I fear for you: A role for serotonin in moral behavior

Heike Tost[a] **and Andreas Meyer-Lindenberg**[b,1]

[a]*Clinical Brain Disorders Branch, Genes, Cognition and Psychosis Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892; and* [b]*Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, 68159 Mannheim, Germany*

Decision making in the face of conflicting ethical demands has intrigued mankind for millennia. A long philosophical tradition has placed emphasis on reasoning, about utilitarian outcomes, for example, in such decisions (1). However, recent work in social neuroscience (2, 3) has identified brain circuits active during moral judgment that have been linked to prosocial emotions such as empathy, guilt, and pity. Using an innovative combination of behavioral research and pharmacological intervention, a study in this issue of PNAS (4) suggests a role for the neurotransmitter serotonin in the neural substrate of ethical decision making.

Moral dilemmas are characterized by the presence of a social behavioral conflict in which either decision would result in the transgression of an ethical imperative, often resulting in harm to others (5). The report by Crockett et al. (4) examines the effects of a single high dose of the selective serotonin reuptake inhibitor (SSRI) citalopram on moral judgment in healthy volunteers using a set of hypothetical scenarios portraying highly emotionally salient personal and less emotionally salient impersonal moral dilemmas with similar utilitarian outcomes (e.g., pushing a person in front of a train to prevent it from hitting five people and flipping a switch to divert a train to hit one person instead of five people, respectively). The experiment shows that increased serotonin makes individuals less likely to endorse moral scenarios that result in the infliction of personal harm to others. Citalopram also increased the likelihood of accepting unfair offers in the Ultimatum Game, an economic experiment sensitive to neurochemical modulation (6). This is consistent with the interpretation that increased serotonin made subjects more likely to tolerate behavior that violates an ethical imperative (fairness) because punishing it would have (financially) harmed fellow coplayers. With these convergent observations, the study by Crockett et al. (4) demonstrates that enhanced serotonin biases moral judgment and decision making toward sociality.

How does serotonin promote prosocial behavior? Crockett et al. (4) contrast a common hypothesis in the field, the idea that serotonin increases the capacity to control prepotent emotional impulses that could lead to socially aversive consequences such as harming someone (7), to the alternate hypothesis that serotonin increases the emotional response to these expected aversive outcomes. In their experiment, Crockett et al. (4) observed a clear bias against the emotionally salient behavioral option (personal harm), thereby making a convincing case for the second account: in enhancing serotonin, citalopram "boosts" aversive emotional reactions linked to the prospective harm of others.

In a broader context, the work by Crockett et al. (4) supports a number of interesting conclusions. First, it extends prior evidence suggesting that there are at least two major pharmacological routes that modulate human social behavior: a direct route ("bottom-up") involving prosocial neuropeptides such as oxytocin and vasopressin, which promote prosocial behaviors such as attachment, empathy (8, 9), and generosity (6), and an indirect route ("top-down") involving serotonin, which delimits antisocial behaviors by reducing negative affect (10) and enhancing the aversiveness of harming others (Fig. 1). Second, if this is true, functional interactions between these transmitter systems are likely. Consistent with this, Crockett et al. (4) report a pronounced impact of serotonin augmentation on social decision making in subjects with high trait empathy, a finding suggestive of additive prosocial

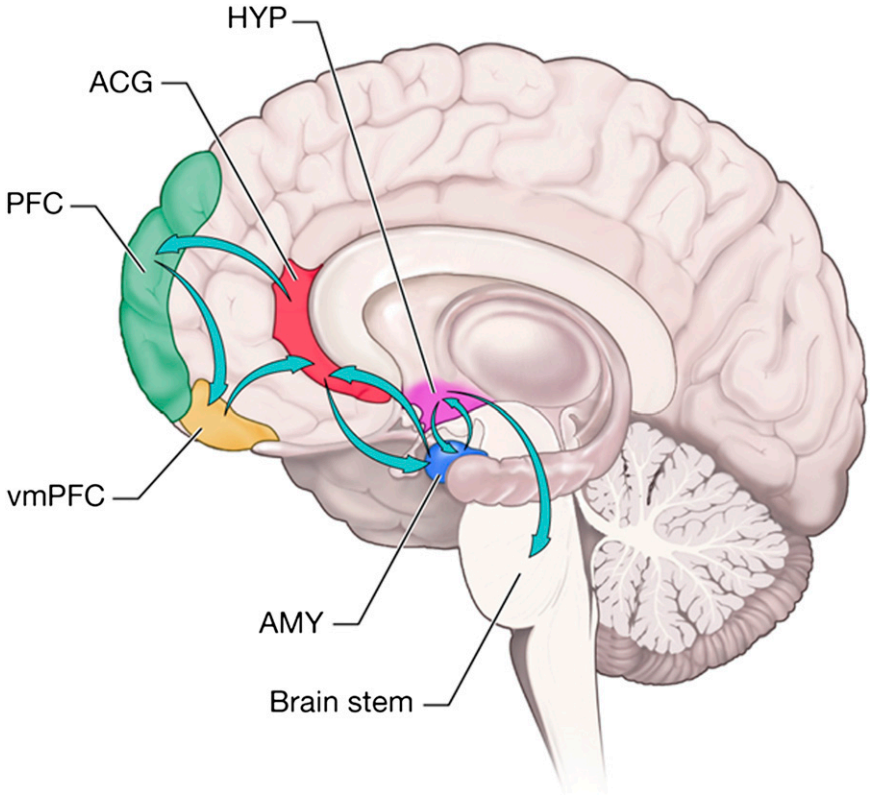

Fig. 1. Regulatory circuits of social-emotional information processing in humans. "Top-down" control of the amygdala (AMY) arises from the anterior cingulate cortex (ACG) and ventral medial prefrontal cortex (vmPFC), with the latter being particularly important for the regulation of moral behaviors. "Bottom-up" modulation arises from neurons in the hypothalamus (HYP) expressing the neuropeptides oxytocin and vasopressin, which target distinct neuronal populations in the central amygdala. Projections from the amygdala to the brainstem, via the hypothalamus, regulate the expression of autonomic reactions to social signals. PFC, prefrontal cortex.

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[1]To whom correspondence should be addressed. E-mail: a.meyer-lindenberg@zi-mannheim.de.

effects of both routes. Third, the study demonstrates that the effects of serotonin on prosocial behavior are relatively specific and are absent under norepinephrine augmentation with atomoxetine.

Which brain regions mediate the prosocial effects of serotonin? Because the experiment by Crockett et al. (4) was restricted to the behavioral level, this question can only be answered tentatively, although valid hypotheses can be drawn from the literature. Our best leads come from studies examining prosocial neuropeptides, which affect brain areas involved in emotion regulation and social threat signaling (11), particularly the amygdala (12) and subgenual cingulate (13). Several key mediators of neural functions related to fear and anxiety are densely innervated by the serotonergic system, particularly the amygdala and its higher-order regulatory areas in the extended limbic system (11). Prior studies have demonstrated that the functional properties of this circuit predict harm avoidance (14, 15), are highly sensitive to the processing of threat (11) and social signals (8, 11, 16), and are sensitive to pharmacological manipulation with SSRIs (17), making it a prime neural candidate for the observed effects on "prosocial harm aversion." Specifically, feedback projections from the ventral medial prefrontal cortex to the amygdala, via the anterior cingulate cortex, could be of particular importance. A plausible model (3)

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proposes that the functional coupling of these regions facilitates the association of harmful actions with the aversive reinforcement of the victims' distress, providing a heuristic framework for successful moral regulation in mental health and the origin of moral transgressions in antisocial personality disorders.

Apart from advancing our understanding of the molecular architecture of human social behavior, could the study by Crockett et al. (4) have clinical implications? Social dysfunction is one of the most persistent and disabling sources of impairment in many severe mental illnesses, particularly in schizophrenia and autism. In addition, abnormal lack of empathy and amoral conduct of individuals with antisocial personality disorders impose considerable distress on their social environment, underscoring the need for effective pharmacological treatments to complement existing cognitive-behavioral approaches. Consistent with the observations of prior studies (10), the work by Crockett et al. (4) suggests that serotonin augmentation might be a promising strategy to increase the emotional response of the amygdala and associated structures in individuals with social dysfunction. As illustrated by the emerging clinical success story of oxytocin (18, 19), the strategy to translate pharmacological results guided by social neuroscience to clinical therapy holds considerable promise.

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