q_M = 3.07$, $p < .05$. Quality, sample size, and experimental design were not related to study outcome; however, year of publication was found to be a significant predictor of the correlation between CSF 5-HIAA and aggression $b = 0.02$, $SE = 0.01$, 95% $CI[0.01, 0.04]$, $p < .01$. The correlation between 5-HIAA and aggression was most negative in early studies and regressed towards zero each year between 1979 and 2010 by an average of 0.02. The second multivariate model tested sample characteristics and is presented in the bottom of Table 1. None of the hypothesized demographic moderators were significantly predictive of study effect size including gender, age, history of aggression, or presence of psychopathology ($Q_M = 0.5$, $p = 0.73$).

Acute Tryptophan Depletion

Our search found 38 studies that measured the effects of acute tryptophan depletion on aggressive behavior and/or mood with 68 effect sizes and a combined sample size of $N = 1188$ (see Figure 4). The weighted mean effect size across the 38 studies that tested the relation between acute tryptophan depletion and aggression was $r = -0.091$ for the fixed effects model, 95% $CI[-0.15, -0.03]$, $p < .01$, and $r = -0.099$ for the random effects model, 95% $CI[-0.18, -0.02]$, $p < .05$, both of which were significant. Criteria were not met for conducting a statistical test of funnel plot symmetry (see Figure 3). Effects sizes exhibited significant heterogeneity across studies $Q(37) = 56.02$, $p < .05$, $I^2 = 33.95$, and therefore, additional moderator analyses were carried out.

As with CSF 5-HIAA, a series of meta-regression models were created to test for possible moderators of acute tryptophan depletion's influence on aggression, hostility, and anger (all presented in Table 2). The first two models tested general and then acute tryptophan depletion-specific methodological variables. The first model was not significant, $Q_M = 0.8$, $p = 0.59$, and included the following variables: overall study quality, randomization procedure, condition masking, experimental design, adequacy of data used to derive effect size estimates, and year of publication. Acute tryptophan depletion-specific methodological variables included control condition (placebo, balanced, augmented, fasting), weight of amino-acid beverages, weight of tryptophan content in balanced and augmented beverages, and time between beverage consumption and aggression measurement, none of which accounted for a significance amount of variance in study effect sizes, $Q_M = 0.75$, $p = 0.95$. In the final model, none of the sample characteristics tested (age, sex, presence of psychopathology, and history of aggression) were related to study outcome, $Q_M = 0.21$, $p = 0.93$.

Pharmacological Challenge Studies

We identified 16 acute pharmacological challenge studies with a total of 48 effect sizes consisting of 395 participants (see Figure 5). The weighted mean effect size was $r = -0.21$ for the fixed effects model, 95% $CI[-0.33, -0.08]$, $p < .01$, and $r = -0.217$ for the random effects model, 95% $CI[-0.35, -0.08]$, $p < .01$, both of which were statistically significant. The test for heterogeneity was not significant, circumventing the need for moderator analyses, $Q(15) = 16.86$, $p = 0.33$, $I^2 = 11.05$. All four criteria were met for statistically testing funnel plot asymmetry (see Ioannidis & Trikalinos, 2007). Funnel plot assessment of small-study bias revealed adequate symmetry in the distribution of study effects, $z = -1.52$, $p = 0.13$ (see Figure 3).

Endocrine Challenge

Prolactin—The weighted mean effect size across the 53 studies that tested the relation between prolactin response and aggression, anger, and hostility was $r = -0.147$ for the fixed effects model, 95% $CI[-0.19, -0.11]$, $p < .001$, and $r = -0.14$ for the random effects model, 95% $CI[-0.21, -0.07]$, $p < .001$, both of which were significant. Individual study effect sizes for both prolactin and cortisol are displayed in Figure 6, and funnel plots are presented in Figure 3. There was significant heterogeneity across studies suggesting the need for moderator analyses, $Q(52) = 129.76$, $p < .001$, $I^2 = 59.93$. Egger's test of funnel plot asymmetry was not significant, suggesting adequate symmetry, $z = 0.38$, $p = 0.71$.

Possible methodological moderators were tested in univariate meta-regression models and then combined in a multiple meta-regression model (see Table 3). The model including sample size, year of publication, quality, and study design did not explain a significant amount of variance in study outcomes, $Q_M = 1.45$, $p = 0.23$. The model including participant gender, age, history of aggression, and psychopathology was also not significant, $Q_M = 1.75$, $p = 0.12$ (Table 3). Mean weighted effects across the various drugs used to elicit endocrine responses did not differ significantly (Table 4), even after taking dose into account.

Cortisol—A total of 22 studies were found that tested the relation between cortisol response and aggression, anger, and hostility (see Figure 6). The mean weighted effect size was $r = -0.023$ for the fixed effects model, 95% $CI[-0.10, 0.06]$, $p = 0.51$, and $r = -0.016$ for the random effects model, 95% $CI[-0.12, 0.09]$, $p = 0.64$, both of which were not significantly different from zero. Dissimilar to prolactin, cortisol studies did not exhibit significant heterogeneity, $Q(21) = 31.73$, $p = 0.06$, $I^2 = 33.83$, and therefore, methodological and sample characteristic moderator analyses were not conducted. However, the moderating impact of different drugs used to elicit the cortisol response was tested and is presented at

the bottom of Table 4. The effects of different drugs did not differ significantly from one another.

Combined Estimate

The weighted mean effect size across $k = 144$ studies that tested the relation between serotonin and aggression was $r = -0.114$ for the fixed effects model, 95% $CI[-0.14, -0.09]$, $p < .001$, and $r = -0.116$ for the random effects model, 95% $CI[-0.16, -0.07]$, $p < .001$, both of which were significantly different from zero. Effect sizes exhibited significant heterogeneity across studies, $Q(143) = 316.59$, $p < .001$, $I^2 = 54.83$. Moderator analyses were conducted and are presented in Table 5. Unsurprisingly, the quality of information used to calculate the effect sizes was significantly related to effect size magnitude in both univariate and multivariate models such that larger magnitude effect sizes were associated with more detailed statistical reporting, $Q_M = 2.63$, $p < .05$. None of the demographic moderators were significantly related to effect size, $Q_M = 0.31$, $p = 0.91$.

A comparison across methods of measuring central serotonergic functioning is presented in Table 6. Findings across methods did not differ significantly one from another, $Q_B(3) = 4.16$, $p = 0.244$. A comparison across aggression, hostility, and anger measures is presented in Table 7. There was significant heterogeneity between measures, $Q_B(17) = 28.90$, $p < .05$, in addition to significant residual heterogeneity after taking measure into account, $Q_W(209) = 445.3$, $I^2 = 53\%$, $p < .001$. Moderator analyses conducted to determine if effect sizes differed across construct, source of information, temporal scope, and modality are presented in Table 8. Measures differed across source of information, but not construct, temporal scope, or modality. Interestingly, the mean weighted effect of studies that relied on *other-reports* was significant in a positive direction, $r = 0.17$, 95% $CI[0.08, 0.26]$, $p < .001$, while measures that relied on *self-reports* of aggression, anger, or hostility were significant in the expected negative direction, $r = -0.11$, 95% $CI[-0.15, -0.08]$, $p < .001$.

Discussion

The current meta-analysis was designed to critically evaluate the serotonin deficiency hypothesis of human aggression by reviewing findings across four methods commonly used to assess central serotonergic functioning. In light of concerns about measurement reliability and the inherent complexity of cerebral serotonergic functioning, we hypothesized that overall, the inverse correlation between serotonin and aggression, anger, and hostility would be small. The results of the meta-analysis, which included 175 independent samples and over 6,500 total participants, supported our primary hypothesis. The combined weighted correlation between serotonin and aggression, anger, and hostility was $r = -.12$, which maps very closely onto Cohen's convention for a "small" effect size (1992, p. 157). Thus, in contrast to Brown and colleague's original finding that CSF 5-HIAA accounted for 80% of the variance in a group of soldiers' aggression (Brown et al., 1979), we have found that serotonin explains just over 1% of the variance in aggression, anger, and hostility. This contrast is even more notable when the comparison is constrained to CSF 5-HIAA measurement only, for which the weighted mean effect size was not significantly different from zero when using a random effects model. As is clear in Figure 2, the magnitude of Brown et al.'s original finding correlating CSF 5-HIAA and human aggression has not been replicated despite more than 30 attempts conducted across a period spanning more than three decades.⁴

⁴See Lehrer, 2010 for other examples of the decline effect.

Our prediction that findings would be highly heterogeneous was only partially supported by the results. Significant heterogeneity was found *within* each method used to assess serotonergic functioning except pharmacological challenge and cortisol challenge. Contrary to expectations, significant heterogeneity *between* methodologies used to test serotonergic functioning was not found. Numerous methodological and sample-level variables were tested to see if they could explain heterogeneous findings. While in a few cases, methodological variables did explain some of the variance within certain assessment methods, there was no consistent pattern of findings. On the other hand, none of the sample-level variables, including percent female, mean age, history of aggression, and the presence of clinical psychopathology were significantly related to the direction or magnitude of study effect size. Significant heterogeneity remained in all of the models even after including potential methodological and sample-level moderators. While these results should not be taken as conclusive evidence that these factors are not important in moderating the influence of serotonin on aggression, anger, and hostility, this study-level analysis suggests that they do not provide an adequate explanation of divergent findings linking serotonin to aggression.

Alternative Interpretations

The relation between serotonin and human aggression as well as the validity of the serotonin deficiency hypothesis remain open to debate. The small, inverse correlation between serotonergic functioning and human aggression found in the present meta-analysis can be interpreted in several different ways. We briefly address four possible interpretations for our findings below.

1. The relation was attenuated by a lack of reliable and valid measures—We have already addressed some of the reliability and validity concerns relevant to measuring human serotonergic functioning; however, the reliability and validity of measures on the other side of the equation (i.e., measures of aggression, hostility, and anger) are also important to consider. Unreliability in serotonin and/or aggression measures could lead to attenuated correlations in spite of the existence of an actual relation (Buckley, Cote, & Comstock, 1990). For example, the subscales of the most commonly used aggression instrument included in this meta-analysis—the *Buss-Durkee Hostility Inventory* (BDHI; Buss & Durkee, 1957)—have been found to lack adequate reliability (Vassar & Hale, 2009) and discriminant validity (Biaggio, Supplee, & Curtis, 1981). Further, there is concern that self-report survey instruments tend to be only weakly correlated with observable aggressive behavior (Ferguson, 2009; Gothelf, Apter, & van Praag, 1997). This is consistent with our finding that the overall relation between serotonergic functioning and aggression was reversed in *other-report* aggression measures (including observational instruments). In other words, observable aggression was positively associated with serotonin levels while self-reported aggression was negatively associated with serotonin levels.

2. The relation is due to ambient correlational noise—“Ambient noise” (Lykken, 1968; referred to as the “crud factor” by Paul Meehl; 1990) refers to the observation that in the social sciences, and to some degree, the biological sciences, “everything correlates to some extent with everything else” (Meehl, 1990, p. 204). That studies of serotonergic functioning may have considerable ambient correlational noise should not be terribly surprising given the observation that “serotonergic neurotransmission contributes to the regulation of virtually every neurobiological function, including sensory, motor, cognitive, and higher order executive functions” (Kerman et al., 2011, p. 35). Inflated correlations are prevalent in the social sciences (see Fiedler, 2011), and it is possible that the serotonin deficiency hypothesis has been reinforced in large part by publication bias (Burdett, Stewart,

& Tierney, 2003; Levine, Asada, & Carpenter, 2009; Rosenthal, 1979; Sutton, Duval, Tweedie, Abrams, & Jones, 2000; Sutton, 2009).

3. The relation is moderated by a higher-order function of serotonin—Serotonin dysfunction has been implicated in a large number of psychopathological conditions and traits that have very different behavioral phenotypes (e.g., Deakin, 2003). For example, serotonergic deficits have been implicated in pathology as divergent as social anxiety (Stein, Westenberg, & Liebowitz, 2002) and antisocial personality (Völlm et al., 2010). It is reasonable to assume that serotonergic dysfunction contributes to these disorders at a relatively broad or primitive level given their *prima facie* differences. Therefore, the small correlation between serotonin and aggression observed in the present meta-analysis may be due to a failure to control for some higher-order function of serotonin.

Tops, Russo, Boksem, and Tucker (2009) argue that the phylogenetically primitive function of serotonin is to modulate the drive to withdraw and seek contentment. They propose that serotonin counteracts the dopaminergic-induced drive to seek stimulation with a drive to withdraw from stimulation. These authors take care to distinguish between *withdrawal* (the drive to reduce stimulation) and *avoidance* (the drive to avoid threat or harm). They suggest that serotonin facilitates the drive to withdraw by decreasing the impact of emotional and environmental cues and inducing a “satiated waking state” (p. 432). Serotonin dysfunction may reduce an organism’s ability to decrease reactivity and increase contentment. A compromised ability to withdraw from aversive stimuli might lead to increased efforts at avoiding (as opposed to withdrawing from) aversive stimuli including unpleasant emotional states such as feelings of rejection or anxiety. The ultimate act of avoidance—suicide—has long been implicated in connection to serotonergic dysfunction, albeit with inconsistent evidence (e.g., Lester, 1995). The earliest human studies linking serotonin and aggression stemmed from observations that depressed inpatients with low CSF 5-HIAA levels attempted more violent forms of suicidal behavior (e.g., Åsberg, Thoren, Traskman, Bertilsson, & Ringberger, 1976; Åsberg, Traskman, & Thoren, 1976). If one cannot withdraw in the face of threat, then the remaining options are to confront the threat or avoid it (i.e., ‘fight or flight’). Anti-social and socially avoidant behavior represent two fundamentally different response tendencies associated with serotonergic dysfunction. By failing to distinguish between these two response alternatives, we may be masking serotonin’s true effects in either one of these domains by aggregating across both. Hence, the limited finding between serotonin and aggression in the current meta-analysis may be due to a missing individual-difference moderator such as the tendency to fight or flight.

4. The relation is specific to certain aspects of serotonergic functioning—

When the serotonin deficiency hypothesis of human aggression was originally conceived our understanding of serotonergic neurotransmission was much simpler than it is today. Over the past several decades, rapid advances in technology and copious amounts of research have led to a much clearer understanding of serotonin’s role in the brain; however, with increased understanding has come an increased awareness of the complexity of serotonin’s role in regulating behavior. The implications of a putative deficit in central serotonin functioning have also become less and less clear. We now know that there are “several anatomically distinct [serotonergic] pathways” (Murphy et al., 1996, p. 212) and at least 7 families of serotonin receptors encompassing well over a dozen different serotonin receptor types. These different receptors are often associated with fundamentally different biological functions or, in some cases, opposite effects on the same function (Kitson, 2007). For example, 5-HT_{1A} and 5-HT_{1B} receptors are often argued to *attenuate* aggressive behavior when activated, while the 5-HT_{2A} and 5-HT_{2C} receptors are thought to *exacerbate* aggression when activated (Quadros et al., 2009). Truly understanding serotonin’s role in the brain requires distinguishing between tonic and phasic effects (e.g., de Boer & Koolhaas,

2005; van der Vegt et al., 2003; van Erp & Miczek, 2000), pre- vs. post-synaptic activity (de Boer & Koolhaas, 2005; Olivier & van Oorschot, 2005), and interactive effects involving other neurotransmitters (Olivier & van Oorschot, 2005). The serotonin deficiency hypothesis does not stipulate why a central deficit should influence some aspects of serotonergic functioning more than others, and it is possible that the countervailing impact of different selective serotonergic effects masks the true extent of the serotonin-aggression relation.

Limitations

The first limitation of this review was that it did not include studies examining serotonin receptor binding potentials or genetic polymorphisms. These methodologies were not included due to concerns over parsimony, feasibility, and interpretability. Studies of binding potentials and genetic polymorphisms are more diverse and fewer in number than studies using the four methodologies included in the present meta-analysis. Serotonin receptor binding potential studies attempt to index serotonin receptor affinity or density by examining peripheral blood platelet binding (e.g., Coccaro, Kavoussi, Sheline, Lish, & Csernansky, 1996) or regional receptor density using positron emission tomography (Witte et al., 2009). Similar to other methods of assessing serotonin, binding potential studies have been characterized by inconsistent, contradictory, and null findings (e.g., Castrogiovanni, Capone, Maremmanni, & Marazziti, 1994; Maguire et al., 1997; Marazziti & Conti, 1991). For example, the two published studies utilizing the high 5-HT_{1A} affinity radioligand [carbonyl-11C]WAY-100635 to measure the density of 5-HT_{1A} receptors in the prefrontal and anterior cingulate cortices and their relation to aggression found opposite results (Parsey et al., 2002; Witte et al., 2009).⁵ Studies examining candidate genes related to serotonin metabolism, morphology, and transport (see Gunter, Vaughn, & Philibert, 2010) have also had mixed results. For example, the short-allele of 5-HTTLPR has been shown to increase antisocial personality disorder by some researchers (Douglas et al., 2011) and to increase social conformity by others (Homberg & Lesch, 2011). The full array of inconsistencies in binding potential and genetic studies relevant to the serotonin-aggression link in humans cannot be adequately addressed here, but to date, there has been no definitive evidence from either of these two approaches supporting the serotonin deficiency hypothesis of human aggression. Therefore, it is unlikely that our primary conclusions would have differed substantially with the inclusion of these two additional methodologies.

A second limitation concerns the moderator analyses conducted to assess whether methodological or sample-level variables accounted for significant variance in study outcomes. Poor reporting practices, a common problem in meta-analysis coding (e.g., Cox, Davidson, & Bynum, 1995; Lipsey & Wilson, 2001) along with measurement issues impeded the resolution with which we could code certain variables (e.g., subtypes of aggression). In several cases, the number of studies having a particular level of a variable was relatively small, leaving open the possibility that some analyses lacked sufficient power.

Conclusion & Recommendations

The evidence for the serotonin deficiency hypothesis of human aggression lacks corroboration. Contradictory findings, unreliable measurement, and a high degree of complexity leave our overall finding of a small inverse correlation between serotonin and human aggression open to multiple, equally plausible interpretations. While the overall relation between serotonin and human aggression is currently unclear, the four recommendations below hold promise in advancing this important area of research and paving the way for future clarity.

⁵Interestingly, Witte and colleagues interpreted the opposite findings as supporting different roles for *pre*- and *post*-synaptic 5-HT_{1A} receptors (Witte et al., 2009).

1. Acknowledge contradictory findings and avoid selective reporting—Our first recommendation is that researchers acknowledge the contradictory findings within the literature and within their own research. Selective citation of the evidence has led to a widespread, demonstrably false belief that the link between serotonin and human aggression is “perhaps the most reliable finding in the history of psychiatry” (Fishbein, 2001, p. 15). The current system of scientific publishing can incentivize researchers to selectively report findings from their data (see Bones, 2012; Ioannidis, 2005; Molloy, 2011). Therefore, we strongly urge researchers to embrace the *open data* and *reproducible research* movements and to make their data available online for reanalysis, critique, and reuse by other investigators (see Gelman, 2011; Molloy, 2011; Peng, 2009, 2011; Simonsohn, 2012).

2. Focus on improving the reliability and validity of aggression and serotonin measures—Our second recommendation follows that made by Tuinier and colleagues in their review of serotonin and disruptive behavior published over a decade and a half ago when they stated that “there is still a need to define the manifestations of aggression more clearly, to develop more reliable assessment methods and to study whether, as in animals, subforms of aggression are distinguishable” (1996, p. 479). We recommend focusing more effort on ensuring that measures of aggression and serotonergic functioning are reliable and valid. It has been observed that advances in theory often follow advances in methodology (Greenwald, 2012); this may very well be the case with respect to serotonin and aggression.

3. Test for interactions involving personality and environmental moderators—Our third recommendation is to study serotonin and aggression in conjunction with, and in the context of, other psychological constructs such as social avoidance, depression, and anxiety. The idea that serotonin is uniquely related to aggression is presumptuous and may confound different individual response tendencies (see Deakin, 2003; Tops et al., 2009), limiting our ability to identify those individuals for whom serotonin deficiency is a key component in their aggressive tendencies.

4. Revise the serotonin deficiency hypothesis to account for serotonin’s functional complexity—Finally, we encourage researchers to recognize the excessive simplicity of the serotonin deficiency hypothesis. Albert Einstein is attributed as saying that “everything should be made as simple as possible, but no simpler” (Calaprice, 2010, p. 475). Given the divergent effects of different serotonin receptor types (e.g., 5-HT_{1A,B} vs. 5-HT_{2A,C}; Quadros et al., 2009) as well as the ongoing debates over pre- vs. post-synaptic activation (de Boer & Koolhaas, 2005; Olivier & van Oorschot, 2005) and the relative importance of phasic vs. tonic serotonergic activity (de Boer & Koolhaas, 2005; van der Vegt et al., 2003; van Erp & Miczek, 2000), it may be time to abandon a nonspecific deficiency model in favor of a specific or selective deficiency model.

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References

References marked with an asterisk indicate studies included in the meta-analysis.

- Ågren H. Symptom patterns in unipolar and bipolar depression correlating with monoamine metabolites in the cerebrospinal fluid: I. General patterns. *Psychiatry Research*. 1980; 3(2):211–223. doi: 10.1016/0165-1781(80)90038-4. [PubMed: 6171840]

- Almeida M, Lee R, Coccaro EF. Cortisol responses to ipsapirone challenge correlate with aggression, while basal cortisol levels correlate with impulsivity, in personality disorder and healthy volunteer subjects. *Journal of Psychiatric Research*. 2010; 44(14):874–880. doi:10.1016/j.jpsychires.2010.02.012. [PubMed: 20378126]
- Altman SE, Shankman S. a. Spring B. Effect of acute tryptophan depletion on emotions in individuals with personal and family history of depression following a mood induction. *Neuropsychobiology*. 2010; 62(3):171–6. doi: 10.1159/000319358. [PubMed: 20664229]
- Anderson, IM.; Mortimore, C. 5-HT and human anxiety: Evidence from studies using acute tryptophan depletion. In: Huether, G.; Kochen, W.; Simat, TJ.; Steinhart, H., editors. *Tryptophan, serotonin, and melatonin: Basic aspects and applications*. Kluwer Academic/Plenum Publishers; New York: 1999. p. 43-55.
- Anthenelli R, Maxwell R. Cigarette smoking decreases the prolactin response to serotonergic stimulation in subgroups of alcoholics and controls. *Alcoholism: Clinical and Experimental Research*. 2000; 24(7):987–995. doi:10.1111/j.1530-0277.2000.tb04641.x.
- Åsberg M. Monoamine neurotransmitters in human aggressiveness and violence: A selective review. *Criminal Behavior and Mental Health*. 1994; 4:303–327.
- Åsberg M, Thorén P, Träskman L, Bertilsson L, Ringberger V. “Serotonin depression”—a biochemical subgroup within the affective disorders? *Science*. 1976; 191(4226):478–480. doi: 10.1126/science.1246632. [PubMed: 1246632]
- Åsberg M, Träskman L, Thorén P. 5-HIAA in the cerebrospinal fluid: A biochemical suicide predictor? *Archives of General Psychiatry*. 1976; 33(10):1193–1197. doi:10.1001/archpsyc.1976.01770100055005. [PubMed: 971028]
- Balaban E, Alper JS, Kasamon YL. Mean genes and the biology of aggression: A critical review of recent animal and human research. *Journal of Neurogenetics*. 1996; 11(1-2):1–43. doi: 10.3109/01677069609107061. [PubMed: 10876648]
- Barr LC, Heninger GR, Goodman W, Charney DS, Price LH. Effects of fluoxetine administration on mood response to tryptophan depletion in healthy subjects. *Biological Psychiatry*. 1997; 41(9): 949–54. doi:10.1016/S0006-3223(96)00224-7. [PubMed: 9110100]
- Bell CJ, Hood SD, Nutt DJ. Acute tryptophan depletion. Part II: Clinical effects and implications. *Australian and New Zealand Journal of Psychiatry*. 2005; 39(7):565–574. doi:10.1111/j.1440-1614.2005.01628.x. [PubMed: 15996137]
- Ben-Jonathan N, Arbogast LA, Hyde JF. Neuroendocrine [corrected] regulation of prolactin release. *Progress in Neurobiology*. 1989; 33(5-6):399–447. doi:10.1016/0301-0082(89)90008-7. [PubMed: 2695976]
- Berman M, McCloskey M, Fanning J, Schumacher J, Coccaro E. Serotonin augmentation reduces response to attack in aggressive individuals. *Psychological Science*. 2009; 20(6):714–720. doi: 10.1111/j.1467-9280.2009.02355.x. [PubMed: 19422623]
- Biaggio MK, Supplee K, Curtis N. Reliability and validity of four anger scales. *Journal of Personality Assessment*. 1981; 45(6):639–648. doi:10.1207/s15327752jpa4506_12. [PubMed: 7310621]
- Bjork JM, Dougherty DM, Moeller FG, Swann AC. Differential behavioral effects of plasma tryptophan depletion and loading in aggressive and nonaggressive men. *Neuropsychopharmacology*. 2000; 22(4):357–69. doi:10.1016/S0893-133X(99)00136-0. [PubMed: 10700655]
- Blennow K, Wallin A, Gottfries CG, Karlsson I, Månsson JE, Skoog I, Wikkelsö C, Svennerholm L. Cerebrospinal fluid monoamine metabolites in 114 healthy individuals 18-88 years of age. *European Neuropsychopharmacology*. 1993; 3(1):55–61. doi:10.1016/0924-977X(93)90295-W. [PubMed: 7682460]
- Bond AJ, Feizollah S, Lader M. The effects of D-fenfluramine on mood and performance, and on neuroendocrine indicators of 5-HT function. *Journal of Psychopharmacology*. 1995; 9(1):1–8. doi: 10.1016/S0006-3223(98)00338-2. [PubMed: 22298686]
- Bond AJ, Verheyden SL, Wingrove J, Curran HV. Angry cognitive bias, trait aggression and impulsivity in substance users. *Psychopharmacology*. 2004; 171(3):331–9. doi:10.1007/s00213-003-1585-9. [PubMed: 13680074]

- Bond A, Wingrove J, Critchlow G. Tryptophan depletion increases aggression in women during the premenstrual phase. *Psychopharmacology*. 2001; 156(4):477–480. doi:10.1007/s002130100795. [PubMed: 11498726]
- Bones AK. We knew the future all along: Scientific hypothesizing is much more accurate than other forms of precognition—a satire in one part. *Perspectives on Psychological Science*. 2012; 7(3): 307–309. doi:10.1177/1745691612441216.
- Booij L, Tremblay RE, Leyton M, Séguin JR, Vitaro F, Gravel P, Benkelfat C. Brain serotonin synthesis in adult males characterized by physical aggression during childhood: A 21-year longitudinal study. *PLoS One*. 2010; 5(6):e11255. doi:10.1371/journal.pone.0011255. [PubMed: 20582306]
- Booij L, Van der Does AJW, Riedel WJ. Monoamine depletion in psychiatric and healthy populations: A review. *Molecular Psychiatry*. 2003; 8(12):951–973. doi:10.1038/sj.mp.4001423. [PubMed: 14647394]
- Borenstein, M. Effect sizes for continuous data. In: Cooper, H.; Hedges, LV.; Valentine, JC., editors. *The handbook of research synthesis and meta-analysis*. 2nd. Russell Sage Foundation; New York: 2009. p. 221-235.
- Brambilla F, Bellodi L, Arancio C, Limonta D, Ferrari E, Solerte B. Neurotransmitter and hormonal background of hostility in anorexia nervosa. *Neuropsychobiology*. 2001; 43(4):225–232. doi: 10.1159/000054894. [PubMed: 11340360]
- Brewerton TD, Berrettini WH, Nurnberger JI, Linnoila M. Analysis of seasonal fluctuations of CSF monoamine metabolites and neuropeptides in normal controls: Findings with 5HIAA and HVA. *Psychiatry Research*. 1988; 23(3):257–265. doi:10.1016/0165-1781(88)90016-9. [PubMed: 2455302]
- Brown GL, Ebert MH, Goyer PF, Jimerson DC, Klein WJ, Bunney WE, Goodwin FK. Aggression, suicide, and serotonin: Relationship to CSF amine metabolites. *American Journal of Psychiatry*. 1982; 139(6):741–746. [PubMed: 6177256]
- Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF. Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Research*. 1979; 1(2):131–139. doi: 10.1016/0165-1781(79)90053-2. [PubMed: 95232]
- Buchanan T. Does the Revised Multiple Affect Adjective Checklist Hostility subscale measure hostility? *Aggressive Behavior*. 1999; 25(3):179–184. doi:10.1002/(SICI)1098-2337(1999)25:3<179::AID-AB2>3.0.CO;2-M.
- Buckley MR, Cote JA, Comstock SM. Measurement errors in the behavioral sciences: The case of personality/attitude research. *Educational and Psychological Measurement*. 1990; 50(3):447–474. doi:10.1177/0013164490503001.
- Burdett S, Stewart LA, Tierney JF. Publication bias and meta-analyses: A practical example. *International Journal of Technology Assessment in Health Care*. 2003; 19(1):129–134. doi: 10.1017/S0266462303000126. [PubMed: 12701945]
- Bushman BJ, Anderson CA. Is it time to pull the plug on the hostile versus instrumental aggression dichotomy? *Psychological Review*. 2001; 108:273–279. doi:10.1037/0033-295X.108.1.273. [PubMed: 11212630]
- Bushman, BJ.; Bartholow, BD. Aggression. In: Baumeister, RF.; Finkel, EJ., editors. *Advanced social psychology: the state of the science*. Oxford University Press; New York: 2010. p. 303-340.
- Bushman, BJ.; Wang, MC. Vote-counting procedures in meta-analysis. In: Cooper, H.; Hedges, LV.; Valentine, JC., editors. *The handbook of research synthesis and meta-analysis*. 2nd. Russell Sage Foundation; New York: 2009. p. 207-220.
- Buss AH, Durkee A. An inventory for assessing different kinds of hostility. *Journal of Consulting Psychology*. 1957; 21(4):343–349. doi:10.1037/h0046900. [PubMed: 13463189]
- Buydens-Branchey L, Branchey M, Fergusson P, Hudson J, McKernin C. The meta-chlorophenylpiperazine challenge test in cocaine addicts: Hormonal and psychological responses. *Biological Psychiatry*. 1997; 41(11):1071–1086. doi:10.1016/S0006-3223(96)00182-5. [PubMed: 9146818]

- Buydens-Branchey L, Branchey M, Hudson J, Fergusson P. Low HDL cholesterol, aggression and altered central serotonergic activity. *Psychiatry Research*. 2000; 93(2):93–102. doi:10.1016/S0165-1781(99)00126-2. [PubMed: 10725526]
- Calaprice, A., editor. *The ultimate quotable einstein*. Princeton University Press; Princeton, New Jersey: 2010.
- Callahan PM, Cunningham KA. Involvement of 5-HT_{2C} receptors in mediating the discriminative stimulus properties of m-chlorophenylpiperazine (mCPP). *European Journal of Pharmacology*. 1994; 257(1-2):27–38. doi:10.1016/0014-2999(94)90690-4. [PubMed: 8082704]
- Carlson, NR. *Physiology of behavior*. Pearson; Boston, MA: 2010.
- Castellanos F, Elia J, Kruesi M, Gulotta C, Mefford I, Potte W, Rapoport J. Cerebrospinal fluid monoamine metabolites in boys with attention-deficit hyperactivity disorder. *Psychiatry Research*. 1994; 52(3):305–316. doi:10.1016/0165-1781(94)90076-0. [PubMed: 7527565]
- Castrogiovanni P, Capone MR, Maremmanni I, Marazziti D. Platelet serotonergic markers and aggressive behaviour in healthy subjects. *Neuropsychobiology*. 1994; 29(3):105–107. doi:10.1159/000119070. [PubMed: 8022528]
- Cherek DR, Lane SD. Effects of d,l-fenfluramine on aggressive and impulsive responding in adult males with a history of conduct disorder. *Psychopharmacology*. 1999; 146(4):473–481. doi:10.1007/PL00005493. [PubMed: 10550498]
- Cherek DR, Lane SD. Acute effects of D-fenfluramine on simultaneous measures of aggressive escape and impulsive responses of adult males with and without a history of conduct disorder. *Psychopharmacology*. 2001; 157(3):221–227. doi:10.1007/s002130100812. [PubMed: 11605076]
- Cherek DR, Lane SD, Pietras CJ, Steinberg JL. Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder. *Psychopharmacology*. 2002; 159(3):266–274. doi:10.1007/s002130100915. [PubMed: 11862359]
- Cherek DR, Moeller FG, Khan-Dawood F, Swann A, Lane SD. Prolactin response to buspirone was reduced in violent compared to nonviolent parolees. *Psychopharmacology*. 1999; 142(2):144–148. doi:10.1007/s002130050873. [PubMed: 10102766]
- Cherek DR, Spiga R, Creson DL. Acute effects of eltopazine on aggressive and point-maintained responding of normal male participants: Phase I study. *Experimental and Clinical Psychopharmacology*. 1995; 3(3):287–293. doi:10.1037/1064-1297.3.3.287.
- Cleare A, Bond A. Ipsapirone challenge in aggressive men shows an inverse correlation between 5-HT_{1A} receptor function and aggression. *Psychopharmacology*. 2000; 148(4):344–349. doi:10.1007/s002130050061. [PubMed: 10928305]
- Cleare AJ, Bond AJ. The effect of tryptophan depletion and enhancement on subjective and behavioural aggression in normal male subjects. *Psychopharmacology*. 1995; 118(1):72–81. doi:10.1007/BF02245252. [PubMed: 7597125]
- Cleare AJ, Bond AJ. Does central serotonergic function correlate inversely with aggression? A study using D-fenfluramine in healthy subjects. *Psychiatry Research*. 1997; 69(2-3):89–95. doi:10.1016/S0165-1781(96)03052-1. [PubMed: 9109176]
- Coccaro EF. Impulsive aggression and central serotonergic system function in humans: An example of a dimensional brain-behavior relationship. *International Clinical Psychopharmacology*. 1992; 7(1):3–12. doi:10.1097/00004850-199200710-00001. [PubMed: 1624755]
- Coccaro EF, Lee R. Cerebrospinal fluid 5-hydroxyindolacetic acid and homovanillic acid: Reciprocal relationships with impulsive aggression in human subjects. *Journal of Neural Transmission*. 2010; 117(2):241–248. doi:10.1007/s00702-009-0359-x. [PubMed: 20069438]
- Coccaro EF, Kavoussi RJ. Neuropsychopharmacologic challenge in biological psychiatry. *Clinical Chemistry*. 1994; 40(2):319–327. [PubMed: 7906209]
- Coccaro EF, Kavoussi RJ, Cooper TB, Hauger RL. Central serotonin activity and aggression: Inverse relationship with prolactin response to d-fenfluramine, but not CSF 5-HIAA concentration, in human subjects. *The American Journal of Psychiatry*. 1997; 154(10):1430–1435. [PubMed: 9326827]
- Coccaro EF, Kavoussi RJ, Shelton YI, Lish JD, Csernansky JG. Impulsive aggression in personality disorder correlates with tritiated paroxetine binding in the platelet. *Archives of General Psychiatry*. 1996; 53(6):531–536. doi:10.1001/archpsyc.1996.01830060075010. [PubMed: 8639036]

- Coccaro EF, Kavoussi RJ, Trestman RL, Gabriel SM, Cooper TB, Siever LJ. Serotonin function in human subjects: Intercorrelations among central 5-HT indices and aggressiveness. *Psychiatry Research*. 1997; 73:1–14. doi:10.1016/S0165-1781(97)00108-X. [PubMed: 9463834]
- Coccaro EF, Lee R, Kavoussi RJ. Aggression, suicidality, and intermittent explosive disorder: Serotonergic correlates in personality disorder and healthy control subjects. *Neuropsychopharmacology*. 2010; 35(2):435–444. doi:10.1038/npp.2009.148. [PubMed: 19776731]
- Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Davis KL. Serotonergic studies in patients with affective and personality disorders: Correlates with suicidal and impulsive aggressive behavior. *Archives of General Psychiatry*. 1989; 46(7):587–599. doi:10.1001/archpsyc.1989.01810070013002. [PubMed: 2735812]
- Cohen J. Statistical power analysis for the behavioral sciences. 2nd. Erlbaum; Hillsdale, NJ: 1988.
- Cohen J. A power primer. *Psychological Bulletin*. 1992; 112(1):155–159. doi:10.1037/0033-2909.112.1.155. [PubMed: 19565683]
- Cowen PJ, Anderson IM, Gartside SE. Endocrinological responses to 5-HT. *Annals of the New York Academy of Sciences*. 1990; 600:250–257. doi:10.1111/j.1749-6632.1990.tb16887.x. [PubMed: 2252313]
- Cox SM, Davidson WS, Bynum TS. A meta-analytic assessment of delinquency-related outcomes of alternative education programs. *Crime & Delinquency*. 1995; 41(2):219–234. doi:10.1177/0011128795041002004.
- Crunelli V, Bernasconi S, Samanin R. Effects of d- and l-fenfluramine on striatal homovanillic acid concentrations in rats after pharmacological manipulation of brain serotonin. *Pharmacological Research Communications*. 1980; 12(3):215–223. doi:10.1016/S0031-6989(80)80004-X. [PubMed: 7190307]
- Davis LL, Clark DM, Kramer GL, Moeller FG. D-fenfluramine challenge in posttraumatic stress disorder. *Biological Psychiatry*. 1999; 45:928–930. doi:10.1016/S0006-3223(98)00215-7. [PubMed: 10202582]
- de Boer SF, Koolhaas JM. 5-HT_{1A} and 5-HT_{1B} receptor agonists and aggression: A pharmacological challenge of the serotonin deficiency hypothesis. *European Journal of Pharmacology*. 2005; 526(1-3):125–139. doi:10.1016/j.ejphar.2005.09.065.
- Deakin JFW. Depression and antisocial personality disorder: Two contrasting disorders of 5HT function. *Journal of Neural Transmission Supplementum*. 2003; 64:79–93. [PubMed: 12830930]
- Debener S, Strobel A, Kürschner K, Kranczioch C, Hebenstreit J, Maercker A, Brocke B. Is auditory evoked potential augmenting/reducing affected by acute tryptophan depletion? *Biological Psychology*. 2002; 59(2):121–133. doi:10.1016/S0301-0511(01)00132-6. [PubMed: 11911935]
- Delgado PL, Charney DS, Price LH, Landis H, Heninger GR. Neuroendocrine and behavioral effects of dietary tryptophan restriction in healthy subjects. *Life Sciences*. 1989; 45(24):2323–2332. doi:10.1016/0024-3205(89)90114-8. [PubMed: 2601581]
- Delva NJ, Matthews DR, Cowen PJ. Brain serotonin (5-HT) neuroendocrine function in patients taking cholesterol-lowering drugs. *Biological Psychiatry*. 1996; 39(2):100–106. doi:10.1016/0006-3223(95)00140-9. [PubMed: 8717607]
- Desmyter S, van Heeringen C, Audenaert K. Structural and functional neuroimaging studies of the suicidal brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2011; 35(4):796–808. doi:10.1016/j.pnpbp.2010.12.026. [PubMed: 21216267]
- Dhondt J. Difficulties in establishing reference intervals for special fluids: The example of 5-hydroxyindoleacetic acid and homovanillic acid in cerebrospinal fluid. *Clinical Chemistry and Laboratory Medicine*. 2004; 42(7):833–841. doi:10.1515/CCLM.2004.137. [PubMed: 15327020]
- Dolan M, Anderson I. The relationship between serotonergic function and the Psychopathy Checklist: Screening Version. *Journal of Psychopharmacology*. 2003; 17(2):216–222. doi:10.1177/0269881103017002011. [PubMed: 12870570]
- Dolan MC. Serotonergic function in personality disordered offenders. *European Psychiatry*. 1996; 11(Suppl. 4):243s–243s. doi:10.1016/0924-9338(96)88731-1.

- Dolan M, Anderson I, Deakin J. Relationship between 5-HT function and impulsivity and aggression in male offenders with personality disorders. *The British Journal of Psychiatry*. 2001; 178(4):352. doi:10.1192/bjp.178.4.352. [PubMed: 11282815]
- Dougherty DM, Bjork JM, Marsh DM, Moeller FG. Influence of trait hostility on tryptophan depletion-induced laboratory aggression. *Psychiatry Research*. 1999; 88(3):227–232. doi:10.1016/S0165-1781(99)00088-8. [PubMed: 10622343]
- Douglas K, Chan G, Gelernter J, Arias AJ, Anton RF, Poling J, Kranzler HR. 5-HTTLPR as a potential moderator of the effects of adverse childhood experiences on risk of antisocial personality disorder. *Psychiatric Genetics*. 2011; 21(5):240–248. doi:10.1097/YPG.0b013e3283457c15. [PubMed: 21399568]
- Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal*. 1997; 315(7109):629–634. doi:10.1136/bmj.315.7109.629. [PubMed: 9310563]
- Eklundh T, Nordin C. Intraspinal pressure influences CSF disposition of tryptophan and 5-HIAA. *Neuropsychobiology*. 2001; 44(2):84–87. doi:10.1159/000054921. [PubMed: 11490176]
- Eklundh T, Fernström V, Nordin C. Influence of tapping-time and atmospheric pressure on concentrations of monoamine metabolites in the cerebrospinal fluid: A prospective study in female volunteers. *Journal of Psychiatric Research*. 1994; 28(6):511–517. doi:10.1016/0022-3956(94)90041-8. [PubMed: 7699610]
- Eklundh T, Gunnarsson T, Nordin C. Monoamine compounds in cerebrospinal fluid of healthy subjects punctured without preceding strict bed rest: A pilot study. *Neuropsychobiology*. 2001; 43(1):5–10. doi:10.1159/000054857. [PubMed: 11150891]
- Ellenbogen, M. a.; Young, SN.; Dean, P.; Palmour, RM.; Benkelfat, C. Mood response to acute tryptophan depletion in healthy volunteers: Sex differences and temporal stability. *Neuropsychopharmacology*. 1996; 15(5):465–474. doi:10.1016/S0893-133X(96)00056-5. [PubMed: 8914119]
- Evans J, Platts H, Lightman S, Nutt D. Impulsiveness and the prolactin response to d-fenfluramine. *Psychopharmacology*. 2000; 149(2):147–152. doi:10.1007/s002139900361. [PubMed: 10805609]
- Evers EAT, van der Veen FM, Fekkes D, Jolles J. Serotonin and cognitive flexibility: Neuroimaging studies into the effect of acute tryptophan depletion in healthy volunteers. *Current Medicinal Chemistry*. 2007; 14(28):2989–2995. doi:10.2174/092986707782794032. [PubMed: 18220735]
- Fava M, Vuolo R, Wright E, Nierenberg A, Alpert JE, Rosenbaum JF. Fenfluramine challenge in unipolar depression with and without anger attacks. *Psychiatry Research*. 2000; 94(1):9–18. doi:10.1016/S0165-1781(00)00120-7. [PubMed: 10788673]
- Felsten G, Hill V. Aggression questionnaire hostility scale predicts anger in response to mistreatment. *Behaviour Research and Therapy*. 1999; 37(1):87–97. doi:10.1016/S0005-7967(98)00104-1. [PubMed: 9922561]
- Ferguson CJ. Media violence effects: Confirmed truth or just another X-file? *Journal of Forensic Psychology Practice*. 2009; 9(2):103–126. doi:10.1080/15228930802572059.
- Ferguson CJ, Savage J. Have recent studies addressed methodological issues raised by five decades of television violence research? A critical review. *Aggression and Violent Behavior*. 2012; 17(2):129–139. doi:10.1016/j.avb.2011.11.001.
- Fiedler K. Voodoo correlations are everywhere—not only in neuroscience. *Perspectives on Psychological Science*. 2011; 6(2):163–171. doi:10.1177/1745691611400237.
- Finn PR, Young SN, Pihl RO, Ervin FR. The effects of acute plasma tryptophan manipulation on hostile mood: The influence of trait hostility. *Aggressive Behavior*. 1998; 24(3):173–185. doi:10.1002/(SICI)1098-2337(1998)24:3<173::AID-AB2>3.0.CO;2-M.
- Fishbein, D. Biobehavioral perspectives in criminology. Wadsworth; Belmont, CA: 2001.
- Fishbein D, Lozovsky D, Jaffe J. Impulsivity, aggression, and neuroendocrine responses to serotonergic stimulation in substance abusers. *Biological Psychiatry*. 1989; 25(8):1049–1066. doi:10.1016/0006-3223(89)90293-X. [PubMed: 2720017]
- Fisher RA. On the “probable error” of a coefficient of correlation deduced from a small sample. *Metron*. 1921; 1:1–32.

- *. Flory JD, Newcorn JH, Miller C, Harty S, Halperin JM. Serotonergic function in children with attention-deficit hyperactivity disorder: Relationship to later antisocial personality disorder. *The British Journal of Psychiatry*. 2007; 190:410–414. doi:10.1192/bjp.bp.106.027847. [PubMed: 17470955]
- *. Fulwiler C, Eckstine J, Kalsy S. Impulsive-aggressive traits, serotonin function, and alcohol-enhanced aggression. *The Journal of Clinical Pharmacology*. 2005; 45(1):94–100. doi: 10.1177/0091270004270457.
- Fusar-Poli P, Allen P, McGuire P, Placentino A, Cortesi M, Perez J. Neuroimaging and electrophysiological studies of the effects of acute tryptophan depletion: A systematic review of the literature. *Psychopharmacology*. 2006; 188(2):131–143. doi:10.1007/s00213-006-0493-1. [PubMed: 16915379]
- *. Gardner DL, Lucas PB, Cowdry RW. CSF metabolites in borderline personality disorder compared with normal controls. *Biological Psychiatry*. 1990; 28(3):247–254. doi: 10.1016/0006-3223(90)90580-U. [PubMed: 1696137]
- Gatch MB. Discriminative stimulus effects of m-chlorophenylpiperazine as a model of the role of serotonin receptors in anxiety. *Life Sciences*. 2003; 73(11):1347–1367. doi:10.1016/S0024-3205(03)00422-3. [PubMed: 12850497]
- Gelman A. Ethics and statistics: Open data and open methods. *Chance*. 2011; 24(4):51–53.
- *. George DT, Umhau JC, Phillips MJ, Emmela D, Ragan PW, Shoaf SE, Rawlings RR. Serotonin, testosterone and alcohol in the etiology of domestic violence. *Psychiatry Research*. 2001; 104(1): 27–37. doi:10.1016/S0165-1781(01)00292-X. [PubMed: 11600187]
- *. Germine M, Goddard AW, Woods SW, Charney DS, Heninger GR. Anger and anxiety responses to m-chlorophenylpiperazine in generalized anxiety disorder. *Biological Psychiatry*. 1992; 32(5): 457–461. doi:10.1016/0006-3223(92)90133-K. [PubMed: 1486151]
- *. Gerra G, Fertonani G, Zaimovic A, Rota-Graziosi I, Avanzini P, Caccavari R, Lucchini A. Hostility in heroin abusers subtypes: Fluoxetine and naltrexone treatment. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 1995; 19(8):1225–1237. doi: 10.1016/0278-5846(95)00262-6. [PubMed: 8868205]
- *. Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, Delsignore R. Serotonin function after (±)3,4-methylene-dioxymethamphetamine ('ecstasy') in humans. *International Clinical Psychopharmacology*. 1998; 13(1):1–9. doi:10.1097/00004850-199801000-00001. [PubMed: 9988361]
- Gleser, LJ.; Olkin, I. Stochastically dependent effect sizes. In: Cooper, H.; Hedges, LV.; Valentine, JC., editors. *The handbook of research synthesis and meta-analysis*. 2nd ed. Russell Sage Foundation; New York: 2009. p. 357-376.
- Gommans J, Hijzen TH, Maes RA, Olivier B. Discriminative stimulus properties of mCPP: Evidence for a 5-HT_{2C} receptor mode of action. *Psychopharmacology*. 1998; 137(3):292–302. doi: 10.1007/s002130050622. [PubMed: 9683007]
- Gothelf D, Apter A, van Praag HM. Measurement of aggression in psychiatric patients. *Psychiatry Research*. 1997; 71(2):83–95. doi:10.1016/S0165-1781(97)00047-4. [PubMed: 9255853]
- *. Gowin JL, Swann AC, Moeller FG, Lane SD. Zolmitriptan and human aggression: Interaction with alcohol. *Psychopharmacology*. 2010; 210(4):521–531. doi:10.1007/s00213-010-1851-6. [PubMed: 20407761]
- Greenwald AG. There is nothing so theoretical as a good method. *Perspectives on Psychological Science*. 2012; 7(2):99–108. doi:10.1177/1745691611434210.
- Gunter TD, Vaughn MG, Philibert RA. Behavioral genetics in antisocial spectrum disorders and psychopathy: A review of the recent literature. *Behavioural Sciences and the Law*. 2010; 28(2): 148–173. doi:10.1002/bsl.923.
- Hagenfeldt L, Bjerkenstedt L, Edman G, Sedvall G, Wiesel FA. Amino acids in plasma and CSF and monoamine metabolites in CSF: Interrelationship in healthy subjects. *Journal of Neurochemistry*. 1984; 42(3):833–837. doi:10.1111/j.1471-4159.1984.tb02756.x. [PubMed: 6198473]
- *. Halperin JM, Newcorn JH, Kopstein I, McKay KE, Schwartz ST, Siever LJ, Sharma V. Serotonin, aggression, and parental psychopathology in children with attention-deficit hyperactivity

- disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36(10): 1391–1398. doi:10.1097/00004583-199710000-00021. [PubMed: 9334552]
- *. Halperin J, Schulz K, McKay K, Sharma V, Newcorn JH. Familial correlates of central serotonin function in children with disruptive behavior disorders. *Psychiatry Research*. 2003; 119(3):205–216. doi:10.1016/S0165-1781(03)00136-7. [PubMed: 12914892]
- *. Halperin J, Sharma V, Siever L, Schwartz S, Matier K, Wornell G, Newcorn J. Serotonergic function in aggressive and nonaggressive boys with attention deficit hyperactivity disorder. *American Journal of Psychiatry*. 1994; 151(2):243. [PubMed: 8296897]
- Hamon M, Fattaccini CM, Adrien J, Gallissot MC, Martin P, Gozlan H. Alterations of central serotonin and dopamine turnover in rats treated with ipsapirone and other 5-hydroxytryptamine1A agonists with potential anxiolytic properties. *Journal of Pharmacology and Experimental Therapeutics*. 1988; 246(2):745–752. [PubMed: 2457083]
- Hancock M, Tapscott JL, Hoaken PNS. Role of executive dysfunction in predicting frequency and severity of violence. *Aggressive Behavior*. 2010; 36(5):338–349. doi:10.1002/ab.20353. [PubMed: 20593426]
- *. Handelsman L, Kahn RS, Sturiano C, Rinaldi PJ, Gabriel S, Schmeidler JP, Cooper TB. Hostility is associated with a heightened prolactin response to meta-chlorophenylpiperazine in abstinent cocaine addicts. *Psychiatry Research*. 1998; 80(1):1–12. doi:10.1016/S0165-1781(98)00048-1. [PubMed: 9727959]
- Hartikainen P, Soininen H, Reinikainen KJ, Sirviö J, Soikkeli R, Riekkinen PJ. Neurotransmitter markers in the cerebrospinal fluid of normal subjects: Effects of aging and other confounding factors. *Journal of Neural Transmission*. 1991; 84(1-2):103–117. doi:10.1007/BF01249114. [PubMed: 1675857]
- *. Hayward G, Goodwin GM, Cowen PJ, Harmer CJ. Low-dose tryptophan depletion in recovered depressed patients induces changes in cognitive processing without depressive symptoms. *Biological Psychiatry*. 2005; 57(5):517–524. doi:10.1016/j.biopsych.2004.11.016. [PubMed: 15737667]
- Hedner J, Lundell KH, Breese GR, Mueller RA, Hedner T. Developmental variations in CSF monoamine metabolites during childhood. *Biology of the Neonate*. 1986; 49(4):190–197. doi:10.1159/000242530. [PubMed: 2423144]
- *. Hennig J, Reuter M, Netter P, Burk C, Landt O. Two types of aggression are differentially related to serotonergic activity and the A779C TPH polymorphism. *Behavioral Neuroscience*. 2005; 119(1):16–25. doi:10.1037/0735-7044.119.1.16. [PubMed: 15727508]
- *. Hibbeln JR, Umhau JC, George DT, Shoaf SE, Linnoila M, Salem N. Plasma total cholesterol concentrations do not predict cerebrospinal fluid neurotransmitter metabolites: Implications for the biophysical role of highly unsaturated fatty acids. *The American Journal of Clinical Nutrition*. 2000; 71(1 Supplement):331S–338S. [PubMed: 10617992]
- Higley, JD.; Barr, CS. Neurochemistry and behavior: Nonhuman primate studies. In: Burbacher, T.; Grant, K.; Sackett, GP., editors. *Primate models of children's health and developmental disabilities*. Academic Press; 2007. p. 161-200.
- Hill KK, West SA, Ekhtator NN, Bruce AB, Wortman MD, Baker DG, Geraciotti TD. The effect of lumbar puncture stress on dopamine and serotonin metabolites in human cerebrospinal fluid. *Neuroscience Letters*. 1999; 276:25–28. doi:10.1016/S0304-3940(99)00778-8. [PubMed: 10586966]
- Hollander, E.; Berlin, HA. Neuropsychiatric aspects of aggression and impulse-control disorders. In: Yudofsky, SC.; Hales, RE., editors. *The American psychiatric publishing textbook of neuropsychiatry and behavioral neurosciences*. 5th ed. American Psychiatric Publishing, Inc.; Arlington, VA: 2008. p. 567-594.
- Homberg JR, Lesch K-P. Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry*. 2011; 69(6):513–519. doi:10.1016/j.biopsych.2010.09.024. [PubMed: 21047622]
- Hood SD, Bell CJ, Nutt DJ. Acute tryptophan depletion. Part I: Rationale and methodology. *Australian and New Zealand Journal of Psychiatry*. 2005; 39(7):558–564. doi:10.1111/j.1440-1614.2005.01627.x. [PubMed: 15996136]

- *. Hughes JH. Effects of acute tryptophan depletion on mood and suicidal ideation in bipolar patients symptomatically stable on lithium. *The British Journal of Psychiatry*. 2000; 177(5):447–451. doi: 10.1192/bjp.177.5.447. [PubMed: 11059999]
- Hyland K. Clinical utility of monoamine neurotransmitter metabolite analysis in cerebrospinal fluid. *Clinical Chemistry*. 2008; 54(4):633–641. doi:10.1373/clinchem.2007.099986. [PubMed: 18310141]
- Ioannidis JPA. Why most published research findings are false. *PLoS Medicine*. 2005; 2(8):e124. doi: 10.1371/journal.pmed.0020124. [PubMed: 16060722]
- Ioannidis JPA, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: A large survey. *Canadian Medical Association Journal*. 2007; 176(8):1091–1096. doi: 10.1503/cmaj.060410. [PubMed: 17420491]
- *. Kahn R, Wetzler S, van Praag HM, Asnis GM, Strauman T. Behavioral indications for serotonin receptor hypersensitivity in panic disorder. *Psychiatry Research*. 1988; 25(1):101–104. doi: 10.1016/0165-1781(88)90163-1. [PubMed: 3217461]
- *. Katz MM, Maas JW, Frazer A, Koslow SH, Bowden CL, Berman N, Stokes PE. Drug-induced actions on brain neurotransmitter systems and changes in the behaviors and emotions of depressed patients. *Neuropsychopharmacology*. 1994; 11(2):89–100. [PubMed: 7530963]
- *. Kaye WH, Gendall KA, Fernstrom MH, Fernstrom JD, McConaha CW, Weltzin TE. Effects of acute tryptophan depletion on mood in bulimia nervosa. *Biological Psychiatry*. 2000; 47(2):151–157. doi:10.1016/S0006-3223(99)00108-0. [PubMed: 10664832]
- *. Kaye W, Barbarich N, Putnam K, Gendall K, Fernstrom J, Fernstrom M, Kishore A. Anxiolytic effects of acute tryptophan depletion in anorexia nervosa. *International Journal of Eating Disorders*. 2003; 33(3):257–267. doi:10.1002/eat.10135. [PubMed: 12655621]
- Kelley, TL. Interpretation of educational measurements. World Book; Yonkers, NY: 1927.
- Kerman IA, Clinton SM, Bedrosian TA, Abraham AD, Rosenthal DT, Akil H, Watson SJ. High novelty-seeking predicts aggression and gene expression differences within defined serotonergic cell groups. *Brain Research*. 2011; 1419:34–45. doi:10.1016/j.brainres.2011.08.038. [PubMed: 21925645]
- Kitson SL. 5-hydroxytryptamine (5-HT) receptor ligands. *Current Pharmaceutical Design*. 2007; 13(25):2621–2637. doi:10.2174/138161207781663000. [PubMed: 17897004]
- *. Klaassen T, Riedel WJ, van Someren A, Deutz NE, Honig A, van Praag HM. Mood effects of 24-hour tryptophan depletion in healthy first-degree relatives of patients with affective disorders. *Biological Psychiatry*. 1999; 46(4):489–497. doi:10.1016/S0006-3223(99)00082-7. [PubMed: 10459398]
- *. Klaassen T, Riedel W, van Praag H, Menheere P, Griez E. Neuroendocrine response to meta-chlorophenylpiperazine and ipsapirone in relation to anxiety and aggression. *Psychiatry Research*. 2002; 113:29–40. doi:10.1016/S0165-1781(02)00250-0. [PubMed: 12467943]
- Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Statistics in Medicine*. 2003; 22(17):2693–2710. doi:10.1002/sim.1482. [PubMed: 12939780]
- *. Knott VJ, Howson AL, Perugini M, Ravindran AV, Young SN. The effect of acute tryptophan depletion and fenfluramine on quantitative EEG and mood in healthy male subjects. *Biological Psychiatry*. 1999; 46(2):229–238. doi:10.1016/S0006-3223(98)00338-2. [PubMed: 10418698]
- Kojima H, Terao T, Iwakawa M, Soya A, Inoue N, Shiraishi Y, Nakamura J. Paroxetine as a 5-HT neuroendocrine probe. *Psychopharmacology*. 2003; 167(1):97–102. doi:10.1007/s00213-003-1406-1. [PubMed: 12601506]
- *. Koren AR, Lieberman JA, Alvir J, Chakos M. The behavioral effect of m-chlorophenylpiperazine (mCPP) and methylphenidate in first-episode schizophrenia and normal controls. *Neuropsychopharmacology*. 1997; 16(1):61–68. doi:10.1016/S0893-133X(96)00160-1. [PubMed: 8981389]
- *. Koszycki D, Zacharko RM, Le Melleo JM, Young SN, Bradwejn J. Effect of acute tryptophan depletion on behavioral, cardiovascular, and hormonal sensitivity to cholecystokinin-tetrapeptide challenge in healthy volunteers. *Biological Psychiatry*. 1996; 40(7):648–655. doi: 10.1016/0006-3223(95)00479-3. [PubMed: 8886299]

- *. Kruesi M, Rapoport J, Hamburger S, Hibbs E, Potter W, Lenane M, Brown G. Cerebrospinal fluid monoamine metabolites, aggression, and impulsivity in disruptive behavior disorders of children and adolescents. *Archives of General Psychiatry*. 1990; 47(5):419. doi:10.1001/archpsyc.1990.01810170019003. [PubMed: 1691910]
- *. Krystal JH, Webb E, Cooney N, Kranzler HR, Charney DS. Specificity of ethanollike effects elicited by serotonergic and noradrenergic mechanisms. *Archives of General Psychiatry*. 1994; 51(11):898–911. doi:10.1001/archpsyc.1994.03950110058008. [PubMed: 7944878]
- *. Kuepper Y, Alexander N, Osinsky R, Mueller E, Schmitz A, Netter P, Hennig J. Aggression-interactions of serotonin and testosterone in healthy men and women. *Behavioural Brain Research*. 2010; 206(1):93–100. doi:10.1016/j.bbr.2009.09.006. [PubMed: 19747510]
- *. Kunisato Y, Okamoto Y, Okada G, Aoyama S, Demoto Y, Munakata A, Yamawaki S. Modulation of default-mode network activity by acute tryptophan depletion is associated with mood change: A resting state functional magnetic resonance imaging study. *Neuroscience Research*. 2011; 69(2):129–134. doi:10.1016/j.neures.2010.11.005. [PubMed: 21078349]
- *. Kunz M, Sikora J, Krakowski M, Convit A, Cooper TB, Volavka J. Serotonin in violent patients with schizophrenia. *Psychiatry Research*. 1995; 59(1-2):161–163. doi:10.1016/0165-1781(95)02782-3. [PubMed: 8771232]
- *. Lanctôt KL, Herrmann N, Eryavec G, van Reekum R, Reed K, Naranjo CA. Central serotonergic activity is related to the aggressive behaviors of Alzheimer's disease. *Neuropsychopharmacology*. 2002; 27(4):646–654. doi:10.1016/S0893-133X(02)00339-1. [PubMed: 12377401]
- *. Landén M, Erlandsson H, Bengtsson F, Andersch B, Eriksson E. Short onset of action of a serotonin reuptake inhibitor when used to reduce premenstrual irritability. *Neuropsychopharmacology*. 2009; 34(3):585–592. doi:10.1038/npp.2008.86. [PubMed: 18596686]
- *. Lappalainen J, Long JC, Virkkunen M, Ozaki N, Goldman D, Linnoila M. HTR2C Cys23Ser polymorphism in relation to CSF monoamine metabolite concentrations and DSM-III-R psychiatric diagnoses. *Biological Psychiatry*. 1999; 46(6):821–826. doi:10.1016/S0006-3223(98)00361-8. [PubMed: 10494451]
- *. Lee R, Garcia F, van de Kar L, Hauger R, Coccaro E. Plasma oxytocin in response to pharmacological challenge to fenfluramine and placebo in healthy men. *Psychiatry Research*. 2003; 118(2):129–136. doi:10.1016/S0165-1781(03)00070-2. [PubMed: 12798977]
- Lehrer, J. The truth wears off: Is there something wrong with the scientific method?. *The New Yorker*. 2010. Retrieved from http://www.newyorker.com/reporting/2010/12/13/101213fa_fact_lehrer?currentPage=all
- *. LeMarquand DG, Benkelfat C, Pihl RO, Palmour RM, Young SN. Behavioral disinhibition induced by tryptophan depletion in nonalcoholic young men with multigenerational family histories of paternal alcoholism. *The American Journal of Psychiatry*. 1999; 156(11):1771–9. [PubMed: 10553742]
- Lester D. The concentration of neurotransmitter metabolites in the cerebrospinal fluid of suicidal individuals: A meta-analysis. *Pharmacopsychiatry*. 1995; 28(2):45–50. doi:10.1055/s-2007-979587. [PubMed: 7542785]
- Levine TR, Asada KJ, Carpenter C. Sample sizes and effect sizes are negatively correlated in meta-analyses: Evidence and implications of a publication bias against nonsignificant findings. *Communication Monographs*. 2009; 76:286–302. doi:10.1080/03637750903074685.
- *. Limson R, Goldman D, Roy A, Lamparski D, Ravitz B, Adinoff B, Linnoila M. Personality and cerebrospinal fluid monoamine metabolites in alcoholics and controls. *Archives of General Psychiatry*. 1991; 48(5):437–441. doi:10.1001/archpsyc.1991.01810290049010. [PubMed: 1708656]
- *. Lindenmayer J, Adityanjee MV, Bark N, Grochowski S, Moynihan N. Heterogeneity of serotonergic response in treatment-refractory schizophrenia patients. *Biological Psychiatry*. 1997; 42(1):6–12. doi:10.1016/S0006-3223(96)00296-X. [PubMed: 9193736]
- *. Linnoila M, Stapleton JM, George DT, Lane E, Eckardt MJ. Effects of fluvoxamine, alone and in combination with ethanol, on psychomotor and cognitive performance and on autonomic nervous system reactivity in healthy volunteers. *Journal of Clinical Psychopharmacology*. 1993; 13(3):175–180. doi:10.1097/00004714-199306000-00004. [PubMed: 8354733]

- *. Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimón R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sciences*. 1983; 33:2609–2614. doi:10.1016/0024-3205(83)90344-2. [PubMed: 6198573]
- Lipsey, MW.; Wilson, DB. *Practical meta-analysis*. Sage; Thousand Oaks, CA: 2001.
- *. Lopez O, Kaufer D, Reiter C, Carra J, DeKosky S, Palmer A. Relationship between CSF neurotransmitter metabolites and aggressive behavior in Alzheimer's disease. *European Journal of Neurology*. 1996; 3(2):153–155. doi:10.1111/j.1468-1331.1996.tb00209.x.
- Lykken DT. Statistical significance in psychological research. *Psychological Bulletin*. 1968; 70(3): 151–159. doi:10.1037/h0026141. [PubMed: 5681305]
- Maguire K, Cheung P, Crowley K, Norman T, Schweitzer I, Burrows G. Aggressive behaviour and platelet 3H-paroxetine binding in schizophrenia. *Schizophrenia Research*. 1997; 23(1):61–67. doi: 10.1016/S0920-9964(96)00092-8.
- *. Mannelli P, Patkar A, Peindl K, Tharwani H, Gopalakrishnan R, Hill K, Berrettini W. Polymorphism in the serotonin transporter gene and moderators of prolactin response to meta-chlorophenylpiperazine in African-American cocaine abusers and controls. *Psychiatry Research*. 2006; 144(2-3):99–108. doi:10.1016/j.psychres.2006.01.012. [PubMed: 17000009]
- *. Manuck SB, Flory JD, McCaffery JM, Matthews K. a. Mann JJ, Muldoon MF. Aggression, impulsivity, and central nervous system serotonergic responsivity in a nonpatient sample. *Neuropsychopharmacology*. 1998; 19(4):287–299. [PubMed: 9718592]
- *. Manuck S, Flory J, Ferrell R, Mann J, Muldoon M. A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. *Psychiatry Research*. 2000; 95(1):9–23. doi:10.1016/S0165-1781(00)00162-1. [PubMed: 10904119]
- *. Manuck S, Flory J, Muldoon M, Ferrell R. Central nervous system serotonergic responsivity and aggressive disposition in men. *Physiology & Behavior*. 2002; 77(4-5):705–709. doi:10.1016/S0031-9384(02)00922-8. [PubMed: 12527023]
- Marazziti D, Conti L. Aggression, hyperactivity and platelet imipramine binding. *Acta Psychiatrica Scandinavica*. 1991; 84(3):209–211. [PubMed: 1659117]
- *. Marks DJ, Miller SR, Schulz KP, Newcorn JH, Halperin JM. The interaction of psychosocial adversity and biological risk in childhood aggression. *Psychiatry Research*. 2007; 151(3):221–230. doi:10.1016/j.psychres.2006.07.010. [PubMed: 17408754]
- *. Marsh DM, Dougherty DM, Moeller FG, Swann AC, Spiga R. Laboratory-measured aggressive behavior of women: Acute tryptophan depletion and augmentation. *Neuropsychopharmacology*. 2002; 26(5):660–671. doi:10.1016/S0893-133X(01)00369-4. [PubMed: 11927191]
- Martin R, Watson D, Wan CK. A three-factor model of trait anger: Dimensions of affect, behavior, and cognition. *Journal of Personality*. 2000; 68(5):869–897. doi:10.1111/1467-6494.00119. [PubMed: 11001152]
- *. Massey AE, Marsh V, McAllister-Williams R. Lack of effect of tryptophan depletion on the loudness dependency of auditory event related potentials in healthy volunteers. *Biological Psychology*. 2004; 65(2):137–145. doi:10.1016/j.biopsycho.2003.03.001. [PubMed: 14706436]
- *. McCann UD, Ridenour A, Shaham Y, Ricaurte GA. Serotonin neurotoxicity after (+/-)3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"): A controlled study in humans. *Neuropsychopharmacology*. 1994; 10(2):129–138. [PubMed: 7517677]
- *. McCloskey MS, Berman ME, Echevarria DJ, Coccaro EF. Effects of acute alcohol intoxication and paroxetine on aggression in men. *Alcoholism, Clinical and Experimental Research*. 2009; 33(4): 581–590. doi:10.1111/j.1530-0277.2008.00872.x.
- Meehl PE. Why summaries of research on psychological theories are often uninterpretable. *Psychological Reports*. 1990; 66(1) doi:10.2466/PR.66.1.195-244.
- Mendelsohn D, Riedel WJ, Sambeth A. Effects of acute tryptophan depletion on memory, attention and executive functions: A systematic review. *Neuroscience and Biobehavioral Reviews*. 2009; 33(6):926–952. doi:10.1016/j.neubiorev.2009.03.006. [PubMed: 19428501]

- *. Menkes D, Coates D, Fawcett J. Acute tryptophan depletion aggravates premenstrual syndrome. *Journal of Affective Disorders*. 1994; 32(1):37–44. doi:10.1016/0165-0327(94)90059-0. [PubMed: 7798465]
- *. Minzenberg MJ, Grossman R, New AS. Blunted hormone responses to ipsapirone are associated with trait impulsivity in personality disorder patients. *Neuropsychopharmacology*. 2006; 31(1): 197–203. doi:10.1038/sj.npp.1300853. [PubMed: 16123761]
- *. Moeller FG, Allen T, Cherek DR, Dougherty DM, Lane S, Swann AC. Ipsapirone neuroendocrine challenge: Relationship to aggression as measured in the human laboratory. *Psychiatry Research*. 1998; 81(1):31–38. doi:10.1016/S0165-1781(98)00081-X. [PubMed: 9829648]
- *. Moeller FG, Dougherty DM, Swann AC, Collins D, Davis CM, Cherek DR. Tryptophan depletion and aggressive responding in healthy males. *Psychopharmacology*. 1996; 126(2):97–103. doi: 10.1007/BF02246343. [PubMed: 8856827]
- *. Møller SE, Mortensen EL, Breum L, Alling C, Larsen OG, Bøge-Rasmussen T, Bennicke K. Aggression and personality: Association with amino acids and monoamine metabolites. *Psychological Medicine*. 1996; 26(2):323–331. doi:10.1017/S0033291700034711. [PubMed: 8685288]
- Molloy JC. The Open Knowledge Foundation: Open data means better science. *PLoS Biology*. 2011; 9(12):e1001195. doi:10.1371/journal.pbio.1001195. [PubMed: 22162946]
- *. Monteleone P, Brambilla F, Bortolotti F, Maj M. Serotonergic dysfunction across the eating disorders: Relationship to eating behaviour, purging behaviour, nutritional status and general psychopathology. *Psychological Medicine*. 2000; 30(5):1099–1110. [PubMed: 12027046]
- *. Monteleone P, Brambilla F, Bortolotti F, Ferraro C, Maj M. Plasma prolactin response to D-fenfluramine is blunted in bulimic patients with frequent binge episodes. *Psychological Medicine*. 1998; 28(4):975–983. doi:10.1017/S0033291798006904. [PubMed: 9723152]
- Montoya ER, Terburg D, Bos PA, van Honk J. Testosterone, cortisol, and serotonin as key regulators of social aggression: A review and theoretical perspective. *Motivation and Emotion*. 2012; 36(1): 65–73. doi:10.1007/s11031-011-9264-3. [PubMed: 22448079]
- Moore P, Landolt H, Seifritz E, Clark C, Bhatti T, Kelsoe J, Gillin JC. Clinical and physiological consequences of rapid tryptophan depletion. *Neuropsychopharmacology*. 2000; 23(6):601–622. doi:10.1016/S0893-133X(00)00161-5. [PubMed: 11063917]
- Moore TM, Scarpa A, Raine A. A meta-analysis of serotonin metabolite 5-HIAA and antisocial behavior. *Aggressive Behavior*. 2002; 28(4):299–316. doi:10.1002/ab.90027.
- Moser PC, Tricklebank MD, Middlemiss DN, Mir AK, Hibert MF, Fozard JR. Characterization of MDL 73005EF as a 5-HT_{1A} selective ligand and its effects in animal models of anxiety: Comparison with buspirone, 8-OH-DPAT and diazepam. *British Journal of Pharmacology*. 1990; 99(2):343–349. doi:10.1111/j.1476-5381.1990.tb14706.x. [PubMed: 1970269]
- *. Moss H, Yao J, Panzak G. Serotonergic responsivity and behavioral dimensions in antisocial personality disorder with substance abuse. *Biological Psychiatry*. 1990; 28(4):325–338. doi: 10.1016/0006-3223(90)90660-T. [PubMed: 2397249]
- *. Mulder R, Joyce P. Relationship of temperament and behaviour measures to the prolactin response to fenfluramine in depressed men. *Psychiatry Research*. 2002; 109(3):221–228. doi:10.1016/S0165-1781(02)00018-5. [PubMed: 11959359]
- Müller-Oerlinghausen B, Roggenbach J, Franke L. Serotonergic platelet markers of suicidal behavior —do they really exist? *Journal of Affective Disorders*. 2004; 79(1-3):13–24. doi:10.1016/S0165-0327(02)00367-1. [PubMed: 15023476]
- Murphy DL, Aulakh C, Mazzola-Pomietto P, Briggs NC. Neuroendocrine responses to serotonergic agonists as indices of the functional status of central serotonin neurotransmission in humans: A preliminary comparative analysis of neuroendocrine endpoints versus other endpoint measures. *Behavioural Brain Research*. 1996; 73(1-2):209–214. doi:10.1016/0166-4328(96)00098-8. [PubMed: 8788504]
- *. Netter P, Hennig J, Rohrmann S. Psychobiological differences between the aggression and psychoticism dimension. *Pharmacopsychiatry*. 1999; 32(1):5–12. doi:10.1055/s-2007-979182. [PubMed: 10071177]

- *. Netter, P.; Reuter, M.; Felger, K. Serotonergic stimulation, psychoticism, and experimentally induced aggression. Germany: 2006. Unpublished manuscript
- *. New A, Trestman R, Mitropoulou V, Goodman M, Koenigsberg H, Silverman J, Siever L. Low prolactin response to fenfluramine in impulsive aggression. *Journal of Psychiatric Research*. 2004; 38(3):223–230. doi: 10.1016/j.jpsychires.2003.09.001. [PubMed: 15003426]
- Nordin C, Lindström L, Wieselgren IM. Acid monoamine metabolites in the CSF of healthy controls punctured without preceding strict bedrest: A retrospective study. *Journal of Psychiatric Research*. 1996; 30(2):127–133. doi:10.1016/0022-3956(95)00038-0. [PubMed: 8816306]
- Nordin C, Swedin A, Zachau A. CSF 5-HIAA and atmospheric pressure. *Biological Psychiatry*. 1992; 31(6):644–645. doi:10.1016/0006-3223(92)90255-X. [PubMed: 1374652]
- Olivier B, van Oorschot R. 5-HT_{1B} receptors and aggression: A review. *European Journal of Pharmacology*. 2005; 526(1-3):207–217. doi:10.1016/j.ejphar.2005.09.066.
- Orwin RG, Cordray DS. Effects of deficient reporting on meta-analysis: A conceptual framework and reanalysis. *Psychological Bulletin*. 1985; 97:134–149. doi:10.1037/0033-2909.97.1.134. [PubMed: 3983295]
- *. Paris J, Zweig-Frank H, Kin NNY, Schwartz G, Steiger H, Nair N. Neurobiological correlates of diagnosis and underlying traits in patients with borderline personality disorder compared with normal controls. *Psychiatry Research*. 2004; 121:239–252. doi:10.1016/j.biopsych.2011.07.033. [PubMed: 14675743]
- Parsey RV, Oquendo MA, Simpson NR, Ogden RT, Heertum RV, Arango V, Mann JJ. Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT_{1A} receptor binding potential measured by PET using [¹¹C]-WAY-100635. *Brain Research*. 2002; 954(2):173–182. doi:10.1016/S0006-8993(02)03243-2. [PubMed: 12414100]
- Passamonti L, Crockett MJ, Apergis-Schoute AM, Clark L, Rowe JB, Calder AJ, Robbins TW. Effects of acute tryptophan depletion on prefrontal-amygdala connectivity while viewing facial signals of aggression. *Biological Psychiatry*. 2012; 71(1):36–43. doi:10.1016/j.biopsych.2011.07.033. [PubMed: 21920502]
- *. Patkar AA, Mannelli P, Peindl K, Hill KP, Gopalakrishnan R, Berrettini WH. Relationship of disinhibition and aggression to blunted prolactin response to meta-chlorophenylpiperazine in cocaine-dependent patients. *Psychopharmacology*. 2006; 185(1):123–132. doi: 10.1007/s00213-005-0261-7. [PubMed: 16418827]
- Peng RD. Reproducible research and biostatistics. *Biostatistics*. 2009; 10(3):405–408. doi:10.1093/biostatistics/kxp014. [PubMed: 19535325]
- Peng RD. Reproducible research in computational science. *Science*. Dec; 2011 334(6060):1226–1227. doi:10.1126/science.1213847. [PubMed: 22144613]
- Pettibone DJ, Williams M. Serotonin-releasing effects of substituted piperazines in vitro. *Biochemical Pharmacology*. 1984; 33(9):1531–1535. doi:10.1016/0006-2952(84)90424-6. [PubMed: 6610423]
- Pigott, TD. Handling missing data. In: Cooper, H.; Hedges, LV.; Valentine, JC., editors. *The handbook of research synthesis and meta-analysis*. 2nd. Russell Sage Foundation; New York: 2009. p. 399-416.
- *. Pihl RO, Young SN, Harden P, Plotnick S, Chamberlain B, Ervin FR. Acute effect of altered tryptophan levels and alcohol on aggression in normal human males. *Psychopharmacology*. 1995; 119(4):353–60. doi: 10.1007/BF02245849. [PubMed: 7480513]
- *. Pine DS, Coplan JD, Wasserman GA, Miller LS, Fried JE, Davies M, Parsons B. Neuroendocrine response to fenfluramine challenge in boys: Associations with aggressive behavior and adverse rearing. *Archives of General Psychiatry*. 1997; 54(9):839–846. doi: 10.1001/archpsyc.1997.01830210083010. [PubMed: 9294375]
- *. Placidi G, Oquendo M, Malone K, Huang Y, Ellis S, Mann J. Aggressivity, suicide attempts, and depression: Relationship to cerebrospinal fluid monoamine metabolite levels. *Biological Psychiatry*. 2001; 50(10):783–791. doi: 10.1016/S0006-3223(01)01170-2. [PubMed: 11720697]
- *. Post RM, Rubinow DR, Uhde TW, Roy-Byrne PP, Linnoila M, Rosoff A, Cowdry R. Dysphoric mania. Clinical and biological correlates. *Archives of General Psychiatry*. 1989; 46(4):353–358. doi:10.1001/archpsyc.1989.01810040059009. [PubMed: 2930331]

- *. Prochazka H, Ågren H. Self-rated aggression and cerebral monoaminergic turnover: Sex differences in patients with persistent depressive disorder. *European Archives of Psychiatry and Clinical Neuroscience*. 2003; 253(4):185–192. doi:10.1007/s00406-003-0423-8. [PubMed: 12910349]
- Quadros, IM.; Takahashi, A.; Miczek, KA. Serotonin and aggression. In: Muller, CP.; Jacobs, BL., editors. *Handbook of the behavioural neurobiology of serotonin*. Academic Press; Waltham, Massachusetts: 2009. p. 687-713.
- Raine A. From genes to brain to antisocial behavior. *Current Directions in Psychological Science*. 2008; 17(5):323–328. doi:10.1111/j.1467-8721.2008.00599.x.
- *. Ravindran AV, Griffiths J, Merali Z, Knott VJ, Anisman H. Influence of acute tryptophan depletion on mood and immune measures in healthy males. *Psychoneuroendocrinology*. 1999; 24(1):99–113. doi:10.1016/S0306-4530(98)00040-7. [PubMed: 10098222]
- Reilly JG, McTavish SF, Young AH. Rapid depletion of plasma tryptophan: A review of studies and experimental methodology. *Journal of Psychopharmacology*. 1997; 11(4):381–392. doi:10.1177/026988119701100416. [PubMed: 9443529]
- *. Richell RA, Deakin JFW, Anderson IM. Effect of acute tryptophan depletion on the response to controllable and uncontrollable noise stress. *Biological Psychiatry*. 2005; 57(3):295–300. doi:10.1016/j.biopsych.2004.10.010. [PubMed: 15691531]
- Rosenthal R. The file drawer problem and tolerance for null results. *Psychological Bulletin*. 1979; 86(3):638–641. doi:10.1037/0033-2909.86.3.638.
- *. Roy A, Adinoff B, Linnoila M. Acting out hostility in normal volunteers: Negative correlation with levels of 5HIAA in cerebrospinal fluid. *Psychiatry Research*. 1988; 24(2):187–194. doi:10.1016/0165-1781(88)90061-3. [PubMed: 2457227]
- *. Rubia K, Lee F, Cleare AJ, Tunstall N, Fu CHY, Brammer M, McGuire P. Tryptophan depletion reduces right inferior prefrontal activation during response inhibition in fast, event-related fMRI. *Psychopharmacology*. 2005; 179(4):791–803. doi:10.1007/s00213-004-2116-z. [PubMed: 15887056]
- Ruhé HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: A meta-analysis of monoamine depletion studies. *Molecular Psychiatry*. 2007; 12(4):331–359. doi:10.1038/sj.mp.4001949. [PubMed: 17389902]
- *. Rydén E, Johansson C, Blennow K, Landén M. Lower CSF HVA and 5-HIAA in bipolar disorder type 1 with a history of childhood ADHD. *Journal of Neural Transmission*. 2009; 116(12):1667–1674. doi:10.1007/s00702-009-0300-3. [PubMed: 19756368]
- *. Salomon RM, Mazure CM, Delgado PL, Mendia P, Charney DS. Serotonin function in aggression: The effect of acute plasma tryptophan depletion in aggressive patients. *Biological Psychiatry*. 1994; 35(8):570–572. doi:10.1016/0006-3223(94)90105-8. [PubMed: 8038301]
- *. Salomon RM, Miller HL, Krystal JH, Heninger GR, Charney DS. Lack of behavioral effects of monoamine depletion in healthy subjects. *Biological Psychiatry*. 1997; 41(1):58–64. doi:10.1016/0006-3223(95)00670-2. [PubMed: 8988796]
- Sambeth A, Blokland A, Harmer CJ, Kilkens TOC, Nathan PJ, Porter RJ, Riedel WJ. Sex differences in the effect of acute tryptophan depletion on declarative episodic memory: A pooled analysis of nine studies. *Neuroscience and Biobehavioral Reviews*. 2007; 31(4):516–529. [PubMed: 17229463]
- Schipper J, Tulp MT, Sijbesma H. Neurochemical profile of eltoprazine. *Drug Metabolism and Drug Interactions*. 1990; 8(1-2):85–114. doi:10.1515/DMDI.1990.8.1-2.85. [PubMed: 1982626]
- *. Schmeck K, Sadigorsky S, Englert E, Demisch L, Dierks T, Barta S, Poustka F. Mood changes following acute tryptophan depletion in healthy adults. *Psychopathology*. 2002; 35(4):234–240. doi:10.1159/000063827. [PubMed: 12239440]
- *. Schulz KP, Newcorn JH, Schmeidler J, Halperin JM. Lack of seasonal rhythms in central serotonergic function in boys with ADHD. *Psychoneuroendocrinology*. 2002; 27(4):463–473. doi:10.1016/S0306-4530(01)00063-4. [PubMed: 11911999]
- Seifert WE, Foxx JL, Butler IJ. Age effect on dopamine and serotonin metabolite levels in cerebrospinal fluid. *Annals of Neurology*. 1980; 8(1):38–42. [PubMed: 6157351]

- Shadish, WR.; Haddock, CK. Combining estimates of effect size. In: Cooper, H.; Hedges, LV.; Valentine, JC., editors. *The handbook of research synthesis and meta-analysis*. 2nd. Russell Sage Foundation; New York: 2009. p. 257-277.
- *. Sher L, Oquendo MA, Li S, Burke AK, Grunebaum MF, Zalsman G, Mann JJ. Higher cerebrospinal fluid homovanillic acid levels in depressed patients with comorbid posttraumatic stress disorder. *European Neuropsychopharmacology*. 2005; 15(2):203–209. doi:10.1016/j.euroneuro.2004.09.009. [PubMed: 15695066]
 - *. Sher L, Oquendo MA, Li S, Huang Y, Grunebaum MF, Burke AK, Mann JJ. Lower CSF homovanillic acid levels in depressed patients with a history of alcoholism. *Neuropsychopharmacology*. 2003; 28(9):1712–1719. doi:10.1038/sj.npp.1300231. [PubMed: 12825091]
 - *. Sher L, Oquendo M, Li S, Ellis S, Brodsky B, Malone K, Mann J. Prolactin response to fenfluramine administration in patients with unipolar and bipolar depression and healthy controls. *Psychoneuroendocrinology*. 2003; 28(4):559–573. doi:10.1016/S0306-4530(02)00040-9. [PubMed: 12689612]
 - *. Sher L, Stanley B, Cooper T, Malone K, Mann J, Oquendo M. Serotonergic responses in depressed patients with or without a history of alcohol use disorders and healthy controls. *European Neuropsychopharmacology*. 2008; 18(9):692–699. doi:10.1016/j.euroneuro.2008.05.005. [PubMed: 18590952]
- Silber BY, Schmitt JAJ. Effects of tryptophan loading on human cognition, mood, and sleep. *Neuroscience and Biobehavioral Reviews*. 2010; 34(3):387–407. [PubMed: 19715722]
- *. Simeon D, Stanley B, Frances A, Mann J, Winchel R, Stanley M. Self-mutilation in personality disorders: Psychological and biological correlates. *The American Journal of Psychiatry*. 1992; 149(2):221–226. [PubMed: 1734743]
- Simonsohn, U. Just post it: The lesson from two cases of fabricated data detected by statistics alone. 2012. Retrieved from <http://ssrn.com/abstract=2114571>
- *. Smith SE, Pihl RO, Young SN, Ervin FR. Elevation and reduction of plasma tryptophan and their effects on aggression and perceptual sensitivity in normal males. *Aggressive Behavior*. 1986; 12(6):393–407. doi:10.1002/1098-2337(1986)12:6<393::AID-AB2480120602>3.0.CO;2-L.
 - *. Smith S, Pihl R, Young S, Ervin F. A test of possible cognitive and environmental influences on the mood lowering effect of tryptophan depletion in normal males. *Psychopharmacology*. 1987; 91(4):451–457. doi:10.1007/BF00216010. [PubMed: 3108925]
- Sobczak S, Honig A, van Duinen MA, Riedel WJ. Serotonergic dysregulation in bipolar disorders: A literature review of serotonergic challenge studies. *Bipolar Disorder*. 2002; 4(6):347–356.
- *. Soderstrom H, Blennow K, Manhem A, Forsman A. CSF studies in violent offenders I: 5-HIAA as a negative and HVA as a positive predictor of psychopathy. *Journal of Neural Transmission*. 2001; 108(7):869–878. doi:10.1007/s007020170036. [PubMed: 11515752]
 - *. Soderstrom H, Blennow K, Sjodin AK, Forsman A. New evidence for an association between the CSF HVA:5-HIAA ratio and psychopathic traits. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2003; 74(7):918–921. doi:10.1136/jnnp.74.7.918.
 - *. Soloff PH, Kelly TM, Strotmeyer SJ, Malone KM, Mann JJ. Impulsivity, gender, and response to fenfluramine challenge in borderline personality disorder. *Psychiatry Research*. 2003; 119(1-2): 11–24. doi:10.1016/S0165-1781(03)00100-8. [PubMed: 12860356]
 - *. Soloff P, Lynch K, Moss H. Serotonin, impulsivity, and alcohol use disorders in the older adolescent: A psychobiological study. *Alcoholism: Clinical and Experimental Research*. 2000; 24(11):1609–1619. doi:10.1111/j.1530-0277.2000.tb01961.x.
- Stadler C, Zepf FD, Demisch L, Schmitt M, Landgraf M, Poustka F. Influence of rapid tryptophan depletion on laboratory-provoked aggression in children with ADHD. *Neuropsychobiology*. 2007; 56(2-3):104–110. [PubMed: 18182830]
- *. Stanislav SW, Crismon ML, Childs NL. Cerebrospinal fluid monoamine metabolites and glucose metabolism in posttraumatic aggression. *Biological Psychiatry*. 1998; 43(8):619–621. doi: 10.1016/S0006-3223(97)00405-8. [PubMed: 9564449]

- *. Stanley B. Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. *American Journal of Psychiatry*. 2000; 157(4):609–614. doi:10.1176/appi.ajp.157.4.609. [PubMed: 10739421]
- Steiger H, Gauvin L, Israël M, Kin NY, Young SN, Roussin J. Serotonin function, personality-trait variations, and childhood abuse in women with bulimia-spectrum eating disorders. *Journal of Clinical Psychiatry*. 2004; 65(6):830–837. [PubMed: 15291661]
- Stein DJ, Westenberg HGM, Liebowitz MR. Social anxiety disorder and generalized anxiety disorder: Serotonergic and dopaminergic neurocircuitry. *Journal of Clinical Psychiatry*. 2002; 63(Supplement 6):12–19. [PubMed: 12027115]
- *. Stein D, Trestman R, Mitropoulou V, Coccaro E, Hollander E, Siever L. Impulsivity and serotonergic function in compulsive personality disorder. *Journal of Neuropsychiatry and Clinical Neurosciences*. 1996; 8(4):393–398. [PubMed: 9116474]
- *. Stoff D, Pasatiempo A, Yeung J, Cooper T, Bridger W, Rabinovich H. Neuroendocrine responses to challenge with dl-fenfluramine and aggression in disruptive behavior disorders of children and adolescents. *Psychiatry Research*. 1992; 43(3):263–276. doi:10.1016/0165-1781(92)90059-C. [PubMed: 1438624]
- Strömbom U, Krotkiewski M, Blennow K, Månsson JE, Ekman R, Björntorp P. The concentrations of monoamine metabolites and neuropeptides in the cerebrospinal fluid of obese women with different body fat distribution. *International Journal of Obesity and Metabolic Disorders*. 1996; 20(4):361–368.
- Su Y, Gelman A, Hill J, Yajima M. Multiple imputation with diagnostics (mi) in R: Opening windows into the black box. *Journal of Statistical Software*. 2011; 45(2):1–31.
- Sutton, AJ. Publication bias. In: Cooper, H.; Hedges, LV.; Valentine, JC., editors. *The handbook of research synthesis and meta-analysis*. 2nd. Russell Sage Foundation; New York: 2009. p. 435–452.
- Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *British Medical Journal*. 2000; 320(7249):1574–1577. doi: 10.1136/bmj.320.7249.1574. [PubMed: 10845965]
- Takeuchi Y, Matsushita H, Sakai H, Kawano H, Yoshimoto K, Sawada T. Developmental changes in cerebrospinal fluid concentrations of monoamine-related substances revealed with a Coulochem electrode array system. *Journal of Child Neurology*. 2000; 15(4):267–270. doi: 10.1177/088307380001500415. [PubMed: 10805197]
- Thorndike, EL. *Notes on child study*. Macmillan; New York: 1903.
- Tops M, Russo S, Boksem MAS, Tucker DM. Serotonin: Modulator of a drive to withdraw. *Brain and Cognition*. 2009; 71(3):427–436. doi:10.1016/j.bandc.2009.03.009. [PubMed: 19423206]
- Tremblay, RE. Aggression, prosocial behavior, and gender: Three magic words but no magic wand. In: Pepler, DJ.; Rubin, KH., editors. *The development and treatment of childhood aggression*. Lawrence Erlbaum Associates; Hillsdale, NJ: 1991. p. 71–78.
- Tuinier S, Verhoeven WMA, van Praag HM. CSF 5-HIAA and aggression: A critical reappraisal of the clinical data. *International Clinical Psychopharmacology*. 1995; 10(3):147–156. doi: 10.1097/00004850-199510030-00003. [PubMed: 8675967]
- Tuinier S, Verhoeven WMA, van Praag HM. Serotonin and disruptive behaviour: A critical evaluation of the clinical data. *Human Psychopharmacology*. 1996; 11(6):469–482. doi:10.1002/(SICI)1099-1077(199611)11:6<469::AID-HUP817>3.0.CO;2-X.
- Van der Does AJ. The effects of tryptophan depletion on mood and psychiatric symptoms. *Journal of Affective Disorders*. 2001; 64(2-3):107–119. doi:10.1016/S0165-0327(00)00209-3. [PubMed: 11313078]
- van der Vegt BJ, Lieuwes N, Cremers TI, de Boer SF, Koolhaas JM. Cerebrospinal fluid monoamine and metabolite concentrations and aggression in rats. *Hormones and Behavior*. 2003; 44(3):199–208. doi:10.1016/S0018-506X(03)00132-6. [PubMed: 14609542]
- van Erp AM, Miczek KA. Aggressive behavior, increased accumbal dopamine, and decreased cortical serotonin in rats. *The Journal of Neuroscience*. 2000; 20(24):9320–9325. [PubMed: 11125011]

- Vassar M, Hale W. Reliability reporting across studies using the Buss Durkee Hostility Inventory. *Journal of Interpersonal Violence*. 2009; 24(1):20–37. doi:10.1177/0886260508314931. [PubMed: 18378813]
- Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*. 2010; 36(3):1–48.
- *. Virkkunen M, Linnoila M. Brain serotonin, type II alcoholism and impulsive violence. *Journal of Studies on Alcohol*. 1993; (Supplement 11):163–169.
 - *. Virkkunen M, Eggert M, Rawlings R, Linnoila M. A prospective follow-up study of alcoholic violent offenders and fire setters. *Archives of General Psychiatry*. 1996; 53(6):523–529. doi: 10.1001/archpsyc.1996.01830060067009. [PubMed: 8639035]
 - *. Virkkunen M, Rissanen A, Naukkarinen H, Franssila-Kallunki A, Linnoila M, Tiihonen J. Energy substrate metabolism among habitually violent alcoholic offenders having antisocial personality disorder. *Psychiatry Research*. 2007; 150(3):287–295. doi:10.1016/j.psychres.2006.01.013. [PubMed: 17316826]
- Völlm B, Richardson P, McKie S, Reniers R, Elliott R, Anderson IM, Deakin B. Neuronal correlates and serotonergic modulation of behavioural inhibition and reward in healthy and antisocial individuals. *Journal of Psychiatric Research*. 2010; 44(3):123–131. doi:10.1016/j.jpsychires.2009.07.005. [PubMed: 19683258]
- Wampold BE, Moody GW, Stich F, Benson K, Ahn H. A meta-analysis of outcome studies comparing bona fide psychotherapies: Empirically, “all have won and all must have prizes”. *Psychological Bulletin*. 1997; 122(3):203–215. doi:10.1037/0033-2909.122.3.203.
- *. Wingrove, J. Doctoral dissertation. Institute of Psychiatry, King’s College, University of London; 2005. Serotonergic mechanisms in human aggression.
 - *. Wingrove J, Bond a. J. Cleare a. J. Tryptophan enhancement/depletion and reactions to failure on a cooperative computer game. *Neuropsychopharmacology*. 1999; 21(6):755–764. [PubMed: 10633481]
 - *. Wingrove J, Bond a. J. Cleare a. J. Sherwood R. Trait hostility and prolactin response to tryptophan enhancement/depletion. *Neuropsychobiology*. 1999; 40(4):202–206. doi:10.1016/S0893-133X(99)00078-0. [PubMed: 10559703]
- Witte AV, Flöel A, Stein P, Savli M, Mien L, Wadsak W, Lanzenberger R. Aggression is related to frontal serotonin-1A receptor distribution as revealed by PET in healthy subjects. *Human Brain Mapping*. 2009; 30(8):2558–2570. doi:10.1002/hbm.20687. [PubMed: 19086022]
- *. Wood RM, Rilling JK, Sanfey AG, Bhagwagar Z, Rogers RD. Effects of tryptophan depletion on the performance of an iterated prisoner’s dilemma game in healthy adults. *Neuropsychopharmacology*. 2006; 31(5):1075–1084. doi:10.1038/sj.npp.1300932. [PubMed: 16407905]
- Yanowitch R, Coccaro EF. The neurochemistry of human aggression. *Advances in Genetics*. 2011; 75:151–169. doi:10.1016/B978-0-12-380858-5.00005-8. [PubMed: 22078480]
- *. Yatham LN. Effects of rapid tryptophan depletion on brain 5-HT₂ receptors: A PET study. *The British Journal of Psychiatry*. 2001; 178(5):448–453. doi:10.1192/bjp.178.5.448. [PubMed: 11331561]
 - *. Young SN, Smith S, Pihl RO, Ervin FR. Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacology*. 1985; 87(2):173–177. doi:10.1007/BF00431803. [PubMed: 3931142]
 - *. Zepf FD, Stadler C, Demisch L, Schmitt M, Landgraf M, Poustka F. Serotonergic functioning and trait-impulsivity in attention-deficit/hyperactivity-disordered boys (ADHD): Influence of rapid tryptophan depletion. *Human Psychopharmacology: Clinical and Experimental*. 2008; 23(1):43–51. doi:10.1002/hup.896. [PubMed: 17926336]

Figure 1.
Literature search flow chart.

Figure 2.
Forest plot of CSF 5-HIAA effect sizes with 95% confidence intervals.

Figure 3.
Funnel plots with pseudo 95% confidence limits.

Figure 4.
 Forest plot of ATD effect sizes with 95% confidence intervals.

Figure 5.
 Forest plot of pharmacological challenge effect sizes with 95% confidence intervals.

Figure 6.
Forest plot of endocrine challenge study effect sizes with 95% confidence intervals.

Table 1

Tests of Weighted Regression Models for CSF 5-HIAA Moderators

Moderator	Methodological Variables							
	Univariate Effects				Simultaneous Effects (k = 51)			
	B	SE	z	95% CI	p	B	SE	z
Intercept						-0.12	0.09	-0.88
Sample Size	-0.00	0.00	-0.19	[-0.00, 0.00]	0.690	-0.00	0.00	-0.87
Year Published	0.02	0.01	0.99	[0.01, 0.03]	0.007	0.02	0.01	0.99
Design	0.06	0.11	0.46	[-0.17, 0.28]	0.551	0.09	0.11	0.66
Quality	-0.05	0.04	-0.82	[-0.14, 0.04]	0.246	-0.03	0.06	-0.42
Demographic Variables								
Univariate Effects				Simultaneous Effects (k = 45)				
Intercept						-0.22	0.21	-0.78
Percent Female	0.05	0.05	0.73	[-0.06, 0.15]	0.345	0.05	0.06	0.69
Mean Age	0.00	0.01	0.67	[-0.01, 0.02]	0.402	0.01	0.01	0.73
Aggression Hx	-0.01	0.12	-0.10	[-0.26, 0.23]	0.728	0.07	0.14	0.49
Psychopathology	0.11	0.20	0.49	[-0.29, 0.47]	0.533	0.13	0.21	0.55

Note. Summary statistics for simultaneous test of methodological moderators: $R^2 = 0.359$, $QM = 3.07$, $p < .05$, $\tau^2_{SE} = 0.02$, $QE = 69.15$, $p < .001$. Summary statistics for simultaneous test of demographic moderators: $R^2 = 0.206$, $QM = 0.50$, $p = 0.73$, $\tau^2_{SE} = 0.061$, $QE = 95.69$, $p < .001$. Hx = history, b = unstandardized regression coefficient, SE = standard error, z = critical ratio test for the weighted coefficient, CI = confidence interval, p = two-tailed probability of z, k = number of samples included in the analyses, QM = test of whether moderators account for a significant amount of the variability in effect sizes, τ^2 = random-variance component, QE = test of residual heterogeneity.

Table 2

Tests of Weighted Regression Models for ATD Moderators

Moderator	Methodological Variables									
	Univariate Effects					Simultaneous Effects ($k = 37$)				
	<i>B</i>	<i>SE</i>	<i>z</i>	95% <i>CI</i>	<i>p</i>	<i>B</i>	<i>SE</i>	<i>z</i>	95% <i>CI</i>	<i>p</i>
Intercept						−0.28	0.26	−0.79	[−0.68, 0.25]	0.284
Sample Size	0.00	0.00	0.55	[−0.00, 0.00]	0.493	−0.00	0.00	−0.29	[−0.00, 0.00]	0.645
Year Published	0.01	0.01	0.66	[−0.01, 0.02]	0.404	0.01	0.01	0.78	[−0.01, 0.02]	0.298
Design	−0.08	0.09	−0.74	[−0.25, 0.09]	0.331	−0.12	0.12	−0.78	[−0.36, 0.12]	0.298
Quality	−0.00	0.04	−0.07	[−0.09, 0.08]	0.736	0.00	0.04	0.04	[−0.09, 0.09]	0.747
Masking	0.17	0.10	0.93	[−0.04, 0.36]	0.106	0.13	0.12	0.80	[−0.11, 0.36]	0.273
Provocation	−0.03	0.10	−0.30	[−0.22, 0.16]	0.639	−0.00	0.10	−0.05	[−0.21, 0.20]	0.745
ATD-specific Methodological Variables										
Univariate Effects					Simultaneous Effects ($k = 38$)					
Intercept						0.01	0.31	0.03	[−0.53, 0.54]	0.753
Control Trp (g)	−0.00	0.01	−0.02	[−0.03, 0.03]	0.753	−0.00	0.02	−0.23	[−0.03, 0.03]	0.671
Depletion Mixture (g)	0.00	0.00	0.39	[−0.00, 0.00]	0.593	0.00	0.00	0.28	[−0.01, 0.01]	0.650
Control Mixture (g)	0.00	0.00	0.31	[−0.00, 0.00]	0.636	−0.00	0.00	−0.03	[−0.01, 0.01]	0.753
Post-mixture Wait	−0.03	0.05	−0.63	[−0.13, 0.06]	0.433	−0.04	0.05	−0.64	[−0.14, 0.06]	0.421
Demographic Variables										
Univariate Effects					Simultaneous Effects ($k = 38$)					
Intercept						−0.10	0.06	−0.95	[−0.21, 0.01]	0.073
Percent Female	−0.04	0.04	−0.68	[−0.12, 0.05]	0.387	−0.04	0.05	−0.68	[−0.15, 0.07]	0.392
Mean Age	0.00	0.01	0.12	[−0.01, 0.02]	0.719	0.00	0.01	0.39	[−0.01, 0.02]	0.594
Aggression Hx	0.02	0.15	0.15	[−0.27, 0.31]	0.706	−0.01	0.16	−0.07	[−0.33, 0.31]	0.736
Psychopathology	−0.03	0.10	−0.27	[−0.23, 0.17]	0.654	−0.00	0.12	−0.03	[−0.24, 0.24]	0.752

Note. Summary statistics for simultaneous test of methodological moderators: $R^2 = 0.342$, $QM = 0.70$, $p = .65$, $2 = 0.033$, $\tau_{SE}^2 = 0.02$, $QE = 48.42$, $p < .05$. Summary statistics for simultaneous test of ATD-specific moderators: $R^2 = 0.254$, $QM = 0.75$, $p = 0.95$, $2 = 0.03$, $\tau_{SE}^2 = 0.02$, $QE = 54.66$, $p < .05$. Summary statistics for simultaneous test of demographic moderators: $R^2 = 0.285$, $QM = 0.21$, $p = 0.93$, $2 = 0.031$, $\tau_{SE}^2 = 0.02$, $QE = 54.78$, $p < .05$. Hx = history, b = unstandardized regression coefficient, SE = standard error, z = critical ratio test for the weighted coefficient, CI = confidence interval, p = two-tailed probability of z , k = number of samples included in the analyses, QM = test of whether moderators account for a significant amount of the variability in effect sizes, 2 = random-variance component, QE = test of residual heterogeneity.

Table 3

Tests of Weighted Regression Models for Endocrine Challenge (Prolactin) Moderators

Moderator	Methodological Variables									
	Univariate Effects					Simultaneous Effects (k = 51)				
	B	SE	z	95% CI	p	B	SE	z	95% CI	p
Intercept						-0.07	0.07	-0.71	[-0.21, 0.08]	0.364
Sample Size	-0.00	0.00	-0.62	[-0.00, 0.00]	0.443	0.00	0.00	0.45	[-0.00, 0.00]	0.559
Year Published	-0.01	0.01	-0.67	[-0.02, 0.01]	0.395	-0.01	0.01	-0.77	[-0.03, 0.01]	0.307
Design	-0.12	0.09	-0.89	[-0.29, 0.05]	0.163	-0.12	0.09	-0.88	[-0.28, 0.05]	0.173
Quality	-0.06	0.04	-0.90	[-0.14, 0.02]	0.153	-0.07	0.04	-0.93	[-0.14, 0.01]	0.102
Demographic Variables										
Univariate Effects										
Intercept						-0.27	0.13	-0.98	[-0.49, -0.03]	0.031
Percent Female	0.00	0.04	0.06	[-0.08, 0.09]	0.741	0.02	0.05	0.48	[-0.07, 0.11]	0.542
Mean Age	-0.00	0.00	-0.87	[-0.01, 0.00]	0.181	-0.00	0.00	-0.53	[-0.01, 0.01]	0.510
Aggression Hx	0.03	0.09	0.29	[-0.16, 0.21]	0.644	-0.00	0.11	-0.04	[-0.22, 0.21]	0.748
Psychopathology	0.16	0.13	0.85	[-0.10, 0.40]	0.209	0.16	0.14	0.80	[-0.13, 0.42]	0.276

Note. Summary statistics for simultaneous test of methodological moderators: $R^2 = 0.056$, $QM = 1.45$, $p = .23$, $\tau^2_{SE} = 0.01$, $QE = 101.85$, $p < .001$. Summary statistics for simultaneous test of demographic moderators: $R^2 = 0.168$, $QM = 1.91$, $p = 0.1$, $\tau^2_{SE} = 0.03$, $QE = 80.31$, $p < .001$. Hx = history, b = unstandardized regression coefficient, SE = standard error, z = critical ratio test for the weighted coefficient, CI = confidence interval, p = two-tailed probability of z, k = number of samples included in the analyses, QM = test of whether moderators account for a significant amount of the variability in effect sizes, τ^2 = random-variance component, QE = test of residual heterogeneity.

Table 4

Categorical Analysis of Drug Influence on Endocrine Response

Drug	Prolactin Response						
	<i>k</i>	<i>r</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% <i>CI</i>	<i>Q_W</i>
Ipsapirone	4	−0.06	0.15	−0.39	0.59	[−0.34, 0.23]	2.30
d,l-Fenfluramine	25	−0.10	0.05	−0.97	0.04	[−0.19, −0.01]	94.49
d-Fenfluramine	15	−0.21	0.07	−1.00	0.00	[−0.34, −0.08]	14.82
mCPP	9	−0.10	0.09	−0.81	0.25	[−0.27, 0.08]	8.47
Overall	53	−0.13	0.04	−1.00	0.00	[−0.19, −0.06]	124.43
Drug	Cortisol Response						
	<i>k</i>	<i>r</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% <i>CI</i>	<i>Q_W</i>
Ipsapirone	5	0.22	0.13	0.94	0.09	[−0.03, 0.45]	10.83
d,l-Fenfluramine	4	0.05	0.15	0.35	0.61	[−0.23, 0.33]	5.56
d-Fenfluramine	5	−0.09	0.13	−0.59	0.46	[−0.33, 0.17]	1.32
mCPP	6	0.06	0.12	0.45	0.56	[−0.18, 0.29]	14.41
Overall	20	0.06	0.07	0.74	0.33	[−0.07, 0.19]	37.30

Note. Heterogeneity test for between-groups prolactin response: $QB(3) = 2.12$, $p = 0.548$ and cortisol response: $QB(3) = 2.89$, $p = 0.408$. k = number of independent effect sizes, r = mean weighted effect size, SE = standard error of the mean weighted effect size, z = critical ratio test for the weighted correlation, CI = 95% confidence interval, p = two-tailed probability of z , QW = within-groups heterogeneity.

Table 5

Tests of Weighted Regression Models of Likely Moderators for All Studies

Moderator	Methodological Variables									
	Univariate Effects					Simultaneous Effects (k = 141)				
	B	SE	z	95% CI	p	B	SE	z	95% CI	p
Intercept						-0.09	0.04	-0.98	[-0.17, -0.01]	0.022
Sample Size	-0.00	0.00	-0.11	[-0.00, 0.00]	0.720	-0.00	0.00	-0.75	[-0.00, 0.00]	0.323
Year Published	0.01	0.00	0.96	[-0.00, 0.02]	0.050	0.01	0.00	0.95	[-0.00, 0.02]	0.069
Design	-0.05	0.05	-0.72	[-0.14, 0.05]	0.346	-0.05	0.05	-0.77	[-0.15, 0.05]	0.300
Quality	-0.05	0.02	-0.98	[-0.10, -0.01]	0.021	-0.05	0.02	-0.97	[-0.09, -0.00]	0.031
Demographic Variables										
Univariate Effects										
Intercept						-0.13	0.05	-0.99	[-0.22, 0.03]	0.008
Percent Female	0.02	0.02	0.62	[-0.03, 0.07]	0.439	0.02	0.03	0.56	[-0.04, 0.07]	0.482
Mean Age	-0.00	0.00	-0.64	[-0.01, 0.00]	0.418	-0.00	0.00	-0.73	[-0.01, 0.00]	0.337
Aggression Hx	-0.02	0.05	-0.31	[-0.12, 0.09]	0.636	-0.02	0.06	-0.38	[-0.14, 0.10]	0.598
Psychopathology	0.02	0.05	0.36	[-0.09, 0.13]	0.610	0.03	0.07	0.44	[-0.10, 0.16]	0.561

Note. Summary statistics for simultaneous test of methodological moderators: $R^2 = 0.136$, $QM = 2.63$, $p < .05$, $\tau^2_{SE} = 0.01$, $QE = 271.83$, $p < .001$. Summary statistics for simultaneous test of demographic moderators: $R^2 = 0.022$, $QM = 0.38$, $p = 0.82$, $\tau^2_{SE} = 0.038$, $QE = 306.65$, $p < .001$. b = unstandardized regression coefficient, SE = standard error, z = critical ratio test for the weighted coefficient, CI = confidence interval, p = two-tailed probability of z , k = number of samples included in the analyses, QM = test of whether moderators account for a significant amount of the variability in effect sizes, τ^2 = random-variance component, QE = test of residual heterogeneity.

Table 6

Comparison of Methods for Assessing Serotonergic Functioning

Method	<i>k</i>	<i>r</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% <i>CI</i>	<i>Q_w</i>
ATD	38	-0.10	0.05	-0.98	0.03	[-0.19, -0.01]	56.02
CSF 5-HIAA	34	-0.06	0.04	-0.88	0.16	[-0.15, 0.02]	97.61
Endocrine	57	-0.14	0.03	-1.00	0.00	[-0.20, -0.07]	137.57
Pharmacological	15	-0.24	0.09	-0.99	0.01	[-0.40, -0.07]	16.76
Overall	144	-0.12	0.02	-1.00	0.00	[-0.16, -0.07]	316.59

Note. Heterogeneity test for between-groups: $QB(3) = 4.16$, $p = 0.244$. k = number of independent effect sizes, r = mean weighted effect size, SE = standard error of the mean weighted effect size, z = critical ratio test for the weighted correlation, CI = 95% confidence interval, p = two-tailed probability of z , QW = within-groups heterogeneity.

Table 7

Measures of Aggression-related Constructs

Measure	<i>k</i>	<i>r</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% <i>CI</i>	<i>Q_w</i>
Anger Rating Scale	11	−0.13	0.09	−0.92	0.11	[−0.29, 0.03]	15.99
Buss-Durkee Hostility Inventory	54	−0.11	0.03	−1.00	0.00	[−0.17, −0.04]	100.42
Brown-Goodwin Lifetime History of Aggression	25	−0.14	0.05	−1.00	0.00	[−0.23, −0.05]	56.75
Child Behavior Checklist: Aggressive Behavior	10	0.17	0.08	0.98	0.02	[0.02, 0.31]	22.13
Diagnostic Interview for Children and Adolescents	8	0.13	0.09	0.87	0.18	[−0.06, 0.30]	17.68
Eigenschaftswörterliste: Anger	3	−0.15	0.18	−0.66	0.40	[−0.47, 0.21]	1.95
Freiburg Personality Inventory-Revised: Aggression	4	0.01	0.14	0.07	0.74	[−0.25, 0.27]	5.24
History of Aggression—Non-standardized	6	0.01	0.11	0.11	0.72	[−0.20, 0.22]	14.83
Violent Crime Convictions	5	−0.21	0.09	−0.98	0.03	[−0.38, −0.02]	13.08
IOWA Conners Teacher Questionnaire	3	0.18	0.13	0.88	0.17	[−0.08, 0.42]	6.81
Life History of Aggression	11	−0.17	0.07	−0.99	0.01	[−0.30, −0.04]	41.75
Multiple Affective Adjective Checklist-Revised	4	−0.16	0.11	−0.89	0.15	[−0.37, 0.06]	2.65
<i>Measures included in less than 3 studies</i>	40	−0.07	0.04	−0.93	0.09	[−0.15, 0.01]	79.91
Profile of Mood States: Angry-Hostility	18	−0.12	0.07	−0.92	0.11	[−0.26, 0.03]	12.98
Point Subtraction Aggression Paradigm	13	−0.46	0.12	−1.00	0.00	[−0.62, −0.26]	19.10
Schedule for Affective Disorders and Schizophrenia	5	−0.06	0.14	−0.41	0.58	[−0.33, 0.21]	1.57
State-Trait Anger Scale	6	−0.12	0.13	−0.74	0.33	[−0.36, 0.13]	6.06
Taylor Aggression Paradigm	10	−0.07	0.08	−0.70	0.37	[−0.22, 0.09]	9.07
Visual Analogue Scale—Non-standardized	11	0.05	0.09	0.47	0.55	[−0.13, 0.22]	27.42
Overall	247	−0.09	0.02	−1.00	0.00	[−0.12, −0.05]	525.27

Note. Heterogeneity test for between-groups: $QB(18) = 42.84$, $p < 0.001$. *k* = number of independent effect sizes, *r* = mean weighted effect size, *SE* = standard error of the mean weighted effect size, *z* = critical ratio test for the weighted correlation, *CI* = 95% confidence interval, *p* = two-tailed probability of *z*, *Q_w* = within-groups heterogeneity.

Table 8

Properties of Measures of Aggression-related Constructs

CONSTRUCT	<i>k</i>	<i>r</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI	<i>Q_w</i>
Aggression	68	−0.08	0.03	−0.99	0.01	[−0.14, −0.02]	198.05
Anger	31	−0.13	0.05	−0.99	0.01	[−0.23, 0.03]	75.34
Hostility	20	−0.04	0.06	−0.63	0.43	[−0.15, 0.06]	28.63
Aggression & Anger	4	−0.19	0.12	−0.91	0.11	[−0.40, 0.05]	8.88
Aggression & Hostility	30	−0.20	0.04	−0.99	0.00	[−0.28, −0.12]	61.18
Anger & Hostility	16	−0.12	0.07	−0.93	0.10	[−0.26, 0.02]	8.73
Aggression, Anger, & Hostility	31	−0.11	0.05	−0.98	0.02	[−0.20, −0.02]	25.57
<i>SOURCE</i>							
Self	181	−0.11	0.02	−1.00	0.00	[−0.15, −0.08]	327.63
Other	29	0.17	0.05	1.00	0.00	[0.08, 0.26]	64.33
<i>TEMPORAL SPAN</i>							
State	62	−0.14	0.04	−1.00	0.00	[−0.22, −0.06]	98.54
Trait	148	−0.07	0.02	−1.00	0.00	[−0.11, −0.03]	355.44
<i>MODALITY</i>							
Questionnaire	148	−0.07	0.02	−1.00	0.00	[−0.11, −0.03]	261.16
Interview	62	−0.08	0.03	−0.99	0.01	[−0.14, −0.02]	181.14
Laboratory	23	−0.20	0.07	−1.00	0.00	[−0.32, −0.07]	37.54
Criminal Record	5	−0.21	0.10	−0.97	0.03	[−0.38, −0.02]	13.08

Note. Between-groups heterogeneity tests for construct: $QB(2) = 1.52$, $p = 0.467$; source: $QB(1) = 32.16$, $p < .001$; temporal span: $QB(1) = 2.56$, $p = 0.11$; and modality: $QB(3) = 5.25$, $p = 0.154$. k = number of independent effect sizes, r = mean weighted effect size, SE = standard error of the mean weighted effect size, z = critical ratio test for the weighted correlation, CI = 95% confidence interval, p = two-tailed probability of z , QW = within-groups heterogeneity.