Serotonin as a biocultural molecule: Circular causality, stress, and psychopathology

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Abstract

Serotonin (5-HT) show important relations to stress, and this relationship is crucial to understanding the psychobiology of common mental disorders. Environmental stressors regulate phasic and tonic serotonin levels, which are related to valence and outcome probabilities. This regulation takes place at smaller timescales, but also at the level of gene expression regulation. Moreover, genes related to the synthesis, metabolism, and transport of 5-HT are also involved in this regulation. Genetic variations in these genes modulate how stressors can lead to mental distress, but stressors also modulate gene expression in a genotype-dependent manner. As a result, the relationship between psychosocial stress and the regulation of the expression of 5-HTergic genes is bidirectional. This suggests a "circular causality" in which gene variations control tonic and phasic 5-HT signals ("upward causality"), while configurations and functions of the entire organism determine which genes are up- or downregulated, or which gene products are actually relevant in each situation ("downward causality"). The highly important role of social factors in human psychopathology is highlighted, and factors such as attachment and socioeconomic status modulate how the circular vertical causality between genes, neurotransmitters, and behavior is organized, representing circular horizontal causality. These complex interrelationships also suggest that more refined epistemologies are needed to fully grasp the relationship between 5-HT and common mental disorders.

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Introduction

Serotonin (5-HT) is a biogenic monoamine that has long been associated with the development of mental distress (Sjoerdsma & Palfreyman, 1990). The depressogenic effect of amine-depleting drugs, such as reserpine, and the use of serotonin reuptake inhibitors to treat mood disorders, including major depressive disorder, led to favoring this neurotransmitter in mechanistic explanations of mood regulation (Cowen & Browning, 2015; Vaswani et al., 2003). While this monoaminergic theory of depression has long been viewed as overly simplistic (Cowen, 2008; Moncrieff et al., 2022), the role of 5-HT in different manifestations of distress has expanded considerably. In part, this is due to the application of selective serotonin reuptake inhibitors (SSRIs) to treat more and more disorders (Vaswani et al., 2003); currently, there is evidence of low-to-moderate quality of positive effect of SSRIs in the treatment of depressive disorders (Arroll et al., 2009; Purgato et al., 2014; Wilkinson & Izmeth, 2016), obsessive-compulsive disorder (Soomro et al., 2008), various anxiety disorders (Bighelli et al., 2018; Williams et al., 2017), and post-traumatic disorder (Williams et al., 2022). While representing widely different symptom presentations, it can be argued that these diagnostic categories are all responses to stress. Indeed, these diagnoses represent less severe but more common “neurotic” conditions, dominated by internalizing symptoms of anxiety, depression, or a combination of both, sometimes called “common mental disorders” (CMDs) (World Health Organization, 2017). The term “internalizing” refers to conditions whose central feature is disordered mood or emotion, while “externalizing” conditions are ones that show dysregulated behavior as its central feature (Kovacs & Devlin, 1998).

While the pattern of high comorbidity across CMDs and the fact that they are currently all treated with SSRIs or other serotonergic drugs has led some to suggest a common neurobehavioral

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mechanism – a serotonin-sensitive "internalizing" trait such as neuroticism or negative emotionality (Krueger, 1999) – and/or a common genetic basis, CMDs are clearly the most stress-sensitive of all diagnostic categories in the DSM (Conway et al., 2012). As a result, not only genetic factors related to the role of gene variants in the serotonergic pathway should be investigated – as is the current trend –, but alternative and complementary hypothesis on the role of 5-HT in stress responsiveness should also be addressed. In what follows, we review some of the known impacts of stress in serotonin physiology, and then review the impacts of different psychosocial stressors in modulating the expression and activity of genes in the serotonin pathway. What emerges is a picture of the serotonergic system as highly plastic, responsive to stress in different time ranges, and able to modulate responses to stress. This points to a "biocultural" interpretation of the relationship between 5-HT, stress, and psychopathology.

Phasic and tonic serotonin in the regulation of stress physiology

Serotonin is what Mesulam (1998) called a "state function" neurotransmitter. Its neurons communicate in more widespread patterns that reflect changes in the *state* of the organism rather than in specific information-processing channels. In mammals, 5-HTergic neurons are located mainly in the seven raphe nuclei of the brainstem, some of which have subnuclei with more specific projections (Hale & Lowry, 2011). The axons of 5-HTergic neurons display varicosities that can release the neurotransmitter upon axonal depolarization, leading to widespread release of the neurotransmitter across an entire pathway (Beaudet & Descarries, 1981). Thus, 5-HTergic neurons project onto extremely large number of other neurons, and the forebrain neurons that receive these projections are widely distributed into the brain, so that a small raphe nucleus can influence neurons in large information-processing channels of the brain simultaneously (Mesulam, 1998).

Serotonergic neurons from the dorsal raphe nucleus (DRN) are among the most well-studied, given their putative role in anxiety and depression (Graeff et al., 1996; Lowry et al., 2008).

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These cells respond to different events, including visual, olfactory, and somatosensory stimuli, incentive events (such as rewards and punishments), movement, and delay (Wong-Lin et al., 2017). The timescale of these responses is also highly variable, including very brief, "phasic" responses to sensory stimuli and "tonic" activity that last across trials (Cohen et al., 2015; Hayashi et al., 2015). This tone is maintained by autoreceptors (including the 5-HT_{1A} and 5-HT_{1B} receptors), as well as by 5-HT_{2C} heteroreceptors located in inhibitory interneurons in the raphe, both of which act as a "thermostat" in the serotonergic tone (McDevitt & Neumaier, 2011). Thus, the initial view of 5-HTergic neurons that fired in an homogeneous and predominantly rhythmic way changed to a view in which cells are phasically responsive to various stimuli at the faster timescales (milliseconds to seconds) and able to modify their tonic firing rate in relation to slower timescales (Okaty et al., 2019).

There is considerable heterogeneity in the electrophysiological, hodological, and anatomical and developmental trajectories of 5-HT neurons in the raphe (Andrade & Haj-Dahmane, 2013; Gaspar & Lillesaar, 2012; Hale & Lowry, 2011; Okaty et al., 2019). For example, neurons in the dorsal portion of the DRN – which project mainly to the central amygdala, paraventricular nucleus of the hypothalamus, and bed nucleus of the stria terminalis (Hale & Lowry, 2011) – are activated by both rewarding and aversive stimuli *in vivo*, and their acute activation increases anxiety-like behavior in rodents (Okaty et al., 2019). Conversely, neurons in the *ventromedial* DRN, which project mainly to the frontal cortex (Hale & Lowry, 2011), are activated by rewards but inhibited by aversive stimuli *in vivo*, and their acute activation promotes active coping in the forced swim test in rodents (Okaty et al., 2019). In monkeys performing Pavlovian conditioning tasks in which visual cues predicted either aversive or appetitive outcomes, single DRN neurons (presumably in the dorsal portion of the DRN) encode both aversive and appetitive information, but tonic activity appears to discriminate the valence (appetitive vs. aversive) of the context, while a relatively phasic activity appears to encode outcome probability (Hayashi et al., 2015). Mirroring neurons from the ventromedial DRN, neurons from the *median* raphe, which project to the hippocampus and septum, are also involved in

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coping, but their acute *silencing* promotes acute coping in the forced swim test (Okaty et al., 2019). In zebrafish, serotonergic tone of median raphe neurons appears to be under the control of the ventral habenula, and this projection represents negative reward expectation value and is essential for avoidance learning (Amo et al., 2014).

In spite of the high diversity of tonic and phasic serotonergic responses in raphe neurons, at least in the case of the dorsal and median raphe these neurons appear to regulate adaptive responses to environmental stress and rewarding or aversive stimuli (Okaty et al., 2019), an effect that is dependent both on the slower, tonic responses (presumably setting the valence or expectation value) and brief, phasic responses (presumably encoding outcome probability)(Cools et al., 2011; Dayan & Huys, 2008, 2009).

While the dorsal (DRD) and ventromedial (DRV) cells are, in the absence of stressors), producing this tonic activity and setting expectancy values, neurons from the lateral wings of the DRN (lwDRN) have a sustained level of low activity, due to the tonic inhibition by projections from the ventromedial prefrontal cortex (VMPFC) which synapse onto a large population of GABAergic interneurons of this subnucleus (Amat et al., 2005). While controllable stressors maintain this inhibition, severe and uncontrollable stressors lead to a massive release of 5-HT in the DRN, disrupting the firing patterns, altering 5-HT release in the forebrain targets of other DRN subnuclei, and leading to raphe-raphe interactions (Jasinska et al., 2012). These stressors activate neurons in the lwDR, producing an ‘alarm’ signal that overrides the inhibition of these neurons by the VMPFC. Jasinska et al. (2012) suggested that, when this happens, lwDR neurons release 5-HT to other raphe subnuclei as well, activating 5-HT_{1A} receptors in serotonergic neurons of the DRD and DRV. This should result in an inhibition of serotonin release in targets of these neurons that can alter the tonus for hours, allowing more extreme, “panic-like” responses to threat mediated by these forebrain and midbrain targets of serotonergic neurons. Likewise, in zebrafish a projection from the habenula to the raphe mediates tonic responses of putative serotonergic neurons, representing the expectation of

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a dangerous outcome and be used for comparison with a real outcome when the fish is learning how to escape from a dangerous to a safer environment (Amo et al., 2014).

Interactions between stress and serotonin physiology

5-HT is synthesized *de novo* in a two-step reaction from tryptophan to 5-hytroxytryptophan and then 5-HT; the rate-limiting enzyme in the process is tryptophan hydroxylase (TPH), which presents two isoforms in vertebrates (Hasegawa & Nakamura, 2010). Based mainly on data on the expression of *TPH2* in rhesus monkeys, Chen and Miller (Chen & Miller, 2012) propose that stress mechanisms regulate expression (and therefore 5-HT synthesis) in different ways depending on the timescale: acute and chronic stressors, which lead to cortisol synthesis and release by the adrenal gland, induces *TPH2* expression and *de novo* 5-HT synthesis; in its turn, serotonin inhibits cortisol secretion by modulating the adrenal sensitivity to adrenocorticotropic hormone (ACTH), thus providing another mechanism for feedback inhibition of cortisol synthesis. This feedback inhibition also means that basal *TPH2* expression influences basal cortisol levels; for example, in rhesus monkeys that are homozygous for the C allele in the 2051A>C single-nucleotide polymorphism of *TPH2*, expression of this protein is reduced, and linked to increased cortisol production in the early morning and in response to an ACTH challenge (Chen et al., 2006).

Importantly, this genotype has been shown to interact with a history of early-life stress (ELS) to modulate the adult stress response. Early-life experiences program the plasticity of the neuroendocrine responses of the hypothalamus-pituitary-adrenal (HPA) axis by regulating the expression of glucocorticoid receptors not only across the axis, but also in brain regions that regulate its activity (Liu & Nusslock, 2018). For example: humans and Rhesus monkeys form important attachment relationships with their mothers and, if maternal separation takes place, long-term neurobehavioral effects take place, impairing stress responses (Meyer et al., 1975; Suomi et al., 1976). Mother-reared rhesus monkeys that were heterozygous A carriers in the 2051A>C polymorphism

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show decreased afternoon cortisol levels, but peer-reared, heterozygous monkeys showed *increased* afternoon cortisol levels (Chen et al., 2010). Moreover, peer-reared homozygous monkeys had lower plasma ACTH levels in both the morning and the afternoon than mother-reared or heterozygous individuals. Since cortisol levels show a circadian control, the effect of the polymorphism (predicted to reduce TPH2 expression) interacts with ELS (rearing conditions) to impair the regulatory control of serotonin on cortisol production.

In humans, a functionally similar polymorphism (rs11178997, or 437T>A) is associated with decreased TPH2 transcriptional activity in primary serotonergic neurons and human small cell lung carcinoma (SHP-77) cells, with substitution of T for A leading to decreased expression (Scheuch et al., 2007). The A allele is associated with decreased cortisol and ACTH stimulation during dexamethasone and CRH administration (Zill et al., 2007), suggesting impaired regulatory control of cortisol production. One study found that carriers of the T allele are more likely to develop symptoms of post-traumatic stress disorder (PTSD) (Goenjian et al., 2012), but another study failed to find an association between the rs11178997 SNP and PTSD symptoms (Goçi Uka et al., 2019). While the A allele is negatively associated with major depressive disorder (MDD)(Van Den Bogaert et al., 2006), this association is probably mediated by stressful life events: individuals homozygous for the A allele were susceptible to major depressive disorder (MDD) only when scores in the Life Events Scale were higher than the 75% percentile, indicative of high frequency and/or impact of negative life events (Ma et al., 2015). Taken together with findings from rhesus monkeys discussed above, these results corroborate the idea that *TPH2* polymorphisms which impact its expression (and therefore the synthesis of serotonin) interact with stressful life events to modulate the responsiveness to stress.

Serotonin is metabolized by monoamine oxidase (MAO), an enzyme that presents two isoforms – MAO-A and MAO-B – that differ in terms of their affinities to specific monoamines (Shih & Ridd, 1999). MAO-A preferentially metabolizes 5-HT and norepinephrine (NE), while MAO-B

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preferentially metabolizes phenylethylamine; both isoforms can metabolize dopamine (DA). *Maoa* knockout mice have elevated brain levels of 5-HT, NE, and DA, and present increased stress reactivity and higher aggressive behavior; *maob* knockout mice exhibit increased stress reactivity, but no changes in aggressive behavior, and only phenylethylamine levels are increased in its brains (Shih et al., 1999). Human *MAOA* polymorphisms have been associated with aggressive behavior as well, with important interactions with stressful life events: a meta-analysis suggested that the association between maltreatment and mental health problems in 7-year-old boys is stronger in individuals that are carriers of the low-activity variants of the main functional polymorphism of this gene (*MAOA-uVNTR*)(Kim-Cohen et al., 2006). Another meta-analysis found significant interactions between childhood maltreatment and the low-activity variant on antisocial behavior (Byrd & Manuck, 2014). When compared with data on TPH2 polymorphisms, it appears that lower MAO-A activity, associated with *higher* levels of biogenic amines (including but not limited to 5-HT), lead to *externalizing* behavior in response to early-life stress, while lower TPH2 expression, associated with *lower* levels of 5-HT, lead to *internalizing* behavior as a result of early-life stress.

Most of the bidirectional links between serotonin-related molecules and stressful life events comes from the serotonin transporter (5-HTT, SERT, or SLC6A4). Caspi and collaborators (2003, 2010), first described the interaction between *5HTTLPR* polymorphisms – an important candidate that was already implicated in genetic research, and stressful life events. The *5HTTLPR* polymorphism is a functional polymorphism of the promoter region of the gene encoding the serotonin transporter; although most researchers report two variations in humans – the short (“s”) form and the long (“l”) form – other isoforms exist (Nakamura et al., 2000). These isoforms generate functional differences in the transporter, with individuals homozygous for the long isoform (l/l genotype) showing faster serotonin reuptake in human platelets (Greenberg et al., 1999). Furthermore, allelic variants of this polymorphism are related to different “intermediate phenotypes” that represent risk factors for mental disorders, including personality traits (Canli & Lesch, 2007; Duman &

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Canli, 2015; Juhasz et al., 2010; Schinka et al., 2004; Sen et al., 2004), impulsivity (Stoltenberg et al., 2012a, 2012b), and responsiveness of brain regions associated with emotional and social behavior, such as amygdaloid nuclei (Holmes, 2008). While the responsiveness of amygdaloid nuclei to fearful stimuli has been established (Holmes, 2008), resting state activity in this region is also increased (Canli et al., 2006; Rao et al., 2007). Canli and Lesch (Canli & Lesch, 2007) proposed a "tonic activation model" of SERT function, in which carriers of the short variant have elevated levels of amygdala activation at rest, leading to alterations in arousal state, enhanced acquisition and impaired extinction of emotional memories, hypervigilance. During stress, individuals with a polymorphism associated with lower efficiency of serotonin reuptake in the DRN would present longer periods in which DRD and DRV projections would be inhibited - that is, a lower tonus on both the VMPFC and amygdalar neurons. However, while phasic serotonergic activity in the VMPFC inhibits these neurons by activating receptors in glutamatergic principal neurons, the amygdaloid nuclei are *disinhibited* by activation of receptors in GABAergic interneurons (Jasinska et al., 2012). In l/l individuals, this pattern of inhibition of the VMPFC and disinhibition of the amygdala is phasic and/or short-lived, as the high efficiency of transporter activity quickly restores the balance; however, in s/s individuals, this stressor-induced pattern is persistent, and the VMPFC may be inhibited before it can inhibit the DRVL, creating a feedback loop between the DRVL, the DRD and the amygdala (Jasinska et al., 2012).

Caspi and colleagues demonstrated a moderation by genotype of the impact of stressful life events on depression symptoms, such that individuals homozygous for the short isoform (genotype s/s) had a greater impact of the amount of stressful life events on depressive symptoms, while individuals homozygous for the long isoform (genotype l/l) had less impact (Caspi et al., 2003). A recent meta-analysis of studies assessing the 5-HTTLPR X stress interaction on depression risk found to this relationship to be moderated by the duration of stress (i.e. chronic vs. acute) and the time interval between end of stress and assessment of depression (Delli Colli et al., 2022). The effect of the

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5-HTTLPR X stress interaction emerged only in the case of chronic stress, and only for intervals within 1 year between stress and assessment. Caspi et al. (2010) interpreted these results to suggest that variations in this promoter region modify organismal responses to environmental stress, leading to intermediate phenotypes for depression and anxiety – namely, alterations in neural circuits for responses to stressors, challenges, and threats, as well as differences in responses of the hypothalamic-pituitary-adrenal axis to stressors. Similarly, Jasinska et al. (2012) suggested that the imbalance between VMPFC and amygdala-mediated responses after repeated exposure to stressors induce plasticity of the lwDR circuits, producing a mechanism that is more sensitive to further stressors.

These findings are commonly interpreted as pointing to a model, which I will call the "filter hypothesis", in which genotypic variations function as "filters" for the effect of psychosocial stressors. This "filter hypothesis" is an additive version of a diathesis-stress model in genetics. In this model, psychosocial stress would be a kind of initiator of pathological processes, but these adverse life events could only lead to a pathological effect from the correct variation of the genotype. Looking at data from rhesus 5-HTTLPR polymorphisms, Canli and Lesch (Canli & Lesch, 2007) suggested that the short variant leads to altered serotonin brain function during development, which in neonates leads to negative emotionality; when neonates are separated from their mothers, this negative emotionality "amplifies" the effect of the psychosocial stressor, leading to increased stress reactivity in adulthood. In any case, the biological effect has "priority" over the psychosocial effects. Some more complex models have been proposed; for example, Belsky (Belsky, 1997; Belsky et al., 2009; Belsky & Pluess, 2009) suggested that, from an evolutionary point of view, a certain variant that represents a vulnerability if associated with psychosocial stressors may have beneficial effects when the socio-cultural context is more positive, from a developmental point of view. Belsky suggests that it would be more interesting to speak of the differential plasticity or differential susceptibility conferred by a given genetic variant, understood as the responsiveness of the phenotype produced by this variant to both positive and negative conditions (Belsky et al., 2009). Indeed, Sim-

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mons et al. (2011) showed that, in a large sample of African-Americans, individuals which carried the s allele and were exposed to adverse environments showed chronic anger and higher aggression, while individuals with the same allele but a protective environment scored lower on anger and aggression. This approach incorporates not only additive and ipsative models of diathesis-stress interaction (Ingram & Luxton, 2005), but also how variations in the environment channel developmental processes in opposite ways.

Beyond polymorphisms and gene X environment interactions: Epigenetics

Epigenetics became, in a recent turn from social sciences, a "revolutionary paradigm" that reapproaches biological and human sciences (Landecker & Panofsky, 2013; Pickersgill et al., 2013; Warin et al., 2016). In large part, this results from the perception that the field of epigenetics allows a departure from biological essentialism, because it considers plasticity in gene expression – allowing not only quantitative (higher or lower expression of proteins leading to a "dimensionality" of traits associated with them) or qualitative (e.g., alternative splicing) variations, but mainly their modulation by various environmental factors, including psychosocial factors (Malabou, 2008, 2016): "The interaction of these plastic modalities sketches an organization that does not at all correspond to traditional representations of the brain as a machine without autonomy, without suppleness, without becoming – representations that today have become true 'epistemological obstacles'" (2008, pp. 29–30).

Taken in a nutshell, epigenetics is the study of the plastic interactions between the environment and the genome. Unlike mutations, epigenetic changes caused by environment and behavior are reversible because they do not alter the DNA sequence; in fact, environmental events can alter the way a particular gene is expressed. DNA *methylation* typically blocks access to that gene sequence by proteins that induce its transcription, thus commonly preventing protein expression; *demethylation* causes the opposite process (Cedar & Bergman, 2009). Another important mecha-

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nism is histone modification, in which chemical groups are added to or removed from histones – proteins that bind strongly to DNA, inhibiting transcription – modifying the state of DNA binding to them (Cedar & Bergman, 2009); in histone *acetylation*, positive charges are removed from histones, decreasing the interaction of these proteins with the negatively charged phosphate groups of DNA, leading to increased gene transcription. Finally, non-coding RNA also regulates protein expression (Mattick & Makunin, 2006). In addition, there is also evidence that these epigenetic mechanisms are also related to the regulation of alternative splicing (Luco et al., 2011), the process of selecting different combinations of splice sites on messenger RNA precursors, producing different proteins from the same DNA sequence.

An interesting finding concerning epigenetics relates to the relationships between gene expression and socioeconomic status. One of the most stable associations that is observed in the sociology of mental disorders is the inverse relationship between socioeconomic status (SES) and mental disorders (Yu & Williams, 1999). Low SES is strongly associated with a number of important social and environmental conditions that contribute to chronic stress burden, including high-density housing, urban violence, noise pollution, discrimination, and other chronic risks or stressors (Baum et al., 1999). There are important effects of SES on the methylation status of specific age-associated DNA sites (i.e., whose methylation status changes with age (Bocklandt et al., 2011)) when comparing individuals with low SES to individuals with medium to high SES (Fiorito et al., 2017). Importantly, SES-associated DNA methylation changes were already present at birth and partially persist through early childhood (Laubach et al., 2019; McDade et al., 2019; Santos et al., 2019), affecting biological processes that regulate immunological function and neurodevelopment (Bush et al., 2018). For example, an exploratory study in trauma-exposed individuals and individuals diagnosed with post-traumatic stress disorder suggested that interactions between methylation and socioeconomic status occur mainly in genes related to central nervous system functions (Uddin et al., 2013).

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The “epigenetic turn” in the neurosciences has recently been proposed as a “bridge” between biological and socio-cultural effects in psychopathology (Frost, 2020; Landecker & Panofsky, 2013; Malabou, 2008, 2012; Meloni & Reynolds, 2021; Reul, 2014). It removes the focus of neurogenetics from a necessarily linear or unidirectional model (the "gene-for" paradigm), bringing it closer to more complex notions of epidemiology (Freitas-Silva & Ortega, 2016, 2014). This “epigenetic turn” led to a rush of research on changes in gene expression and/or DNA methylation/histone acetylation as mediators of the psychosocial effects on mental health (Gottschalk et al., 2020). The bulk of these studies focus on effects of stressors that are currently present, as it is difficult to study longer-term effects on DNA methylation or gene expression without large longitudinal cohorts. These studies do, however, point to a complexification of the filter and differential susceptibility hypotheses.

Epigenetic regulation of TPH2

The expression of *TPH2* is also subject to epigenetic regulation by many factors, including stressful life experiences. In rats, histone acetylation of *tph2* is decreased in the hippocampus of male adults that have been subjected to prenatal stress, an effect that is accompanied by decreased TPH2 expression in the raphe and hippocampus, and increased depressive-like behavior (Dang et al., 2018). Treatment with trichostatin A, a nonselective inhibitor of histone deacetylases, reversed the effects of prenatal stress, suggesting that this effect is causally related to decreased histone acetylation. Interestingly, the effect was not observed in females (Dang et al., 2018). In patients with MDD, methylation levels at two CpG sites of *TPH2* interact with ELS (indexed by the Life Events Scale) to reduce antidepressant response (Shen et al., 2020). Thus, while TPH2 expression and/or activity is related to the ability to cope with stressful events, stressful life events are also able to modulate the expression of this enzyme, dynamically and bidirectionally changing the ability of individuals to respond to stress. It is currently unknown whether the epigenetic regulation of TPH2

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expression is mediated only by ELS, or whether actual/current stressful life events are also able to modulate this response.

Epigenetic regulation of TPH2 expression by maternal and early-life stress can be relevant to psychopathology not only because of the important links between ELS and distress (MacLaughlin, 2020), but also because 5-HT has been implicated in neurodevelopment and fetal programming (Bonnin & Levitt, 2011; Goeden et al., 2013; Rakers et al., 2020; St-Pierre et al., 2016). This is a potential mechanism through which maternal stress and ELS could shape how neural circuits involved in coping, stress reactivity, and/or emotion.

Epigenetic regulation of SERT

As is the case with TPH2, the serotonin transporter is also a very important target of epigenetic regulation by stressful life events. Epigenetic SLC6A4 gene regulation occurs mainly through direct DNA methylation at CpG islands or presupposes modifications in the acetylation or methylation status of chromatin-associated histones (Iurescia et al., 2017). *In vitro* studies using human lymphoblasts cell lines showed that the methylation status of a 799-bp CpG island surrounding untranslated exon 1A of *SLC6A4* negatively affects mRNA transcription; this effect is mediated by the 5-HTTLPR genotype, with increased methylation in s carriers and, consequently, lower expression (Philibert et al., 2007). Given the fact that promoter methylation is highly susceptible to environmental influences, this interaction between genotype and methylation status is of relevance to the biocultural aspect of 5-HT signaling. Duman and collaborators studied not only the interaction between ELS (insecure attachment, abuse and neglect, exposure to violence, family economic hardship) and 5-HTTLPR polymorphisms, but also the association of chronic stress experiences, gene expression, and cortisol responses to an acute experimental psychosocial stressor (Triers Social Stress Test). Compared to s/s and s/l subjects, l/l subjects who experienced greater early adversity and chronic stress showed greater increases in serotonin transporter expression in peripheral blood

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after the Triers Social Stress Test, as well as greater methylation of the gene for the transporter (*SLC6A4*) (Duman & Canli, 2015). Similarly, in a cohort of nurses from low- and high-stress work environments, less methylation of the same region of the *SLC6A4* gene was observed in the cohort from the high-stress work environment; moreover, higher methylation levels were associated with higher burnout levels in this cohort (Alasaari et al., 2012). Methylation levels in this region of *SLC6A4* were associated with MDD risk (Zhao et al., 2013), suggesting that this region can represent a methylation site that is highly dynamic and responsive to recent chronic daily stressors (Gottschalk et al., 2020). Indeed, Gottschalk et al. (2020) hypothesize that the hypo-methylation of the *SLC6A4* gene promoter region may reflect a kind of genotype-independent adaptive mechanism in response to occupational stress. This mechanism has a physiological function in minimizing stress exposure and preserving psychological functioning, but results, in the long run, in pathological and dysfunctional consequences, including maladaptive coping strategies and depressed mood (Gottschalk et al., 2020).

Interesting examples of the relationship between epigenetics, SES, and mental disorders can be seen by turning again to the *SLC6A4* gene. In a study investigating the relationship between SES, attachment types, and methylation of the *SLC6A4* promoter, individuals with “unresolved” forms of attachment show an association between promoter methylation and low SES – unlike individuals with a secure attachment type, where no such association is observed (Jones-Mason et al., 2016). . Taken together with research on *SLC6A4* commented above (Alasaari et al., 2012; Duman & Canli, 2015; Zhao et al., 2013), these results suggest that safe attachment can act as a protective effect against the effects of low SES on *SLC6A4* promoter methylation. Likewise, in adolescents lower SES predicted changes methylation levels of the *SLC6A4*, which in turn predicted change in threat-related reactivity of the centromedial amygdala (Swartz et al., 2017). In a small study with 25 patients diagnosed with major depressive disorder, Frodl et al. (2015) showed an association between *SLC6A4* methylation and differential modulation of activity in the insula, operculum, hippocampus

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and amygdala during emotional attention processing. Thus, epigenetic impacts on *SLC6A4* can represent a biocultural mechanism through which important psychosocial stressors that represent differential susceptibility to mental distress can produce maldaptive neurobiological and behavioral effects. This strengthens the view that 5-HTTLPR is a "plasticity" site, instead of a "vulnerability" allele (Shattuck, 2019).

Conclusion

The present review outlined mechanisms by which sociocultural and psychosocial stressors dynamically change the expression and activity of genes in the serotonin pathway, suggesting novel ways through which to understand the bidirectional relation between serotonin and stressors which are relevant for common mental disorders (CMDs). A mechanistic understanding of the complex relationships between serotonin and these factors requires understanding not only the physiology of this neurotransmitter (e.g., the phasic vs. tonic regulation presented here) and its myriad receptors (Mengod et al., 2010), but also the bidirectional regulation of 5-HT and stress-related responses. The view presented herein is more akin to that of a "circular causality" (Fuchs, 2012, 2018). This notion characterizes the systemic interplay and feedback between organism and its environment, or between levels of organization of the body. Thus, genetic variation in alleles of the serotonin pathway control the production of specialized components and functions (e.g., transporters, or enzymes in the biosynthetic pathways), while configurations and functions of the entire organism determine which genes are up- or downregulated, or which gene products are actually relevant in each situation ("downward causality"). In this context, variants such as 5-HTTLPR can emerge not as susceptibility factors, determining the function of the nervous system ("upward causality"), but as plasticity factors (Shattuck, 2019), interacting with and being "selected" or "blocked" by the upper levels of organization (including social levels) (Campbell, 1974; Fuchs, 2012; Haken, 1993; Moreno & Umerez, 2000).

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The data reviewed in the present work also suggests that a purely reductionist approach to the neurobiology of serotonin and its relation to CMDs is not attainable. While methodological reductionism might be an important strategy, care must be taken not to reify results derived from reductionist and mechanistic research (Kirmayer & Gold, 2012). In fact, successfully applying a reductionist approach "often depends on on using the higher order phenomena to guide the search for lower level explanations and to recognize an adequate explanation when it has been found" (Kirmayer & Gold, 2012, p. 309). This might be a reason why the "chemical imbalance" hypotheses never seem to hold up to experimental scrutiny, in spite of being commonly held view by health professionals and layperson alike (Moncrieff et al., 2022).

Finally, the data reviewed in this work also points to the role of social factors as crucial events in the interactions between 5-HT and CMDs. Whether or not we understand these social factors as separate ontologies in relation to biological things hacking 2002, they are clearly decisive for an individual's experiences of health and distress (Krieger, 2001; Rose et al., 2022). As a result, psychobiological theories of mental distress must include knowledge of social contexts (Kirmayer & Gold, 2012). Whether or not this requires a different ontology, it is now more clear that an appropriate understanding of the role of lower levels of biological organization, such as genes and neurotransmitters, on mental distress will require a different epistemology (Choudhury & Kirmayer, 2009; Frost, 2020; Kirmayer & Gold, 2012; Shattuck, 2019).

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