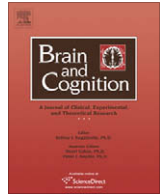




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## Serotonin: Modulator of a drive to withdraw

Mattie Tops<sup>a,b,\*</sup>, Sascha Russo<sup>c</sup>, Maarten A.S. Boksem<sup>d</sup>, Don M. Tucker<sup>b,e</sup><sup>a</sup> Centre for Child and Family Studies, University of Leiden, P.O. Box 9555, NL-2300 RB Leiden, The Netherlands<sup>b</sup> Neuroinformatics Center, University of Oregon, 1600 Millrace Drive, Eugene, OR 97403, USA<sup>c</sup> VUmc University Medical Center, De Boelelaan 1117, NL-1081 HV Amsterdam, The Netherlands<sup>d</sup> Department of Social Psychology and JuST, Tilburg University, Warandelaan 2, NL-5000 LE Tilburg, The Netherlands<sup>e</sup> Electric Geodesics, Inc., University of Oregon, 1600 Mill Race Drive, Eugene, OR 97403, USA

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## ABSTRACT

Serotonin is a fundamental neuromodulator in both vertebrate and invertebrate nervous systems, with a suspected role in many human mental disorders. Yet, because of the complexity of serotonergic function, researchers have been unable to agree on a general theory. One function suggested for serotonin systems is the avoidance of threat. We propose and review evidence for an alternative hypothesis, that a phylogenetically primitive function of serotonin is to oppose the activating neuromodulators (particularly noradrenalin and dopamine). The functional effect of this opposition can be seen as applying a drive to withdraw from dangerous, aversive or high stimulation environments. Proposing that serotonin is involved in a drive to withdraw and seek contentment, instead of a drive to avoid, may be compatible with several lines of evidence on serotonin function and may facilitate a better understanding of serotonergic neuromodulation in human psychopathology.

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## 1. Introduction

The serotonergic system is phylogenetically ancient, and yet has become exceedingly complex in the vertebrate brain. For example, there are over a dozen subtypes of serotonin receptors, many of which have separate functions. Not surprisingly, it has been difficult to specify general behavioral and psychological functions of serotonin systems, and this has led to reluctance to formulate a general theory (Deakin, 1996; Spont, 1992). However, if it were possible to formulate a general theory, this could be critical to understanding the strong evidence that serotonin plays a key role in certain psychiatric disorders. Serotonin has been implicated in many psychiatric disorders, but the most consistent evidence for an impairment of serotonin function has been found for depression (where selective serotonin reuptake inhibitors or SSRIs have been clinically effective) and impulsive aggressive personality disorders (where abnormally low serotonin levels have been observed; Deakin, 2003). We will review support for a novel hypothesis, that a phylogenetically old function of serotonin – as a neuromodulator of a drive to withdraw – provides a common framework for interpreting the apparently diverse functions of serotonergic systems in

modern humans. By this notion of a drive to withdraw we mean a primitive motive to reduce the present or anticipated environmental stimulation mentally or behaviorally, such as by moving into an environment of lower stimulation levels.

There are multiple groups of serotonin containing cells within the brainstem raphe nucleus, and these project to different forebrain areas. Cells of the dorsal raphe nucleus project to dopaminergic structures of the forebrain, whereas cells in the median raphe nucleus project to the hippocampus, in parallel with noradrenergic nerve terminals (Imai, Steindler, & Kitai, 1986; Vertes, 1991; Vertes, Fortin, & Crane, 1999). Deakin (2003) proposed that projections of the dorsal group of raphe serotonin cells oppose the action of dopamine and mediate avoidance of threats. In humans, impaired function of this serotonergic projection sensitizes the dopamine system, thereby resulting in symptoms such as impulsivity and drug addiction. Posterior serotonin cells innervate the hippocampus and cingulate gyrus and suppress memory and awareness of current and past adversity (see Deakin, 2003, for details and references). Deakin proposed that impaired function of this serotonergic projection results in low mood, low self-esteem, hopelessness, pessimism and reduces stress resilience. With this theory Deakin (2003) explained why the symptoms of one so-called low serotonin syndrome (depression) are very different from those of another syndrome (antisocial personality disorder).

Although Deakin's (2003) model provides a useful conceptual approach in differentiating functions of the major serotonin projections, we propose it may be possible to simplify and improve this

\* Corresponding author. Address: Centre for Child and Family Studies, University of Leiden, P.O. Box 9555, NL-2300 RB Leiden, The Netherlands. Fax: +31 71 5273945.

E-mail addresses: [mtops@fsw.leidenuniv.nl](mailto:mtops@fsw.leidenuniv.nl) (M. Tops), [sashar@GGZBuitenamstel.nl](mailto:sashar@GGZBuitenamstel.nl) (S. Russo), [maarten@boksem.nl](mailto:maarten@boksem.nl) (M.A.S. Boksem), [dtucker@egi.com](mailto:dtucker@egi.com) (D.M. Tucker).

URL: <http://www.centerofjust.com> (M.A.S. Boksem).

theory by identifying a common denominator of the functions of the two serotonergic projection groups originating from the raphe. Suppression of awareness and memory of current and past adversity facilitates withdrawal, and hence is compatible with the present primitive withdrawal drive hypothesis of serotonin function. In contrast, reduction of aversive memory does not seem to fit the threat avoidance framework; threat avoidance would be better served by improved aversive memory. However, we will argue that a subtly different interpretation of the function of the anterior serotonergic cells, in favor of increased withdrawal drive in response to threats instead of avoidance of threats, will suggest a common functional framework for both serotonergic projection groups. At the same time this interpretation is a better fit to the physiological properties of the serotonergic system. Finally, the withdrawal hypothesis may be compatible with other evidence on serotonergic function, such as in fatigue.

## 2. The serotonergic drive to withdraw

Testing a general theory of opposing effects of serotonin vs. noradrenalin on arousal and behavioral activation (Brodie & Shore, 1957), Ellison (1979) applied serotonin and noradrenalin neurotoxins to rats and compared the effects on behavior in a familiar environment with effects on behavior in a novel environment. He concluded that the low-serotonin animal can be thought of as being in a state of central functioning appropriate for any animal out in the environment, foraging for food: it is hyperaroused, sensitive to stimulation and vigilant and it is extremely frightened when confronted with a novel situation. Furthermore, Ellison suggested two antagonistic types of positive affect (drives): one which pulled the animal out of hiding into the environment by positively rewarding it when it engaged in appetitive consummatory responses (dopaminergic and noradrenergic), and another which pulled it back into the security of the nest by satisfying a reciprocal set of needs (serotonergic). The positive affects that Ellison associated with serotonergic function were security and relaxation, which served functions of energy conservation and recuperation.

Several findings suggest that serotonin is involved in reinforcement processes. For instance, in studies by Fantegrossi, Ullrich, Rice, Woods, and Winger (2002), monkeys self-administered MDMA (“ecstasy”), which was abolished by serotonin antagonists that did not affect cocaine-maintained behavior. In the terrestrial snail serotonergic cells have been found to reinforce withdrawal behavior and mediate acquisition of aversive withdrawal conditioning (Balaban et al., 2001).

Considering such elementary control functions that have been conserved through evolution, we propose that serotonin’s neuro-modulatory function can best be conceptualized as a primitive drive, “functioning in a higher-order capacity to integrate a variety of behavioral functions” (Lucki, 1998). The serotonergic projections apply a neurophysiological modulatory influence and this has very general, vectoral drive properties, meaning that behavior is oriented in a certain direction, in this case toward withdrawal from stimulation. The drive properties of the serotonergic projection systems can be described as primitive, in that they are not directed toward a single adaptive goal, such as feeding, but serve as substrates for multiple behavioral functions. Despite serotonin being involved in temperature regulation, feeding, sexual behavior, responding to painful stimuli, escape and stress, most of these response systems continue to function without serotonin (Lucki, 1998). A general primitive drive theory of serotonin function in behavior can help to account for why serotonin appears to influence so many behaviors, but also is an unlikely neurotransmitter to be the principle or sole mediator of any of these behaviors (Lucki, 1998).

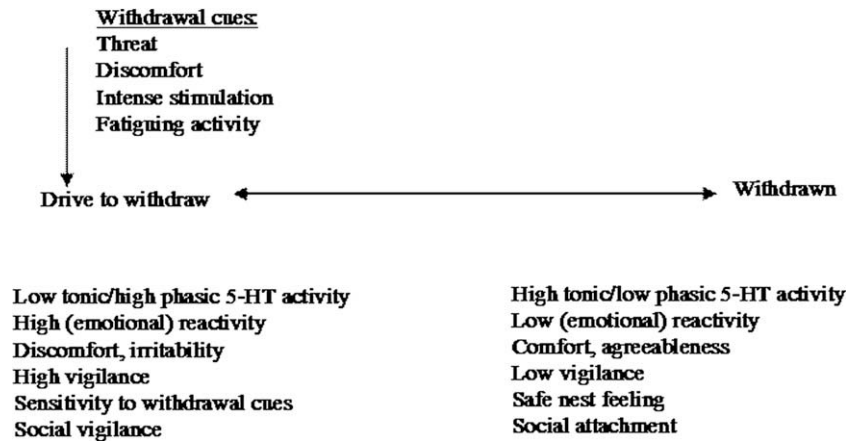
The concept of primitive drive may be similar to the explanation required for understanding the function of other phylogenetically old neuromodulator systems, for instance dopamine. Elsewhere we proposed that recent insights and theory regarding dopamine function may help understand the function of other neuromodulators including serotonin (Tops, 2004; Tops, van Peer, Wijers, Korf, & Tucker, 2007). Whereas the popular concept of a dopamine “reward system” implicated in hedonic or consummatory aspects of reward could be easily incorporated into behavioral and even psychological explanations, this concept may not fit with the more specific evidence on the role of mesolimbic dopamine in regulating behavior. Berridge (2007) points to evidence that dopamine is not implicated in the hedonic response to rewards, or “liking.” Rather, the more consistent evidence suggests that dopamine supports the sensitisation of incentives, or “wanting.” Although incentive sensitisation is a more elementary influence and not as easy to incorporate into behavioral explanations as a reward system, it may be more consistent with the widespread, primitive influence of the dopaminergic neuromodulatory system in multiple behaviors, including habit formation and avoidance conditioning (Robbins & Everitt, 2007).

Indications have been found for a drive-reduction function in the dopaminergic system (Liu & Wang, 2003). Low levels and high phasic activity in dopaminergic systems seem to mediate the approach motivational/reward-seeking drive (“wanting”) aspect of reward processing, while high levels of tonic activity may be associated with drive reduction, and perhaps the reward aspect of ‘liking’ (Berridge, 1999; Daw & Touretzky, 2002; Grace, 1991; Phillips et al., 2003). Part of this mechanism is that the depletion of tonic dopamine increases the dynamic range and thus the impact of changes in phasic dopamine, thus shifting the system from a tonic mode of neurotransmission to a phasic mode of neurotransmission, effectively increasing the signal to noise ratio (Cools, Roberts, & Robbins, 2008a; Cools, Robinson, & Sahakian, 2008b; Grace, 1991).

In a similar fashion, we think a theoretical analysis of the behavioral function of the serotonergic system suggests a primitive, widespread influence on behavior that can best be characterized as a drive for withdrawal into safety and/or comfort (Ellison, 1979; Erickson et al., 2005; Mawson, 1999). See Fig. 1. Serotonin influences the termination rather than the initiation of eating, and has been suggested to mediate the satiation that motivates meal termination and withdrawal (Leibowitz & Alexander, 1998; Mawson, 1999). In analogy to the dopaminergic system (Tops, 2004; Tops et al., 2007), low levels and high phasic activity (in response to withdrawal cues) may be involved in a drive to withdraw, while high levels or tonic activity may be involved in the actual withdrawal, by inhibiting other activating systems (e.g. Mawson, 1999). Similar antagonistic interactions between phasic and tonic neurotransmission have been proposed for dopamine, where tonic levels regulate the phasic dopamine responses to biological relevant stimuli (Grace, 1991).

The rewarding feelings associated with withdrawal may not be directly mediated by serotonin, if the analogy with the dopaminergic system holds through (Berridge, 1999). Moreover, the strength of withdrawal drive may not only depend on serotonergic activity, but also on the context of activities in other systems (Briand, Gritton, Howe, Young, & Sarter, 2007), as we will discuss below. Finally, the withdrawal drive is triggered and increased by internal and external stimuli that are recognized as cues to withdraw.

A similar analogy between dopamine and serotonin function, and regulation of phasic serotonin responses by tonic levels, has been proposed before (Cools et al., 2008a, 2008b; Daw, Kakade, & Dayan, 2002). However, those authors proposed that phasic serotonergic responses carry punishment information. We will argue that the present hypothesis better integrates information that serotonin



**Fig. 1.** Characteristics of a low withdrawal/high drive to withdraw state compared to a withdrawn/low drive to withdraw state. We propose that in healthy individuals serotonin flexibly and appropriately modulates gradual transitions between these states. Notice that especially the low withdrawal state may feature activities of other neuromodulators (e.g. dopamine, noradrenalin and acetylcholine), which are not considered in this figure. The activity of serotonergic and other neuromodulator systems depends on the constellation of external and internal stimuli, including circadian and seasonal cues and the context of activities in other interacting modulator systems.

not only modulates punishment reactivity and anxiety, but modulates emotional and sensory reactivity in a more general way, including reactivity to reward.

In an influential review Spooont (1992) also argued for a general modulation by serotonin of sensory reactivity. She reviewed evidence that increasing serotonin decreases reactivity to sensory stimuli and protects against overstimulation, while low serotonin states elicit an exaggeration of signal saliency and amplified signal passage. Behaviors modulated by serotonin appear to be especially facilitated by decreased serotonin when facilitatory signals of either internal or external origin drive the behavior; in terms of human personality this may result in an increased propensity for affective instability and greater stress reactivity (Spooont, 1992). Our present proposal is compatible with the view of Spooont. However, we propose, similarly to what has been proposed for dopamine, that the function of the phylogenetically old brainstem sourced serotonergic neuromodulator system can most likely be conceptualized as a primitive drive, orienting behavior in a certain direction. By proposing the withdrawal drive function, we integrate, or at least bridge part of the gap between, the proposal of Spooont (1992) and other proposals that focused on anxiety and avoidance of punishment. Instead of a function of serotonin in withdrawal from stimulation we propose a function of serotonin in a drive to withdraw from high stimulation.

Although we propose that serotonin facilitates withdrawal from sensory input, this does not mean that serotonin necessarily decreases motoric output. It has been suggested that serotonin facilitates motor output, partly by suppressing ongoing processing of sensory input that might disrupt motor output (Jacobs & Fornal, 1995). This is consistent with neuroimaging studies in depressed patients that suggest that serotonergic antidepressants shift a balance between cortical control systems from dominance of ventral, sensory reactive systems to relative dominance of dorsal, proactive/implemental systems (Tucker & Luu, 2007).

Withdrawal entails either neuromodulation that decreases reactivity to sensory stimuli and protects against overstimulation or behavior that decreases sensory stimulation, while a drive to withdraw entails a drive to decrease sensory stimulation and aversion of high stimulation.

### 3. Serotonin and anxiety

The hypothesis that serotonin possesses a positive relation to anxiety-related traits derives primarily from animal studies using

punishment paradigms which, for a number of reasons (including their motoric and positive motivational components), may not represent an appropriate model for assessing anxiety (Soubrie, 1986; see Harro, 2002, for a similar argument). In fact, the burial of the serotonin theory of anxiety was announced more than 20 years ago (Panksepp & Cox, 1986). The majority of findings in humans relate serotonin function to impulsiveness rather than anxiety, and when relations do emerge in the data, then low serotonin tends to relate to high anxiety, as well as to depression and high impulsiveness (see for a review Carver & Miller, 2006).

However, antidepressants with 5-HT<sub>2</sub> receptor antagonist properties have anti-anxiety effects (see Harro & Orelund, 2001). Some forms of behavioral inhibition and a restraint of the fight-flight response may be mediated by serotonergic projections from the dorsal raphe nucleus (Deakin, 1998). One of the functions of this 5-HT<sub>2</sub> system may be to facilitate anticipatory anxiety, perhaps paradoxically, because a high withdrawal drive is not satisfied. As part of an adaptive evolved mechanism, when threat is increasingly perceived or anticipated in the environment, a drive to withdraw may increase, pulling humans as well as rodents “back into the security of the nest” (Ellison, 1979). As long as the individual does not succeed in withdrawing, the presence of a high withdrawal drive may lead to anxiety.

However, in this example, the anxiety would be a secondarily induced activated state, not due to serotonergic mechanisms primarily. Although serotonin function has repeatedly been related to avoidance of threat (e.g. Deakin, 2003), it is important to notice that the withdrawal drive as proposed here is different from avoidance as this term is usually used in animal behavioral research. In this research, a distinction is made between passive or inhibitory avoidance and active avoidance. Both forms of avoidance are accompanied by high levels of arousal and vigilance that are not likely to be mediated by serotonergic systems. As one candidate mechanism, basal forebrain cortical cholinergic activity may foster vigilance and the attentional processing of novel or threat-related stimuli and associations, and thereby contribute to cortical/cognitive aspects of anxiety (Berntson, Sarter, & Cacioppo, 2003). Furthermore, whereas the cholinergic system is involved in inhibitory avoidance (Gray, 1987, 1989; Mawson, 1999), the noradrenalin-driven locus coeruleus is aroused in active avoidance and coping efforts to maintain or gain control (Henry, 1993). McClelland, Davidson, Saron, and Floor (1980) proposed that brain noradrenalin mediates a power drive, i.e. a drive to gain control. The locus coeruleus modulates vigilance and the initiation of

adaptive behavioral responses (Aston-Jones, Valentino, Van Bockstale, & Meyerson, 1994). The intense locus coeruleus activity that occurs during stress interrupts internally oriented behaviors such as sleep and grooming, which are associated with the lessened vigilance that is appropriate in the context of a predictable low stimulus, nonstressful environment. In contrast, serotonin appears to decrease attentional vigilance to threat stimuli (Murphy, Longhitano, Ayres, Cowen, & Harmer, 2006) and focused attention (Riedel, 2004), which may be due to its opponent effect on cholinergic and noradrenergic activity and cortical arousal (Robbins, 1997). This counteraction or modulation of other systems involved in attentional vigilance may underlie the anxiolytic effects of serotonergic agents.

Although we argue that a drive to withdraw from danger or discomfort is different from a drive to avoid it, anticipatory withdrawal from a potentially dangerous environment is a way to passively avoid potential harm. However, the difference is that the withdrawal behavior is motivated by a primitive drive to withdraw and decrease stimulation intensity. In contrast, avoidance motivation may involve anxiety and vigilance rather than withdrawal into low stimulation environments or lower arousal states. A drive to avoid would be characterized by vigilance but would not involve a drive to decrease vigilance. In contrast, if serotonin is involved in a drive to withdraw then it need not mediate vigilance, but rather a drive to reduce vigilance. We argue that the second position is more compatible with serotonin effects. Nevertheless, a drive to withdraw implies an aversion to intense stimulation, including self-stimulation, and is manifested in a tendency to avoid sources of intense light and sound, or other arousing stimuli (Mawson, 1999). Proposing that serotonin is involved in a drive to withdraw instead of a drive to avoid seems more compatible with general characteristics of serotonin function, and seems to allow the incorporation of different known or suspected serotonergic functions in a single framework.

One reason why the withdrawal framework seems able to explain more functions of serotonin than the threat avoidance hypothesis, is that the drive to withdraw from threat is merely a subset of the drive to withdraw from stimulation. Indeed, not all proposed withdrawal functions of serotonin are related to (avoidance of) threats, as will be illustrated below by the examples of the serotonergic role in fatigue and social interactive behavior. In contrast, we do not know of examples of serotonergic function that could be explained by a role in threat avoidance but not in withdrawal from stimulation. Hence, the withdrawal from stimulation hypothesis seems more inclusive than the threat avoidance hypothesis. Discriminating withdrawal from stimulation from threat avoidance may also help differentiating serotonin function from sometimes similar or overlapping functions of other neuromodulators involved in threat avoidance.

#### 4. Serotonin, impulsivity and aggression

The concept that impulsivity is a failure in serotonergically mediated behavioral inhibition has proved remarkably fertile. In most cases, serotonin appears to exert an inhibitory influence on behavior, whereby reductions of serotonin result in exaggerated behavioral responding (see Lucki, 1998; Zald & Depue, 2001). Previous reviews of serotonergic function concluded that serotonin seems to decrease responsiveness to current motivational stimuli, increasing constraint by allowing for responding to cues of longer-term outcomes and delay of gratification (Carver & Miller, 2006; Depue, 1995; Depue & Spoont, 1986; Soubrie, 1986; Zuckerman, 2005). Alternatively formulated, it has been proposed that serotonergic function disengages stimuli from their emotional consequences (Deakin, 1998; Handley & McBlane, 1991).

There has been notable convergence on the notion that impulsive aggression and auto-aggression correlate with serotonergic hypofunction and respond to treatment with serotonin reuptake blockers (Stein, Hollander, & Liebowitz, 1993). Furthermore, a strong genetic association exists between genes of the serotonergic systems and aggressive behavior (Popova, 2006). The serotonergic systems may serve to dampen and oppose the actions of the cholinergic, noradrenergic and dopaminergic systems, for example by promoting behavioral inhibition and cortical de-arousal (Robbins, 1997). Thus, serotonin promotes sleep, quiet non-aroused waking, parasympathetic activation and the antistress relaxation response (Buck, 1988; Miller & O'Callaghan, 2006). However, in some forms of serotonergic mediated inhibition, an impulsive and antisocial, even violent, state may develop paradoxically due to a lack of anxiety responses to normal social cues and low vigilance (Deakin, 1998; Ellison, 1979).

Multiple neuromodulators have been related to aggressive behavior. For instance, cholinergic deficiency has been related to deficient inhibition of aggression (Garcia-Alloza et al., 2005). High noradrenergic activity has been related to aggression and assertiveness (Haller, Makara, & Kruk, 1998; Tse & Bond, 2006), possibly because aggression is often involved in the (re)gaining of control (Henry, 1993). In Alzheimer's disease preservation of dopaminergic function has been related to aggression (Lanctôt, Herrmann, & Mazzotta, 2001), perhaps because aggression and anger often follow on frustration of reward obtainment and may function to facilitate reward and goal obtainment and approach motivation (Carver & Harmon-Jones, 2009). Lanctôt et al. (2001) argue that it is plausible that cholinergic and serotonergic dysfunction may also be present in the Alzheimer's disease patients, and that this may be necessary for the disinhibition of dopaminergically-mediated aggressive behavior. Serotonin seems indirectly involved in the damping of aggression by inhibiting these other neuromodulator systems, thus inhibiting impulsive (emotional) behavior (Mawson, 1999), and perhaps by increasing affiliation (see below). Moreover, at a high drive to withdraw, irritation may be aimed at obstacles preventing withdrawal. For instance, manipulations intending to induce fatigue, and thereby the drive to withdraw, also increase self-reports of state anger (Van der Linden & Eling, 2006).

Tryptophan, the precursor of serotonin, is the amino acid most sensitive to depletion. Russo et al. (2003) propose that tryptophan has a signaling role in physiology. The state in which tryptophan becomes depleted is associated with both external and internal unfavorable circumstances such as inflammation, stress and food shortage. Chances of survival may increase by more aggressiveness in an (perhaps ultimate) attempt to obtain food (Russo et al., 2003). Decreases in serotonin may facilitate such behavior by disinhibition of catecholaminergic systems.

#### 5. Serotonin and depression

Deakin (1996) proposes that forebrain serotonin has a special general role in minimizing the impact of aversive events on behavior, and when severe psychosocial and other stressors disturb it then depression and anxiety are the result. Also other authors suggested that the primary effect of serotonin may be to inhibit negative emotion and induce sanguinity, i.e. a quiet, low-arousal or satiated waking state (e.g. Healey & McMonagle, 1997; Jones, 2003; Miller & O'Callaghan, 2006; Tse & Bond, 2002a). Functional roles of serotonergic projections from the dorsal raphe nucleus to upper brain structures have been investigated by recording neural activity in this nucleus, and by observing effects of stimulation of this nucleus (Kayama & Koyama, 2003). According to Kayama and Koyama, "functions of the serotonergic projections are still mysterious, since its action on upper brain is inhibitory in spite



of waking-specific activity of the neurons." However, this pattern of activity and action is compatible with a role of serotonin in inducing a low-arousal or satiated waking state.

A large animal literature implicates serotonin in the modulation of both positive and negative affective behavior (e.g. Panksepp, 1982). Serotonin is known to inhibit approach behavior in conflict situations (Soubrie, 1986). In contrast, data from human studies emphasize serotonin modulation of negative emotional processing. In a study by Knutson et al. (1998), a selective serotonin reuptake inhibitor (paroxetine) reduced focal indices of hostility through a more general decrease in negative affect, and increased a behavioral index of social affiliation, after both 1 week and 4 weeks of treatment. Positive affect decreased nonsignificantly but in a similar effect size as the negative affect. Positive affect was measured using the PANAS, which intends to measure high excitement, dopamine related positive affect (Watson, Wiese, Vaidya, & Tellegen, 1999). In a study by Zald and Depue (2001), the prolactin response to DL-fenfluramine demonstrated a significant inverse correlation with mean ratings of both positive affect and negative affect, providing evidence that serotonin exerts an inhibitory influence over both positive and negative affect. Recent studies found that increasing serotonin produces biases on emotional processing away from negative and towards positive emotional material (Harmer, Shelley, Cowen, & Goodwin, 2004; Kemp, Gray, Silberstein, Armstrong, & Nathan, 2004; Murphy et al., 2006; Roiser et al., 2008).

There is much evidence that depression is characterized by defective serotonergic neurotransmission (Deakin, 2003; Lucki, 1998). Depressed people do not show the positive biases in emotional processing, and may even show negative biases (Leppanen, 2006). Although depressed people often tend to withdraw (Fenton et al., 2004), they lack the ability to disengage or to withdraw into a comforted state of security and sanguinity. There is evidence that depression is bound up with a general failure to disengage, and in some sense this failure seems to be at the core of the dynamics of depression (see Carver & Scheier, 1990; Gilbert, 1984). A compromised serotonergic system may prevent them from effectively disengaging and withdrawing in a self-soothing manner, and this inability may be at the core of the depressed state (as has been proposed for both depression and obsessive compulsive disorder: Handley & McBlane, 1991). In short, depression seems characterized by a high drive to withdraw from adversity, but an inability to effectively do so.

In contrast to the internally hyperaroused melancholic or agitated depression that features an inability to disengage, insomnia, decreased appetite and weight loss, many patients present with the opposite pattern of hypersomnia, increased appetite and weight gain, leaden paralysis (i.e. psychomotor retardation), fatigue and extreme sensitivity to interpersonal rejection. This atypical depressive presentation that also characterizes seasonal affective disorder, the depressed phase of type II bipolar disorder and premenstrual syndrome, is more suggestive of a state of hypoarousal than of hyperarousal (Chrousos & Gold, 1992). Despite low arousal, atypical depression is characterized by high reactivity; expressions of social anxiety may have primacy in this syndrome (Parker, Parker, Mitchel, & Wilhelm, 2005). Furthermore, the increased sleep, food intake, carbohydrate-craving, social withdrawal and highly co-morbid alcohol dependence all have been proposed to be ways to decrease reactivity or prevent arousal by withdrawing from conflictual situations (e.g. Levitan, Hasey, & Sloman, 2000). Indeed, both carbohydrate and alcohol intake increase serotonin and a relationship between carbohydrate craving and alcohol craving has been found in alcohol-dependent men under stress (Moorehouse et al., 2000). Scores on degree of two self-comforting behaviors, craving 'comfort' (high-carbohydrate) foods and 'warming up' behaviors such as having a hot bath (serotonin regulates

skin blood flow, which is a major mechanism in thermoregulation (Maurer-Spurej, 2005)), were found positively associated with increasing number of DSM-IV accessory atypical depressive symptoms (Parker & Crawford, 2007). We suggest that the mentioned behaviors partly reflect attempts at self-medication by reducing (i.e. satisfy) a drive to withdraw.

Large epidemiological studies have shown strong associations between atypical depression and migraine (e.g. Angst et al., 2006) and between migraine and the combination anxiety disorder and major depression (Merikangas, Angst, & Isler, 1990), which led to the suggestion that they share a common predisposition (Breslau & Davis, 1993). Migraine is often treated with serotonergic medication and among the features of migraine are aversive reactions to intense sensory stimulation (e.g. "phonophobia", "photophobia"; Leniger, von den Driesch, Isbruch, Diener, & Hufnagel, 2003). In the context of the present hypothesis, these aversive responses to intense sensory stimulation may reflect the function of the drive to withdraw; they may reflect affective responses to stimuli that frustrate this drive to withdraw.

In melancholic depression the patient seems relentlessly engaged with a distressing problem; although the problem may be beyond the patient's control, he does not accept this and is unable to disengage and withdraw. In contrast, it seems that in atypical depression the patient displays "learned helplessness" or "the involuntary defeat syndrome" (Levitan et al., 2000) which drives him to withdraw. Based on observations that depression with atypical features is associated with high rates of childhood physical and sexual abuse, Levitan et al. (2000) argue that these individuals may have developed long-lasting effects on brain mechanisms relevant to social defeat. An efficient involuntary defeat strategy would be highly adaptive for a defenseless child, de-escalating conflict in a potentially traumatic situation. This could include the promotion of a "freezing" response, a strategy often seen in animals to quickly terminate overwhelming encounters. If this type of de-escalation strategy is mediated by a particular brain circuit, and is activated repeatedly in childhood, it is likely that the threshold for activation would be progressively lowered over time. Later in life, activation of such a circuit might contribute to the experience of leaden paralysis with prominent fatigue and psychomotor slowing described by individuals with atypical depression. Another characteristic symptom, rejection sensitivity, may be conceptualized as the anticipation of defeat in response to even slight competitive or social escalation; this may again reflect the residual effects of early traumatic experiences (Levitan et al., 2000).

Different types of depression may also have mechanisms in common. In terms of a model proposed by Tucker and Luu (2007), high reactivity and the inability of depressed patients to disengage or withdraw may both reflect the activity of a ventral cortical control system that is very reactive to sensory input, associated with a negative emotional bias, and with rumination. Neuroimaging studies of depressed patients suggest that successful serotonergic antidepressant treatment shift dominance from this ventral network to a dorsal network. This dorsal system, according to the model of Tucker and Luu (2007), displays a positive bias in emotional stimulus processing to facilitate a proactive, implemental mode of behavioral approach. According to the present hypothesis, the role of serotonin in this shift would be to facilitate withdrawal from adversity and rumination by inhibiting the reactive ventral system. As noradrenalin is believed to be a prominent modulator of the dorsal system (Tucker & Luu, 2007), noradrenergic antidepressants may induce a similar shift between systems by activating the dorsal system. Indeed, similar to serotonin, noradrenergic antidepressants increase positive biases in the processing of emotional material (Harmer et al., 2004; Norbury, MacKay, Cowen, Goodwin, & Harmer, 2007; Serra et al., 2006).

In short, although there are different types of depression, and precise mechanisms of depression and of features such as carbohydrate craving are not known, the withdrawal drive hypothesis of serotonin function does seem to offer novel hypotheses regarding depression.

## 6. Serotonin and fatigue

It appears that important relations exist between brain serotonin and central fatigue (Davis, Alderson, & Welsh, 2000; Davis & Bailey, 1996; Newsholme, Acworth, & Blomstrand, 1987). In a challenge test of the serotonergic system, serotonergic reactivity related strongly to the fatigability and asthenia subscale of the Harm Avoidance scale of the Cloninger Tridimensional Personality Questionnaire, but to no other scales (Hennig, Toll, Schonlau, Rohrmann, & Netter, 2000). Increases in brain serotonin concentrations and overall activity have been associated with increased physical and perhaps mental fatigue during endurance exercise. Results led Davis et al. (2000) to hypothesize that a high ratio of serotonin to dopamine favors tiredness, lethargy and decreased motivation (see also Meeusen, Watson, Hasegawa, Roelands, & Piacentini, 2006). Pharmacological manipulations in rats have shown that increased serotonergic activity causes fatigue to occur earlier, while decreased serotonergic activity has the opposite effect. These modulations in run time to fatigue occurred despite no apparent alterations in body temperature, blood glucose, muscle and liver glycogen, or various stress hormones. Similar studies were conducted in human subjects in which serotonergic activity was increased. Fatigue occurred earlier during running or cycling, and ratings of perceived exertion were increased relative to placebo (see Davis et al., 2000). After major surgery, often causing post-operative fatigue, a correlation was found between fatigue scores and plasma free tryptophan, and the ratio tryptophan/branched chain amino acids (McGuire et al., 2003). The relations between serotonin and fatigue are important in the present discussion, because fatigue is associated with a drive to withdraw.

Fatigue is a feeling or emotion that is directly related to a drive to withdraw, but in contrast to for instance fear, it is not directly triggered by threat stimuli. The term fatigue is used when prolonged activity, time awake or circadian rhythm increase a drive to withdraw into a lower stimulation environment. But also the withdrawn post-exercise state of decreased arousal and arousability is referred to as fatigue. However, fatigue during compared to after exercise refers to different states, feelings and mechanisms. Post exercise fatigue, when one is allowed to rest, can be quiet pleasant. This withdrawn state may be mediated by high tonic/low phasic serotonergic activity (see Fig. 1), as serotonin is thought to induce a satiated waking state (Jones, 2003; Mawson, 1999). This post-exercise state actually seems similar to the serotonin-mediated satiated state after consuming a heavy meal (Leibowitz & Alexander, 1998), and may be the reward aspect of fatigue. The withdrawn, low arousability state after long lasting exertion (Fig. 1) makes it difficult for individuals to motivate, exert effort, re-activate and overcome fatigue after a period of recuperation (Schellekens, Sijtsma, Vegter, & Meijman, 2000). However, during exercise, high phasic serotonergic activity (Fig. 1) may mediate a drive to withdraw, and hence a resistance to continue; this drive to withdraw or resistance to continue is an important aspect of the motivational component of fatigue (Hockey, 1997).

Associations between serotonin and withdrawal in fatigue are important to our discussion of serotonergic function. However, fatigue is not a single phenomenon and involves other mechanisms as well. The drive to withdraw state, due to low inhibition by serotonin, features the activities of many other neuromodulators (Fig. 1). Exercise has been reported to increase the synthesis and

metabolism of dopamine and noradrenaline in the brain (Chaouloff et al., 1987). Chaouloff et al. (1987) suggest that an increased concentration of dopamine in some parts of the brain could inhibit the synthesis of serotonin during exercise and thereby delay fatigue. Similarly, noradrenergic locus coeruleus neurons prevent de-arousal and are able to enforce arousal (Jones, 2003). It has been suggested that an increase in central ratio of serotonin to dopamine is associated with feelings of tiredness and lethargy, accelerating the onset of fatigue, whereas a low ratio favors improved performance through the maintenance of motivation and arousal (Davis et al., 2000; Meeusen et al., 2006). This suggests that rewarding activities, and physical exercise, both may postpone fatigue by increasing dopaminergic activity (Boksem, Meijman, & Lorist, 2006). Fatigue will set in inevitably, though, as with increasing time on task and increasing time awake, adenosine will progressively inhibit neuronal activity, apparently with high affinity for dopaminergic cells (see Lorist & Tops, 2003).

One reason why the withdrawal framework seems able to explain more functions of serotonin than the threat avoidance hypothesis, is that not all proposed withdrawal functions of serotonin are related to (avoidance of) threats. Fatigue is a feeling or emotion that is directly related to a drive to withdraw, but in contrast to for instance fear, it is not directly triggered by threat stimuli. Hence, the withdrawal hypothesis of serotonin function seems better able to explain associations between serotonin and fatigue.

## 7. Serotonin and social behavior

Although the serotonergic drive to withdraw may originally have evolved to withdraw from dangerous, aversive, or high stimulation environments, during evolution animals developed new behavioral repertoire. Some of these behaviors were best performed in safe and relatively low arousal conditions. Hence serotonergic function may have become involved in these behaviors by providing a drive to seek out suitable environments and arousal states. One important class of behaviors in humans to which this may apply is the class of social interactive and attachment-related behaviors. Serotonin may also facilitate social behaviors by decreasing responsiveness to current motivational stimuli, increasing constraint by allowing for responding to cues of longer-term outcomes and delay of gratification (Carver & Miller, 2006; Depue, 1995; Depue & Spoont, 1986; Soubrie, 1986; Tanaka et al., 2007; Zuckerman, 2005). For instance, a recent study in healthy volunteers demonstrated that tryptophan depletion induced a shift away from cooperative behavior associated with more long-term gain in favor of short-term profit (Wood, Rilling, Sanfey, Bhagwagar, & Rogers, 2006).

There are different types of social interactions, some of which can be described as lively, energetic, impulsive, reactive and highly rewarding and arousing. Dopamine is likely involved in these high arousal rewarding interactions. We propose serotonin is involved in another type of social interactions, in which immediate reward value is traded for delayed rewards (Tanaka et al., 2007). To do so, serotonin decreases both aversive and appetitive reactivity. The drive for these low-arousal social behaviors may have been derived from a serotonergic drive to withdraw into a safe place.

Most activities reflecting attachment behavior are most successfully maintained when the organism is relatively relaxed and free from challenge by the need for self-preservation (Henry, 1993). Serotonergic sanguinity and comfort may be important to the facilitation of social interactions by reducing the associated anxiety and inhibition. Indeed, for many attachment-related and other affiliative social interactions, people tend to withdraw into safe and low stimulation environments, like their homes (“nests”), or to public places like bars and restaurants furnished like “nests”.

The theory of Porges (2001) states that, when the individual perceives the environment as dangerous, first of all there is a degrading of the function of the social engagement system. The social engagement system, which is a phylogenetically younger system, controls looking, listening, vocalizing, facial gesturing, promotes self-soothing behaviors and calm behavioral states and supports the metabolic requirements for mobilization and communication behaviors (Porges, 2001). It is related to parasympathetic and oxytocinergic control and modulation (Porges, 2001).

Social contact is believed to enhance the stress-protective serotonin (5-HT<sub>1A</sub>) receptor-mediated function of serotonergic neurotransmission (Deakin, 1996). This social anti-stress, increased social confidence effect of serotonergic function is very similar to functions ascribed to oxytocin (McCarthy, 1995). Serotonin, like oxytocin, by promoting social confidence and reducing the associated anxiety and inhibition, might promote social activities, especially in anxiety-provoking situations (McCarthy, 1995). The oxytocin and serotonin systems are interconnected. Oxytocin fibers project to the raphe nuclei and oxytocin may influence the secretion of serotonin and the release of oxytocin is enhanced in response to administration of 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> receptor agonists. Recent studies have demonstrated that oxytocin is released in response to treatment with selective serotonin reuptake inhibitors, opening up the possibility that oxytocin may mediate some of the social effects caused by serotonin, some of which are described next (see Anderberg & Uvnäs-Moberg, 2000; Uvnäs-Moberg, Björkstrand, Hillegaard, & Ahlenius, 1999).

In vervet monkeys, when central serotonergic sensitivity is high, the frequency of initiated aggressive behavior is low; animals are more relaxed socially, minimally vigilant of other group members, and more tolerant of the behavior of other animals and they more frequently initiate and respond to affiliative gestures. If the frequency of submissive displays by subordinate males declines, peripheral serotonin levels decline among dominant males; this is not mediated by a reduction in dominance displays by dominant males. Essentially the opposite findings apply to animals with low central serotonin sensitivity: animals initiate and receive fewer affiliative behaviors; they receive and initiate more threats; and they devote a high percentage of their time to interanimal vigilance (see Gilbert & McGuire, 1998; McGuire, Fawzy, Spar, & Troisi, 2000). Higley et al. (1996) conclude that serotonin plays a crucial role in both male and female social affiliation and de-escalation by controlling impulses that regulate aggression and promote competent social behavior.

In vervet monkeys tryptophan treatment facilitates the acquisition of dominance in males and increases affiliative behavior (Raleigh & McGuire, 1989; Raleigh, McGuire, Brammer, Pollack, & Yuwiler, 1991). In a study of healthy volunteers, Moskowitz, Pinar, Zuroff, Annable, and Young (2001) found that relative to placebo, tryptophan treatment increased dominant behavior and decreased quarrelsomeness (increased agreeableness). Similar results were obtained with a 2-week treatment with a selective serotonin reuptake inhibitor (citalopram) relative to placebo, results indicating increased dominance and affiliative behavior (Tse & Bond, 2002b). However, regarding dominance, there are contradictory results where indications of lower serotonergic activity have been found in dominant male monkeys (e.g. Kaplan, Manuck, Fontenot, & Mann, 2002). Kaplan et al. offer an explanation of contradictory results by noting that negative relations between serotonergic function and dominance tend to be found in tightly constrained social and physical conditions allowing neither for escape nor exploitation of social resources. Animals achieving dominant status under such circumstances may differ temperamentally from monkeys categorized as dominant in a single, larger heterosexual grouping with a longer and more complex social history. In terms of the present proposal, this indicates that low serotonin

levels tend to be found in dominant male monkeys when dominance is achieved by reactive, impulsive behavior, while high serotonin levels tend to be found in dominant male monkeys when dominance is achieved by social behavior that is guided more by longer-term outcomes and delay of gratification.

Based on our framework and the above, we suggest that serotonin may drive withdrawal into the safety and protection of social groups and support. Protection from threats by withdrawal into the safety of female social groups has been proposed to be a stress response that selectively evolved in women (“tend-and-befriend response”; Taylor et al., 2000). Emotionally supportive social relationships are substantially more protective against major depression for women than for men (Dalgard et al., 2006; Kendler, Myers, & Prescott, 2005). Both the social support and associated increases in serotonin function and oxytocin may increase stress resilience (Deakin, 1996; Taylor et al., 2000). Atypical depression is especially prevalent in premenopausal women (Antonijevic, 2006). Perceptions of unsafety, e.g. of potential rejection, may degrade the functions of the social engagement system, serotonin and oxytocin (Porges, 2001). It seems an important avenue for future research to investigate if atypical depression may involve impaired employment by women of “the withdrawal into the safety of female social groups” stress resilience response.

We argued that serotonergic function may have become involved in certain (e.g. social) behaviors by providing a drive to seek out suitable environments and arousal states. This suggests that although serotonin generally reduces cortical activation, certain serotonergic systems may facilitate the activation and functioning of areas or networks involved in these low arousal-requiring behaviors. Functional magnetic resonance imaging studies seem to support this. The intravenous infusion of a drug that stimulates 5-HT<sub>2</sub> receptors, mCPP, significantly enhanced a ventrolateral frontal focus associated with behavioral inhibition (Anderson et al., 2002). This activation was similar to activations when subjects view angry rather than neutral faces, a powerful inhibitory social signal for humans (Blair, Morris, Fritch, Perrett, & Dolan, 1999). Similar results after a serotonergic manipulation have been found in nearby right inferior and ventrolateral prefrontal regions and left insula during performance of a go/no-go task on no-go response inhibition trials (Del-Ben et al., 2005; Rubia et al., 2005; Völlm et al., 2006), but opposite results were reported in response to aversive faces (Del-Ben et al., 2005). This is not to say that serotonin modulates this activity on a trial-to-trial basis, but rather that it facilitates the activation of these networks, either directly or by inhibiting or disinhibiting other neuromodulatory systems.

## 8. Conclusion

Some understanding of what serotonin normally does seems crucial for a deep understanding of its suspected role in many mental disorders. Because of the complexity of serotonergic function, researchers have been reluctant to formulate a general theory. However, serotonin systems have been suggested to be involved in the avoidance of threat. We propose that there is substantial evidence for an alternative hypothesis, that a phylogenetically old function of serotonin is to mediate a drive to withdraw from dangerous, aversive or high stimulation environments. This hypothesis provides a common framework for understanding the multiple functions of serotonergic systems in modern humans.

We suggest that the withdrawal framework of serotonergic function may facilitate a better understanding of various forms of psychopathology. For instance, we discussed differences between withdrawal and avoidance. Research on depression and anxiety has addressed the role of threat avoidance motivation, but has neglected withdrawal motivation. We also discussed the possibility



that an impaired employment by women of “the withdrawal into the safety of female social groups” stress resilience response, may be implicated in atypical depression and related disorders. Serotonin may be involved in defenses against deleterious effects of stress, and hence increase resilience (Deakin, 2003). The withdrawal that is motivated by serotonergic activity may physically or psychologically protect the individual from harm, and in other situations it may allow for recuperational processes to take place (Ellison, 1979).

The present hypothesis proposes that serotonergic systems can be explained in relation to a single behavior control function, a primitive drive to withdraw. Because, the effects of serotonin are exerted at a neurophysiological level, with inhibitory or modulatory effects on multiple activating neuromodulators (such as acetylcholine, noradrenalin and dopamine), it may seem simplistic to try to capture the multiple functions of serotonin within a single drive concept. Alternatively, serotonin's role may be seen as opposing and balancing the unique control effects of each of the activating neuromodulators, in which case it would have differing functional roles depending on what activating function was being inhibited. Even if the single function of withdrawal proves explanatory, aspects of the present hypothesis will almost certainly need further detailing in order for the theory to inform our understanding of psychopathology and its treatment. Especially important is the discrimination of the high withdrawal drive (hypothetically low tonic/high phasic serotonergic activity) state, from the withdrawn (hypothetically high tonic/low phasic activity) state of serotonergic systems. Differences between these two extreme states of serotonergic function may be reflected in the opposite effects of serotonergic antidepressants during the 1st weeks of treatment compared to after prolonged treatment, and again after discontinuation. Both the 1st weeks of serotonergic antidepressant treatment, and abrupt discontinuation of drugs with a short half-life, coincide with increases in depressive symptoms, anxiety and agitation, irritability, fatigue, clinical global severity scores and difficulty in social functioning (Judge, Parry, Quail, & Jacobson, 2002; Schatzberg et al., 1997; Zajecka, Tracy, & Mitchell, 1997).

Serotonergic medication has shown some efficacy in the treatment of many psychopathologies. This nonspecific efficacy may be explained by the serotonergic inhibition of other neuromodulatory systems that may be more selectively involved in psychopathologies and by increased serotonin-mediated stress resilience. This suggests that even though serotonergic medications have had some success in treating psychopathology, this treatment may often not address the functional origin of the specific psychopathology. Treatment of different psychopathologies may benefit from attention to alternative treatment strategies and research into fundamental functional origins of psychopathologies, be it psychopharmacological or psychosocial origins.

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