

# What has serotonin to do with depression?

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The “serotonin hypothesis” of clinical depression is almost 50 years old. At its simplest, the hypothesis proposes that diminished activity of serotonin pathways plays a causal role in the pathophysiology of depression. This notion was based on the depressogenic effects of amine depleting agents such as reserpine, as well as the actions of antidepressant drugs such as monoamine oxidase inhibitors and tricyclic antidepressants, discovered by clinical serendipity, but later found in animal experimental studies to potentiate the effects of serotonin and other monoamines at the synapse (1).

This pattern of theory making – moving from the pharmacological actions of drugs with some efficacy in treatment to biochemical notions of causation – has been common in biological psychiatry. In such an undeveloped field this approach, though logically precarious, has been a useful heuristic and, in the case of the dopamine hypothesis of psychosis, has been strikingly upheld by advanced brain imaging techniques (2). However, the serotonin hypothesis of depression has not been clearly substantiated. Indeed, dogged by unreliable clinical biochemical findings and the difficulty of relating changes in serotonin activity to mood state, the serotonin hypothesis eventually achieved “conspiracy theory” status, whose avowed purpose was to enable industry to market selective serotonin reuptake inhibitors (SSRIs) to a gullible public (3).

## IS SEROTONIN STILL RELEVANT TO AN UNDERSTANDING OF DEPRESSION?

In biological psychiatry, pathophysiological hypotheses are not easily refuted. More often they simply seem to become irrelevant as new models of causation take their place. In an era of neural networks and systems level neuroscience, “single” neurotransmitter theories of depression look increasingly implausible. Is serotonin still worth thinking about in relation to depression?

The best evidence that serotonin plays a role in the pathophysiology of depression comes from studies of “tryptophan depletion”, where an acute dietary manipulation is employed to produce a transient lowering in brain serotonin activity through diminishing availability of its precursor amino acid, tryptophan. In healthy participants with no risk factors for depression, tryptophan depletion does not produce clinically significant changes in mood; however, recovered depressed patients free of medication can show brief, clinically relevant, depressive symptomatology (4). Interestingly, the same is true of recovered depressed patients undergoing catecholamine depletion with alpha-methyl-para-tyrosine (5).

Overall, this evidence suggests that impairing serotonin function can cause clinical depression in some circumstances, but is neither necessary nor sufficient. In addition, the depressogenic effects of tryptophan depletion are much more apparent in people who have experienced prior episodes of depression than in those simply at high risk of illness, for example by virtue of a strong family history (6). This suggests that low serotonin function may compromise mechanisms involved in maintaining recovery from depression rather than having a primary effect to lower mood in all vulnerable people.

These findings also hint at a role for diminished tryptophan availability in triggering depression, particularly in people with a previous history of illness. Interestingly, lower plasma levels of tryptophan are one of the few reasonably robust findings in patients with more severe forms of depression (7) and, more recently, have been linked to peripheral inflammation and consequent induction of the tryptophan metabolizing enzyme indoleamine 2,3-dioxygenase (8). Inflammation could therefore produce depression in vulnerable individuals by lowering plasma tryptophan and diminishing brain serotonin activity. Conceivably, such an effect could explain the diminished efficacy of SSRIs in depressed patients with high levels of inflammatory biomarkers (9).

## SEROTONIN AND ANTIDEPRESSANT ACTION

Undoubtedly, a major reason for the continuing interest in serotonin and depression is the fact that SSRIs are useful antidepressant drugs for some patients. Elegant basic studies have revealed intriguing molecular and cellular consequences of repeated SSRI administration in animals, for example increases in hippocampal cell proliferation and enhanced expression of neuroplasticity related proteins such as brain derived neurotrophic factor (BDNF) (10). However, linking such changes to resolution of the clinical depressive syndrome is challenging. More pertinent in this respect are neuropsychological studies which show that, in both healthy participants and depressed patients, administration of SSRIs leads to positive shifts in the way the brain appraises emotionally-valenced information. This effect occurs very early in treatment, prior to clinical antidepressant effects, and appears to be mediated via serotonergic innervation to limbic circuitry, particularly the amygdala (11).

This work gives a new insight into how serotonin pathways may influence mood in depressed patients, that is by altering the way the brain appraises emotionally-laden information at an implicit level. Unlike mood, emotions are

relatively short-lived, automatic responses to internal or external stimuli, and in depressed patients emotional responses are reliably negatively biased (12). Thus, from this viewpoint, increasing serotonin activity in depressed people does not influence subjective mood directly but, rather, as a secondary consequence of positive shifts in automatic emotional responses.

Over time, it is suggested, this positive biasing of automatic processing would, in an appropriate interpersonal environment, lead to changes in the strategic processing associated with conscious emotional experience. This psychological process is likely to involve re-learning a range of emotional associations, which might account for the gradual onset of clinical antidepressant activity (11). In addition, the notion that “re-learning” is involved in subjective improvement in depression sits well with the finding noted above that antidepressants such as SSRIs promote synaptic plasticity, an effect classically associated with learning (13).

## COMPUTATIONAL APPROACHES TO SEROTONIN FUNCTION

Computational neuroscience offers a framework that allows the role of specific neurotransmitters to be dissected from within a complex, interconnected and dynamic system such as the brain. The paradigmatic example of a computational approach to understanding the function of a central neurotransmitter is the finding that activity in a subset of dopaminergic neurons, projecting from the ventral tegmentum throughout the brain, sharply increases when an unexpected reward occurs (14). Computational accounts suggest that these dopamine neurons contain information about the “reward prediction error”, which is calculated simply as the difference between the reward the animal “expected” to receive and what it actually received (15). This provides a compelling quantitative account of the role of dopaminergic neurons in updating beliefs about the environment.

The role of serotonin in cognition has not, to date, been characterized as successfully as the dopaminergic reward prediction error signal. This may in part be due to the technical challenges of identifying serotonergic neurons electrophysiologically or the low concentrations of serotonin compared to dopamine in the central nervous system, problems which may be more readily circumvented in the future by advances in optogenetics (16). Whatever the cause, no existing computational account of serotonergic function commands the empirical support enjoyed by the dopaminergic model.

As a result, before reviewing the specific proposed models of serotonergic function, it is useful to consider the broad type of information that the serotonergic system *could* transmit, given its gross anatomy and neurochemistry. Serotonergic neurons, in keeping with other central monoaminergic neurotransmitters such as noradrenaline and dopamine, project from small central nuclei throughout much of the rest

of the central nervous system. This anatomical layout is ideal for broadcasting relatively simple messages which are of general interest to many different regions of the brain, such as the reward prediction error signal carried by dopamine. This is not to say that the serotonergic system has a limit of only one kind of signal; there may be some anatomical specificity in the information transmitted, and the complex range of serotonergic receptors allows for signals to be multiplexed even in neurons projecting to the same region (17).

Current models of serotonergic function have tried to account for three broad observations about the effects of enhancing serotonergic function in animals and humans: first, that it influences response to aversive stimuli; second, that it increases behavioural inhibition; and third, that it improves the symptoms of depression (18).

An initial computational account of serotonergic transmission suggested that it acted in opponency to dopamine, transmitting a “punishment prediction error”. That is, phasic serotonergic activity reports when events were worse than expected (19). This model is able to account for the effect of serotonergic modification on behavioural responses to stress and threat, as it suggests that serotonin broadcasts crucial information for learning about aversive outcomes. An elaboration of the model suggests that, in addition to the *phasic* punishment prediction error signal, *tonic* serotonergic activity represents the average, or expected frequency of punishments (20). This links the effect of serotonin on aversive processing to behavioural inhibition, as the more frequently punishments are expected to occur when actions are taken, the more advantageous does a cautious approach to action become.

A second variant of this model frames the role of serotonin as controlling “delay-discounting”, which describes the observation that an immediate reward (say, being given a bar of chocolate now) is generally valued to a greater extent than a delayed reward (being given a bar of chocolate in a week’s time). Computationally, this effect can be described by representing the value of a reward numerically (a bar of chocolate could have an immediate reward value of 100) and then systematically reducing this value as a function of how long a delay there is until it is received (the value of the same chocolate bar to be eaten in a week’s time may be 50) (21). Serotonin has been suggested to control how “steep” this discounting process is – specifically, high levels of serotonin make the process flatter and thus reduce the difference between immediate and distant rewards (22,23). Flattening the discount rate in this manner makes it more likely that the animal will be willing to wait for a delayed reward, and explains why enhancing serotonergic function reduces impulsive behaviour.

A third computational model, developed by Dayan and Huys (18), may be more relevant to the role of serotonin in depression and its treatment. Here, serotonin is perceived as influencing the way that one thought leads to another, specifically by inhibiting chains of thoughts predicted to lead to negative affective states (“let’s not go there”). From this

viewpoint, the role of serotonin is to ensure that thoughts with potentially negative emotional consequences are relatively underexplored; hence facilitation of serotonin produces a bias towards optimistic valuations, as rewarding thoughts are “visited” more frequently than punishing thoughts. This is consistent with actions of SSRIs on emotional processing described earlier (11). Conversely, tryptophan depletion would be expected to undermine this effect of serotonin, leading to greater access to negative thinking patterns. In an individual where particularly bleak patterns of negative thoughts have been established during previous depressive episodes, tryptophan depletion could result in such experiences being readily re-accessed, leading to the return of clinically significant depressive symptoms.

## CONCLUSIONS

Simple biochemical theories that link low levels of serotonin with depressed mood are no longer tenable. However, experimental and computational accounts of how serotonin influences emotional processing throw an intriguing light on the neuropsychology of depression and its pharmacological treatment.

Whether this information can be harnessed to predict therapeutic response to SSRI treatment at an individual level is an important topic for clinical translation.

## References

- Coppen A. The biochemistry of affective disorders. *Br J Psychiatry* 1967;113:1237-64.
- Howes OD, Kambeitz J, Kim E et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment: meta-analysis of imaging studies. *Arch Gen Psychiatry* 2012;69:776-86.
- Cowen PJ. Serotonin and depression: pathophysiological mechanism or marketing myth? *Trends Pharmacol Sci* 2008;29:433-6.
- Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. *Lancet* 1997;349:915-9.
- Berman RM, Narasimhan M, Miller HL et al. Transient depressive relapse induced by catecholamine depletion: potential phenotypic vulnerability marker? *Arch Gen Psychiatry* 1999;56:395-403.
- 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. *Mol Psychiatry* 2007;12:331-59.
- Anderson IM, Parry-Billings M, Newsholme EA et al. Decreased plasma tryptophan concentration in major depression: relationship to melancholia and weight loss. *J Affect Disord* 1990;20:185-91.
- Wichers MC, Koek GH, Robaey G et al. IDO and interferon- $\alpha$ -induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. *Mol Psychiatry* 2005;10:538-44.
- Uher R, Tansey KE, Dew T et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *Am J Psychiatry* 2014;171:1278-86.
- Sharp T, Cowen PJ. 5-HT and depression: is the glass half-full? *Curr Opin Pharmacol* 2011;11:45-51.
- Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry* 2009;195:102-8.
- Beck AT, Rush AJ, Shaw BF et al. *Cognitive therapy of depression*. New York: Guildford, 1979.
- Duman RS. Pathophysiology of depression: the concept of synaptic plasticity. *Eur Psychiatry* 2002;17:306-10.
- Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science* 1997;275:1593-9.
- Sutton R, Barto AG. *Reinforcement learning*. Cambridge: MIT Press, 1998.
- Miyazaki KW, Miyazaki K, Tanaka KF et al. Optogenetic activation of dorsal raphe serotonin neurons enhances patience for future rewards. *Curr Biol* 2014;24:2033-40.
- Dayan P, Huys QJM. Serotonin in affective control. *Annu Rev Neurosci* 2009;32:95-126.
- Dayan P, Huys QJM. Serotonin, inhibition, and negative mood. *PLoS Comput Biol* 2008;4.
- Daw N, Kakade S, Dayan P. Opponent interactions between serotonin and dopamine. *Neural Networks* 2002;15:603-16.
- Cools R, Nakamura K, Daw ND. Serotonin and dopamine: unifying affective, motivational and decision functions. *Neuropsychopharmacology* 2011;36:98-113.
- Daw ND, Doya K. The computational neurobiology of learning and reward. *Curr Opin Neurobiol* 2006;16:199-204.
- Schweighofer N, Bertin M, Shishida K et al. Low-serotonin levels increase delayed reward discounting in humans. *J Neurosci* 2008;28:4528-32.
- Miyazaki K, Miyazaki KW, Doya K. The role of serotonin in the regulation of patience and impulsivity. *Mol Neurobiol* 2012;45:213-24.

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