The Modulatory Role of Serotonin on Human Impulsive Aggression

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ABSTRACT
The hypothesis of chronically low brain serotonin levels as pathophysiological linked to impulsive aggression has been around for several decades. Whereas the theory was initially based on indirect methods to probe serotonin function, our understanding of the neural mechanisms involved in impulsive aggression has progressed with recent advances in neuroimaging. The review integrates evidence based on data from several neuroimaging domains in humans. In vivo molecular neuroimaging findings demonstrate associations between impulsive aggression and high serotonin 1B and serotonin 4 receptor binding, high serotonin transporter levels, and low monoamine oxidase A levels, suggesting that low interstitial serotonin levels are a neurobiological risk factor for impulsive aggressive behavior. Imaging genetics suggests that serotonergic-related genetic polymorphisms associate with antisocial behavior, and some evidence indicates that the low-expressing monoamine oxidase A genotype specifically predisposes to impulsive aggression, which may be mediated by effects on corticolimbic function. Interventions that (presumably) alter serotonin levels have effects on brain activity within brain regions involved in impulsive aggression, notably the amygdala, dorsal striatum, anterior cingulate, insula, and prefrontal cortex. Based on these findings, we propose a model for the modulatory role of serotonin in impulsive aggression. Future studies should ensure that clinical features unique for impulsive aggression are appropriately assessed, and we propose investigations of knowledge gaps that can help confirm, refute, or modify our proposed model of impulsive aggression.

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Impulsive aggression as a result of impaired prefrontal inhibition of the amygdala has long been attributed to deficient serotonin signaling (1,2). The theory of low brain serotonin levels in the etiology of impulsive aggression has influenced the field for more than 3 decades. However, the evidence linking low serotonin levels with impulsive aggression has been based on indirect methods to probe serotonin function, and a meta-analysis of such studies has questioned the validity of this hypothesis (3). Our understanding of the neural mechanisms involved in impulsive aggression has progressed with recent advances in neuroimaging. This review synthesizes evidence on serotonergic function in human impulsive aggression, integrating data from several domains including imaging genetics, positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and multimodal and pharmaco-neuroimaging. We operationalize human aggression as “any behavior directed toward another individual that is carried out with the proximate (immediate) intent to cause harm, the perpetrator must believe that the behavior will harm the target and the target should be motivated to avoid the behavior” (4). Studies that link serotonin markers with suicide or self-directed aggression have been reviewed elsewhere (5,6).

ASSESSMENT OF ANGER AND IMPULSIVE AGGRESSION
A common categorical approach divides human aggression into two subtypes: impulsive (reactive) and premeditated (proactive) aggression (7). Whereas impulsive aggression has harm as an end goal, is unplanned, and is associated with emotional arousal, premeditated aggression has harm as the means to some other end and is considered planned and cold (4). Even though there is neurobiological support for a bimodal classification of human aggression (8), the two types of aggression can sometimes be expressed in the same act and therefore difficult to distinguish: for example, when an individual frustrated by a conflict becomes angry (reactively) and later plots the revenge (proactively) (7).

Exaggerated aggression is present across several disorders; intermittent explosive disorder (IED) and borderline personality disorder (BPD) mainly present with impulsive aggression (9), whereas individuals with psychopathy often exert both impulsive and premeditated aggression (10). Investigating diagnostically heterogeneous patient groups can make it difficult to tease out features specific for impulsive aggression. We propose that impulsive aggression is best conceptualized as a behavioral trait along a spectrum and that, when addressing specific categorical diagnoses, assessments of specific traits should be included.

Aggression and related constructs can be determined based on self-report questionnaires. Figure 1 shows intercorrelations between traits related to impulsive aggression, indicating that such psychometric items are manifestations of a unidimensional latent construct, whereas the trait cold-heartedness (included for comparison) clearly captures something different. We recently integrated these self-report
Serotonin and Impulsive Aggression

Extensive research on animals supports a role of serotonin in aggression, involving several components of the serotonin system (12). A “serotonin deficiency hypothesis” in humans emerged from early studies demonstrating lower concentrations of the serotonin metabolite 5-HIAA (5-hydroxyindoleacetic acid) in cerebrospinal fluid from impulsive violent offenders compared with violent offenders acting instrumentally (13). One of these initial studies found an inverse association between aggression scores and 5-HIAA with a large effect size ($r = -0.78$) (14), but a meta-analysis published 34 years later found only a weak negative correlation ($r = -0.12$) between aggression and serotonin across several methodologies assessing serotonin levels in various diagnostic groups (3). However, this meta-analysis did not include in vivo studies of cerebral serotonergic receptors.

**Serotonin-Related Genetic Modifiers**

Several genes related to serotonin function have been tested for associations with aggression, including variants of the genes encoding for serotonin 1B and 2A (5-HT$_1$B, 5-HT$_2$A) receptors and tryptophan hydroxylase, but sample sizes have been small and the outcomes conflicting (15,16). The serotonin transporter (5-HTT) linked polymorphic region (5-HTTLPR) is a polymorphism of the gene coding for 5-HTT and is associated with brain serotonin levels (17). A meta-analysis demonstrates significant interaction effects between the 5-HTTLPR and early adversity on level of antisocial behavior, but not impulsive aggression specifically (18).

So far, the most robust evidence is the association between the low-activity monoamine oxidase A (MAOA) genotype and antisocial behavior, an association moderated by early-life adverse experience (19–23). Antisociality captures several behavioral domains, and MAOA degrades serotonin, dopamine, and norepinephrine. Therefore, the genetic association cannot necessarily be attributed to serotonin and impulsive aggression only. One review based on both preclinical and human work highlights that the low-activity MAOA variant (MAOA-L) predisposes the risk for impulsive aggression specifically and suggests that these effects are due to dysregulated serotonin signaling during a critical developmentally sensitive period (24).

The link between MAOA-L and antisocial behavior could be explained by effects of MAOA on corticolimbic function. For example, in a mixed-sex sample of 142 healthy individuals, MAOA-L carriers showed heightened amygdala reactivity and reduced anterior cingulate cortex (ACC), orbitofrontal cortex, and insula reactivity in response to angry and fearful faces (25). In 60 healthy male MAOA-L carriers, there was a negative coupling between the amygdala and ventromedial prefrontal cortex (vmPFC), and amygdala–vmPFC connectivity was correlated with trait harm avoidance (26). In a mixed-sex sample of 219–254 healthy individuals, MAOA-L associated with hyperconnectivity between lobes, with pronounced involvement of frontotemporal connections in the context of implicit emotion processing, resting-state, and diffusion tensor imaging, but not other cognitive domains (27).

**Molecular In Vivo Imaging of Serotonin in Impulsive Aggression**

PET studies have identified several serotonergic components associated with constructs related to impulsive aggression, including 5-HT$_{1A}$ (28,29), 5-HT$_{1B}$ (30,31), 5-HT$_{2A}$ (32–37), and 5-HT$_{4}$ receptors (38), the 5-HTT (36,39–41), and MAOA (42–44); their distribution in the brain is shown in Figure 2. Even though evidence from PET studies is based on relatively few and often small studies, PET is state-of-the-art in assaying in vivo serotonin signaling in humans. Table 1 summarizes PET studies of the serotonergic system in aggression, excluding...
study populations with Axis I psychiatric comorbidity (e.g., major depressive disorder).

The two 5-HT1A receptor studies of healthy control subjects show opposite associations with aggression scores (28,29). Two studies of BPD patients with comorbid depressive symptomatology found higher hippocampal 5-HT2A receptor levels in BPD (32,33), which did not correlate with trait aggression (33). Another study found higher 5-HT2A receptor binding in IED subjects with current physical aggression compared with IED subjects without current aggression (35). However, several studies in healthy control subjects (33,34,36) and impulsive aggressive subjects without current comorbidity (35,36) do not support the 5-HT2A receptor as a trait marker of impulsive aggression.

One study found higher brainstem 5-HTT in impulsive aggressive males meeting criteria for BPD or antisocial personality disorder (ASPD), with positive correlations between brainstem 5-HTT and trait aggression, impulsivity, and anger (36). By contrast, studies that included patients with psychiatric comorbidities, such as past major depressive disorder (40,41) or current alcoholism (39), did not find such an association.

One study used global 5-HT4 receptor binding as a proxy for serotonergic tonus (chronic levels of interstitial serotonin levels) (45) and found that healthy men with low serotonergic tonus scored high on self-reported trait aggression (38).

Given the established effects of MAOA genotype on antisocial behavior, we find it reassuring that three PET studies consistently show inverse associations between cortical and subcortical MAOA levels and trait measures of aggression in healthy control subjects (42,43) and in male violent offenders with ASPD (44). In addition, orbitofrontal cortex and ventral striatum (VS) MAOA was lower in the offenders compared with control subjects (44).

In summary, some evidence indicates that impulsive aggression is related to high brainstem 5-HTT, high global 5-HT4 and striatal 5-HT1B receptor binding, and low global MAOA levels. Collectively, these findings support an inverse association between serotonin and impulsive aggression, as considered in the following.

A high receptor binding potential as measured with PET could reflect an increased receptor density as a trait marker of impulsive aggression, or it could be explained by a reduction in interstitial serotonin. Low serotonin levels reduce the occupancy of the receptors, which may induce a compensatory upregulation of the receptor if the reduction is (semi-)chronic (46). In either case, the observed increases in 5-HT1B and 5-HT4 receptor binding support the serotonin deficiency theory of impulsive aggression, further supported by low brain levels of MAOA, which may be interpreted as an index of low serotonin turnover. A high brainstem 5-HTT presumably leads to more efficient reuptake of serotonin and thus lower brainstem interstitial serotonin. This leads to less firing from the 5-HT1A autoreceptors, resulting in higher serotonin production and subsequently higher postsynaptic release of serotonin, unless, of course, brainstem 5-HTT density is increased in response to chronically low brainstem serotonin levels.

In general, the relationship between serotonin levels and its receptors seems to be dynamically regulated. The cerebral 5-HT4 receptor desensitizes in response to subchronically (weeks) elevated serotonin levels, as measured with
| Target                     | Subjects                                                                 | Radioligand               | Aggression Assessment | Main Finding                                                                                                   | References   |
|----------------------------|--------------------------------------------------------------------------|---------------------------|-----------------------|----------------------------------------------------------------------------------------------------------------|--------------|
| 5-HT<sub>1A</sub> Receptors | 25 healthy subjects (12 female/13 male)                                  | (Carbonyl-<sup>11</sup>C)WAY-100635 | BGLA                  | Negative association between 5-HT<sub>1A</sub> receptor binding and lifetime aggression score within raphe, amygdala, cingulate, and prefrontal cortex. | Parsey et al., 2002 (28) |
| 5-HT<sub>1A</sub> Receptors | 33 healthy subjects (16 female/17 male)                                  | (Carbonyl-<sup>11</sup>C)WAY-100635 | Questionnaire for Measuring Factors of Aggression | Positive correlation between anterior cingulate and frontal 5-HT<sub>1A</sub> receptor binding and total aggression score. | Witte et al., 2009 (29) |
| 5-HT<sub>2A</sub> Receptors | Fourteen IED subjects with current physical aggression (4 female/10 male), 15 IED subjects without current physical aggression (3 female/12 male) and 25 healthy subjects (10 female/15 male) | [<sup>11</sup>C]MDL100907 | BPAQ, BDHI, OAS-M | Increased orbitofrontal 5-HT<sub>2A</sub> receptor availability in patients with current physical aggression compared with patients without current physical aggression and healthy control subjects. Positive correlation between state irritability and orbitofrontal 5-HT<sub>2A</sub> In IED subjects combined. | Rosell et al., 2010 (35) |
| 5-HT<sub>2A</sub> Receptors | 94 healthy subjects (34 female/60 male)                                  | [<sup>18</sup>F]altanserin | BPAQ, BIS             | No significant association between frontal 5-HT<sub>2A</sub> receptor binding and trait aggression or trait impulsivity. | da Cunha-Bang et al., 2013 (34) |
| 5-HT<sub>2A</sub> Receptors and 5-HTT | 14 subjects with high impulsive aggression (ASPD or BPD), and 13 subjects with low levels of impulsive aggression (27 male) | [<sup>11</sup>C]DASB and [<sup>11</sup>C]MDL100907 | EAQ, PPI, IVE, BIS, STAXI, BDHI | Higher brainstem/midbrain and lower cortical 5-HTT in men with impulsive aggression. Positive correlation between brainstem 5-HTT and impulsivity, aggression, and anger scores across all subjects. No significant group differences or associations between 5-HT<sub>2A</sub> and impulsive aggression. | Rylands et al., 2012 (36) |
| 5-HT<sub>4</sub> Receptors | 61 healthy subjects (14 female/47 male)                                  | [<sup>11</sup>C]SB207145 | BPAQ, BIS             | Positive correlation between global 5-HT<sub>4</sub> receptor binding and trait aggression among male subjects. | da Cunha-Bang et al., 2016 (39) |
| 5-HT<sub>1B</sub> Receptors | 19 violent offenders and 24 healthy subjects (43 male)                  | [<sup>11</sup>C]AZ1045    | BPAQ, BIS, PCL-R, STAXI, PPI | Positive correlation between dorsal striatum 5-HT<sub>1B</sub> receptor binding and trait anger and level of psychopathy in the violent offender group. | da Cunha-Bang et al., 2017 (30) |
| MAOA                       | 27 healthy subjects (27 male)                                           | [<sup>11</sup>C]clorgyline | MPQ                   | Inverse correlation between global MAOA levels and trait aggression.                                            | Alia-Klein et al., 2006 (42) |
| MAOA                       | 37 healthy subjects (17 female/20 male)                                  | [<sup>11</sup>C]harmine   | NEO PI-R              | Negative correlation between prefrontal MAOA binding and trait angry-hostility.                                | Soliman et al., 2011 (43) |
Impulsive aggression is suggested to be mediated by the hypothalamus [the acute threat response (53,54)]. Whereas aggression can vary substantially across studies (Box 1 in the Supplement).

Anger can be triggered by other stimuli such as provocations, threats, or verbal descriptions or outward expressions of the emotional experience. A review including 13 fMRI studies that induced anger internally or externally (Box 1 in the Supplement) identified activation patterns relevant to the self-regulation, mentalizing, and saliency network, but it concluded that there is not enough evidence to substantiate a region-specific uniqueness to anger (57). When measuring a subjective experience such as feelings, we must rely on verbal descriptions or outward expressions of the emotional response. In addition, emotions may change quickly, which can affect the description of a previous emotional experience. Although measuring emotions can be difficult, it is possible in humans, as opposed to animals, which has obvious implications for translational research.

Table 1. Continued

| Target | Subjects | Radioligand | Aggression Assessment | Main Finding | References |
|--------|----------|-------------|-----------------------|--------------|------------|
| MAOA   | 18 ASPD subjects and 18 healthy subjects (36 male) | [11C]harmine | The Iowa gambling task, NEO PI-R, PCL-R | Lower orbitofrontal and ventral striatum MAOA levels in ASPD patients compared with control subjects. Inverse correlation between ventral striatum MAOA-A levels and trait impulsivity in ASPD subjects. | Kolla et al., 2015 (44) |

- 5-HT, serotonin; 5-HTT, serotonin transporter; ASPD, antisocial personality disorder; BPD, borderline personality disorder; BDHI, Buss-Durkee Hostility Index; BGLA, Brown-Goodwin Lifetime Aggression Score; BIS, Barratt Impulsiveness Scale; BPAQ, Buss-Perry Aggression Questionnaire; BPD, borderline personality disorder; EAQ, Expression Aggression Questionnaire; IED, intermittent explosive disorder; IVE, Impulsiveness-Venturesomeness-Empathy Questionnaire; MAOA, monoamine oxidase A; MPQ, Multidimensional Personality Questionnaire; NEO PI-R, NEO Personality Inventory Revised; OAS-M, Overt Aggression Scale Modified; PCL-R, Psychopathy Checklist Revised; PPI, Psychopathic Personality Inventory; STAXI, State-Trait Anger Expression Inventory.

[11C]SB207145 PET (49), whereas an acute intervention with a selective serotonin reuptake inhibitor (SSRI) does not change receptor binding (47). Binding of [11C]AZ1041934 to 5-HT1B receptors decreases after acute administration of fenfluramine (a potent serotonin releaser) in nonhuman primates (48) and pigs (49). In humans, [11C]AZ1041934 binding decreases in response to visual stimuli (50), whereas it increases in response to an acute dose of SSRI (51), possibly because of stimulation of serotonin autoreceptors. That is, the concept of a sustained serotonin deficiency may be too simple, and perhaps, serotonin exerts a more dynamic modulation of the behavior.

In addition to acute or chronic serotonergic brain levels, specific serotonin receptors may regulate impulsive aggression via interaction with other neurotransmitter systems. For example, 5-HT1B receptors are located presynaptically on axon terminals of serotonergic neurons and postsynaptically as heteroreceptors on neurons from other neurotransmitter systems: dopamine, GABA (gamma-aminobutyric acid), glutamate, and acetylcholine (52).

In conclusion, current evidence based on in vivo molecular imaging supports the hypothesis that low endogenous serotonin levels are a neurobiological trait risk factor in impulsive aggression. It would be reassuring to see replications with focus on the assessments of impulsive aggression, as considered in the first section. Moreover, more knowledge is warranted regarding how serotonin dynamically modulates impulsive aggression.

NEURAL CIRCUITS OF ANGER AND IMPULSIVE AGGRESSION

fMRI and Emotional States Related to Impulsive Aggression

The context in which impulsive aggression in fMRI has been investigated and the impact of a subjective emotional state vary substantially across studies (Box 1 in the Supplement). Impulsive aggression is suggested to be mediated by the same neural circuit as fear—amygdala, periaqueductal gray, hypothalamus [the acute threat response (53,54)]. Whereas threat is a situational trigger of fear and anger, anger can also be triggered by other stimuli such as provocations, frustrations, or unfairness. What is the role of discrete emotion categories? One theory is that the subjective feeling of fear is not a product of the subcortical circuits underlying defensive responses but instead depends on circuits that underlie any form of conscious experience: the cortical general network of cognition, including the lateral and medial PFC, ACC, insula, and parietal cortex (55). It is argued that the subcortical circuits underlying defensive responses process threats subconsciously and do not themselves generate an emotional experience, but can rather modulate conscious feelings (55,56). In this view, a subjective feeling of anger would depend on brain circuits within the general network of cognition, which is in line with activation of several cortical regions during anger-induction in fMRI (57). A meta-analysis of laboratory-induced aggression in fMRI found convergent activity within the ACC and anterior insula/inferior frontal gyrus, which was related to state anger (58). However, many of the included studies did not ask the participants whether they felt angry during the tasks (58). Not all neuroimaging studies focus on the subjective experience of anger. Even though angry and fearful faces may represent a signal of threat, and “real” social interactions (e.g., PSAP and TAP) are used to elicit provocations, these stimuli are also generally salient and do not necessarily lead to a subjective feeling of anger. Some, but far from all, studies measure state anger before and after and a task [e.g., (59–61)], and we believe that correlating brain activity with such assessments will help tease out whether task-related brain activations can be attributed to the emotional experience. A review including 13 fMRI studies that induced anger internally or externally (Box 1 in the Supplement) identified activation patterns relevant to the self-regulation, mentalizing, and saliency network, but it concluded that there is not enough evidence to substantiate a region-specific uniqueness to anger (57). When measuring a subjective experience such as feelings, we must rely on verbal descriptions or outward expressions of the emotional response. In addition, emotions may change quickly, which can affect the description of a previous emotional experience. Although measuring emotions can be difficult, it is possible in humans, as opposed to animals, which has obvious implications for translational research.
Functional Neuroimaging Evidence for Brain Circuit Involvement

The dominant conceptual framework of how neural circuits regulate impulsive aggression is that the PFC modulates or inhibits subcortical activity mediating the aggressive response (1,2,8,53,62). That is, reduced PFC activity combined with heightened subcortical activity in the context of aggression-inducing stimuli poses an increased risk for impulsive aggression. Studies showing reduced functional connectivity between the amygdala and prefrontal regions in aggressive individuals putatively reflect such framework (63–67). High levels of impulsive aggression (or constructs closely linked to it) have repeatedly been associated with heightened amygdala reactivity in the context of angry faces (63,64,68–70), fearful faces (1,11), and provocations in the PSAP (67,71). A recent review suggested that brain regions involved in threat sensitivity (amygdala, hypothalamus, periaqueductal gray) and frustrative nonreward (amygdala, VS, caudate nucleus) represent activation conditions, and regions involved in cognitive control (PFC, insula, inferior parietal lobules) represent regulating conditions for impulsive aggression (72). This is in line with another review of nine IMRI TAP studies concluding that a neural circuitry mediating emotional reactivity and cognitive control is implicated in reactive aggression (73), although a meta-analysis revealed that the left postcentral gyrus was the only region consistently activated across these TAP studies (74).

The vmPFC is often highlighted in studies of impulsive aggression because of its role in inhibiting negative emotion (75). The vmPFC also subserves other domains of psychological function, including value-based decision making (75). Indeed, Blair (53,54) argues that the vmPFC shapes representation of expected rewards and punishments associated with an action. A person impaired with respect to decision making owing to poor prefrontal function might fail to recognize when aggression is disadvantageous based on anticipated consequences and therefore be more likely to engage in aggression (9). Although impulsive aggression may be an automatic response to an extreme threat, this view suggests that it may also be a selected response (as the aggressive responses in the TAP and PSAP are), which places an instrumental component in some impulsive aggressive acts (53). We believe that this view in many cases is the most compatible with “real-life” impulsive violent acts.

Serotonergic Effects on Aggression-Related Brain Circuits

Serotonin signaling has repeatedly been implicated in emotional processing in the context of aversive faces through its effects on corticolimbic function (76). Multimodal neuroimaging studies in healthy control subjects demonstrate associations between low amygdala reactivity to aversive emotional faces and high dorsal raphe 5-HT1A receptor binding (77,78), although one recent study revealed opposing directionality in the association (79). Interventions that presumably increase (SSRI) or decrease (acute tryptophan depletion [ATD]) brain serotonin levels influence amygdala reactivity and/or amygdala–prefrontal connectivity in the context of aversive faces (80–88). The interpretation is complicated by opposing directionalities in the findings; some studies show increased amygdala reactivity (80–83), whereas other studies find decreased amygdala reactivity (84,85) after SSRI intervention. 5-HT2A receptor neuroimaging in healthy control subjects suggests that as serotonin levels increase after 3-week intervention with SSRI, amygdala reactivity decreases (89).

Evidence from other paradigms related to anger, impulsivity, and aggression is limited. To our knowledge, only one study has directly investigated in vivo serotonin signaling and amygdala reactivity during provocations, revealing that male subjects with high global 5-HT1B receptor levels had heightened amygdala reactivity to PSAP-elicited provocations (90). Another multimodal neuroimaging study found a positive correlation between VS MAOA density and resting-state functional coupling with the VS and dorsomedial PFC in male patients with ASPD (91). In a TAP study, ATD-induced lowering of brain serotonin levels reduced anterior insula reactivity during a phase in which the participants decided the punishment level for the opponent, but there was no effect on task-related behavior (92). Depleting serotonin levels with ATD in a mixed-sex sample of healthy participants resulted in higher rejection rates to unfair (but not to fair) offers in the Ultimatum Game (93). ATD increased activity in the bilateral DS during rejection of unfair offers when healthy male and female participants played the Ultimatum Game, which was specific to costly punishment and not to fairness preferences (94). In contrast to the effects of ATD on retaliation, enhancing serotonin levels with SSRI increased harm aversion in a task in which healthy subjects could decide to inflict pain on themselves or others for financial gain (95). Moreover, intervention with SSRI made healthy subjects more likely to judge harmful actions as forbidden in a set of moral dilemmas pitting utilitarian outcomes (e.g., saving five lives) against aversive harmful actions (e.g., killing an innocent person), but only in cases when harms were emotionally salient (96). Other effects of ATD include reduced connectivity between the amygdala and bilateral supramarginal gyrus in healthy males during violent versus nonviolent actions in a video game (97).

Some limitations to the use of SSRI and ATD should be mentioned. It is possible that acute changes in raphé serotonin levels induce a 5-HT1A receptor–mediated autoinhibition, thereby increasing serotonin levels in projection areas after ATD and decreasing levels after SSRI, that is, exerting the opposite effect of expected. Moreover, there is large interindividual variation in serotonin levels after intervention with SSRI (98). In light of these limitations, the effects of ATD and SSRI should be interpreted with caution.

In conclusion, interventions that (presumably) alter serotonin levels have effects on brain activity within brain regions implicated in impulsive aggression, notably the amygdala, DS, ACC, insula, and PFC.

PHARMACOLOGICAL SEROTONERGIC INTERVENTIONS

If impulsive aggression is caused by low brain serotonin levels, one would expect that pharmacological enhancement of serotonin levels would reduce impulsive aggression. The few studies that have directly assessed the effects of SSRI on impulsive aggression were open label and included only 11 to
49 impulsive aggressive individuals (e.g., IED or BPD patients) and suggest that SSRI treatment reduces impulsive aggression (99–104). One double-blind, randomized, placebo-controlled trial of 100 patients with IED (of which 55 completed the study) found significant reductions in aggressive behavior after treatment with the SSRI fluoxetine (105).

The effects of interventions targeting specific serotonergic receptors have also been studied. In a small open-label study of 10 patients with IED, treatment with the 5-HT2C receptor agonist lorcaserin reduced TAP-induced aggression compared with placebo (106). Numerous animal studies have convincingly shown that pharmacological compounds that activate 5-HT1A/1B and antagonize 5-HT2A/2C receptor subtypes suppress aggression (107). The recent findings of altered 5-HT1B receptor levels in human aggression support that this receptor represents a relevant molecular target in antiaggressive treatment. In a study of 11 healthy individuals, the 5-HT1B agonist zolmitriptan decreased PSAP-induced aggression, although only after intake of alcohol (108). Replications are needed, preferentially with 5-HT1B agonists with higher blood-brain barrier penetrance (109).

In conclusion, the quality of evidence is low for both SSRI and other serotonergic agents in treating impulsive aggression, and much more work is needed to identify suitable pharmacological treatments.

**A SUGGESTED MODEL FOR SEROTONERGIC EFFECTS ON IMPULSIVE AGGRESSION**

Collectively, data from in vivo molecular imaging findings support that low brain interstitial serotonin levels are a neurobiological trait risk factor for impulsive aggression. The MAOA and 5-HTTLPR genetic variants predispose one to the risk for antisocial behavior, which may be due to low serotonin levels, but that remains to be further experimentally verified.

How do low serotonin levels contribute to impulsive aggression? The main view has been that serotonin facilitates prefrontal inhibition of amygdala reactivity, as suggested 20 years ago (1). Subsequent research combining fMRI with PET or serotonin-modulating interventions demonstrates serotonergic effects on brain activity not only within the amygdala but also within the DS, ACC, insula, and PFC.

Given the wealth of preclinical evidence supporting 5-HT1B receptors in impulsivity and aggression (110,111), we find it intriguing that 5-HT1B receptors are involved in human aggression; high global 5-HT1B receptor binding, putatively reflecting low serotonergic tonus, associates with heightened amygdala reactivity to provocations (90), in line with several

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**Figure 3.** Systems involved in impulsive aggression and their putative roles. A situational trigger (e.g., provocations, frustrations) activates a neural circuit comprising the amygdala, GNC, DS, and PFC. Serotonergic tonus modulates amygdala and DS reactivity, which may also be modulated by the PFC. DS 5-HT1B receptors facilitate heightened DS reactivity, which may modulate anger, harm aversion, and retaliatory motives. Activation of the GNC induces a subjective experience of anger, which may be modulated by amygdala and/or DS, or vice versa: subjective experience of anger induces amygdala and/or DS activation. This is integrated in the PFC, in particular, the ventromedial PFC that can evaluate and regulate the behavior accordingly by either inhibiting amygdala/DS activity or by shaping representations of expected rewards and punishments associated with the action. Impulsive aggression may sometimes be an automatic response to extreme threat, mediated by the same neural circuit as fear (acute threat response). The figure was created with BioRender.com. 5-HT, serotonin; 5-HTTLPR, serotonin-transporter-linked promoter region; Amy, amygdala; DS, dorsal striatum; GNC, general network of cognition; HYP, hypothalamus; MAOA, monoamine oxidase A; PAG, periaqueductal gray; PFC, prefrontal cortex; vmPFC, ventromedial PFC.
studies showing effects of interventions that alter serotonin levels on amygdala reactivity (80–88). Moreover, individuals scoring high on measures linked to impulsive aggression (trait anger and self-centered impulsivity) have both high DS reactivity to provocations (67) and high DS 5-HT$_{1B}$ receptor binding (30). The DS is activated when rejecting unfair offers in the Ultimatum Game, and depleting serotonin levels leads to increased DS reactivity (9–4). Serotonin is thus thought to modulate DS responses to retaliatory motives, and enhancing serotonin levels (with SSRIs) increases aversion to harming others (35,96). This implies that serotonin promotes prosocial behavior by enhancing aversion to harming others (36). We suggest a model in which low serotonergic tonus facilitates heightened amygdala reactivity, whereas DS 5-HT$_{1B}$ receptors modulate DS activity during anger, harm aversion, and retaliatory motives. A subjective feeling of anger is generated in the general network of cognition (56), which may be modulated by the amygdala and/or DS, or vice versa; the subjective feeling of anger induces amygdala and/or DS activation. This is integrated in the PFC, in particular the vmPFC, which can evaluate and regulate the behavior accordingly. Below, we propose a model that integrate these key findings (Figure 3).

**FUTURE DIRECTIONS**

Future research should emphasize the context in which impulsive aggression is studied, for example, in relation to acute threat or in relation to experienced anger elicited by aggression-inducing stimuli. This may help determine whether anger is a prerequisite for neural mechanisms that contribute to impulsive aggression. Studying resilient individuals—people frequently experiencing subjective feelings of anger but without responding with aggression—will also be helpful to understand which factors modulate impulsive aggression. Multimodal neuroimaging studies with hybrid PET/fMRI of responses to provocations as evaluated during serotonin-modulating interventions, in particular specific serotonin receptor agonists or antagonists, can critically help elucidate the relationship between the dynamics of brain serotonin function and brain circuits in aggression. To investigate the role of specific serotonergic subsystems, we suggest pharmacological interventions that target the 5-HT$_{1B}$ Receptor. Until such selective compounds have been developed, repurposing of approved drugs could be tested: eltoprazine, a mixed 5-HT$_{1A}$/1B receptor agonist with antiaggressive effects in animals, or zolmitriptan, although it has low blood-brain barrier penetrance (103). Given that the 5-HT$_{1B}$ has an inhibitory effect on serotonin release, it would also be relevant to block 5-HT$_{1B}$ receptors, but we are not aware of any 5-HT$_{1B}$ antagonists approved for clinical use. The dynamics of serotonin signaling can be tested with drugs that release serotonin (e.g., dexamphetamine) in conjunction with PET radioligands sensitive to changes in serotonin levels, such as $[^{11}C]$Cimbi-36 (112). Such future studies could help to critically support, refute, or refine our proposed model of brain mechanisms involved in impulsive aggression.

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