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Top-down control of serotonin systems by the prefrontal cortex: a path towards restored socioemotional function in depression

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Abstract

Social withdrawal, increased threat perception and exaggerated reassurance seeking behaviors are prominent interpersonal symptoms in major depressive disorder (MDD). Altered serotonin (5-HT) systems and corticolimbic dysconnectivity have long been suspected to contribute to these symptomatic facets, however, the underlying circuits and intrinsic cellular mechanisms that control 5-HT output during socioemotional interactions remain poorly understood. We review literature that implicates a direct pathway between the ventromedial prefrontal cortex (vmPFC) and dorsal raphe nucleus (DRN) in the adaptive and pathological control of social approach-avoidance behaviors. Imaging and neuromodulation during approach-avoidance tasks in humans point to the cortical control of brainstem circuits as an essential regulator of socioemotional decisions and actions. Parallel rodent studies using viral-based connectomics and optogenetics are beginning to provide a cellular blueprint of the underlying circuitry. In these studies, manipulations of vmPFC synaptic inputs to the DRN have revealed bidirectional influences on socioaffective behaviors via direct monosynaptic excitation and indirect disynaptic inhibition of 5-HT neurons. Additionally, adverse social experiences that result in permanent avoidance biases, such as social defeat, drive long-lasting plasticity in this microcircuit, potentiating the indirect inhibition of 5-HT output. Conversely, neuromodulation of the vmPFC via deep brain stimulation (DBS) attenuates avoidance biases by restoring the direct excitatory drive of 5-HT neurons and strengthening a key subset of forebrain 5-HT projections. Better understanding the cellular organization of the vmPFC-DRN pathway and identifying molecular determinants of its neuroplasticity can open fundamentally novel avenues for the treatment of affective disorders.

Keywords

dorsal raphe; ventromedial prefrontal cortex; serotonin; optogenetics; electrophysiology; depression; mood disorders; social perception; social defeat; social avoidance

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Why study socioemotional deficits in MDD?

Humans are social by nature. Almost all of their actions are directed towards or generated in response to other individuals. The ability to regulate one's social behavior in order to optimize social relationships and capitalize on opportunities in the social environment is referred to as social competence, which involves a multitude of cognitive and affective abilities.[1, 2] For example, achieving emotional attunement and tempering avoidant and aggressive impulses are necessary skills to establish novel relationships and sustain those relationships through adversity. Impairments in social competence are one of the most prominent and disabling characteristics of psychiatric illnesses that affect a third of the world's population at some point in their life.[3] Socioemotional deficits figure among the core symptoms of several psychiatric disorders such as autism, schizophrenia, and social anxiety disorder, but are not traditionally viewed as a cardinal characteristic of major depressive disorder (MDD). As a result, socioemotional behaviors are rarely used as endpoints in antidepressant clinical trials (Table 1).[4, 5] Yet consistent evidence shows that humans suffering from MDD withdraw socially and engage in behaviors that trigger hostility and rejection from interaction partners. These patients often rate their interpersonal difficulties as the most disabling aspect of the disease, which results in the erosion of social support and eventually isolation.[6]

Clinical studies that did include interpersonal functioning as a measurable outcome found that patients with remitted mood-related symptoms, but residual socioemotional deficits had a greater risk of relapse.[7, 8] In contrast, the ability to maintain social engagement or affiliation in the immediate aftermath of adverse life events was a robust early predictor of resilience and stable recovery from depressive episodes.[9] Furthermore, evidence that interpersonal psychotherapies specifically targeting social function are among the most efficacious forms of behavioral treatment for MDD points to socioemotional and interpersonal deficits as an essential pathogenic dimension of the disorder.[10, 11] Thus, a greater emphasis on the social facets of MDD symptomatology in neurobiological and preclinical studies is essential for successfully moving towards novel and more effective treatments.

Human studies of socioemotional processing

Substantial progress has been made during the last decade in identifying circuits that mediate our ability to detect, appraise and respond to the emotional state of others using non-verbal cues. These emotion-relevant cues are delivered during human social interaction via multiple sensory modalities. Visually detected facial expressions are the most salient of these cues and the neural mechanisms underlying this form of emotional recognition have been the focus of most clinical investigations,[12] however other sensory modalities (e.g. vocal prosody, olfaction and biological motion) have also been emphasized in related research.[13–17] Though a thorough description of the circuits involved in each of these specific forms of sensory processing and their multimodal integration is beyond the scope of this paper, this topic has been the object of several recent reviews.[18, 19]

A widely used standardized laboratory task to evaluate socioaffective processing consists of exposing subjects to sets of composite images representing calibrated facial emotions (i.e. sad, happy, angry).[20] The subjective evaluation of the valence of these images is commonly assessed through the use of rating scales (Figure 1). Typical questions include “how many feet would you stay away from this person” or “how trustworthy is this person.”[21] Other experiments have relied on implicit measures of emotion processing, such as reaction time in emotional Stroop tasks.[22] These studies have consistently shown that presentation durations as low as 50 milliseconds are sufficient for humans to extract basic emotional content from visual facial stimuli.[21] This affective information is processed unconsciously and takes precedence over other aspects of visual processing that allow individual recognition. This is revealed by the fact that subjects are often able to emit consistent valence judgments or inferences about complex traits of a facial stimulus (e.g. trustworthiness, dominance) while lacking the ability to describe the physical features of the face.[21, 23]

Socioemotional cues processed either unconsciously or explicitly have been shown to prompt valence-specific social tendencies in the perceiver, particularly the facilitation of approach or avoidance behavioral responses. These effects are evident in tasks where subjects are instructed to produce motor responses upon presentation of valenced facial stimuli.[24] For instance, in a recently developed approach-avoidance laboratory task, subjects must move towards or away from a visual social target presented on a screen using push-pull movements of a joystick (Figure 1).[25] Convergent results during this task show that healthy subjects avoid threatening stimuli faster than neutral pictures, even if these stimuli are not consciously detected. Functional imaging and neurophysiological methods such as EEG have been used in combination with these laboratory tasks to identify regions and neural networks implicated in the automatic and explicit processing of socioemotuional stimuli as well as during the execution of rapid approach-avoidance responses. Additional studies (mentioned in table 2) have utilized pharmacology or non-invasive neuromodulation methods such as transcranial magnetic stimulation (TMS) and direct current stimulation to provide causal evidence for the role of specific biological mechanisms, brain regions or circuits in healthy subjects and patients with affective disorders.[25, 26] Although early views posited a predominant role of subcortical alarm systems in the rapid processing of salient biologically relevant affective signals, current neurobiological models have evolved to emphasize the interactions between cortical and subcortical structures through multiple parallel bottom-up and top-down modulations.[27]

Biased socioemotional processing and social avoidance in depression

Interpersonal deficits of MDD patients may arise in part from neurobiological abnormalities that disrupt the normal processing of socioaffective stimuli.[13, 28] This concept is based on the observation that subjects suffering from MDD and anxiety tend to preferentially attend to, process and remember negatively valenced information in their environment, whereas a bias towards positive information is generally observed in healthy subjects.[10] In social contexts, this cognitive bias leads to neutral or ambiguous social stimuli that are normally neglected by healthy subjects to break into consciousness as threats for MDD patients.[29–31] Indeed, during explicit rating tasks, MDD patients consistently rated ambiguous or negative

social stimuli more negatively than a healthy individual would. Administration of the Approach-Avoidance Task to social anxiety[20] or MDD[31] patients also revealed increased attention towards negative or threatening social stimuli (i.e. angry, sad) and a tendency to initiate withdrawal responses faster regardless of the emotional valence of the stimuli,[23, 32–34]. In real world interactions, this negatively biased socioemotional processing might lead MDD patients to misattribute negative intentions and motives to others and anticipate negative judgment or rejection with exaggerated defensiveness and withdrawal.[32, 35]

Circuits underlying biased socioaffective processing in MDD: Key role of the ventromedial prefrontal cortex

In the last 10 years, consistent imaging and neurophysiological data have revealed the aberrant morphology and reactivity of the prefrontal cortex in MDD patients[36–43] and its normalization after successful chronic antidepressant treatment.[32, 44–50] In socioemotional processing studies, classical antidepressants rapidly remediate negative biases in MDD patients. This rapid action contrasts with the slow onset of the therapeutic effects on mood. It has been proposed that restored emotional processing may slowly foster improvement in mood by providing a more positive social environment in which the patient can relearn positive emotional associations.[51] Neural signatures of this neuroplastic process have been repeatedly identified in the ventromedial prefrontal cortex (vmPFC), a cluster of contiguous and functionally related areas in the primate frontal lobe comprised of Brodmann areas 10, 11, 12, 13, 14, 25 and 32.[52–54] It is important to note that the rationale for considering the vmPFC a single functionally homogenous structure remains controversial,[55] as several areas within the vmPFC cluster have distinct cytorachitecture and a unique pattern of input-output connections.[56, 57] Nevertheless, the vmPFC has been the focus of numerous studies in humans and animals leading to its classification as a control center for executive function, emotional valuation, autonomic control and social cognition.[58, 59]

Functional abnormalities in the vmPFC may contribute in particular to the socioemotional facets of MDD symptoms, as this collection of regions shows striking overlap with the networks engaged when individuals make social approach or avoidance decisions.[60] Seminal observations that connected the vmPFC to social function were made by Damasio and colleagues who characterized the deficits of patients suffering from frontal lesions.[61] These individuals had abnormal autonomic responses to visual social stimuli and social decision-making deficits. A more recent eye tracking study in a cohort with similar lesions revealed a decreased capacity of these patients to attend to the specific features of the face that carry high emotional value such as the eyes or mouth.[62] These observations are in line with results in healthy individuals that show that the vmPFC is engaged during social attention and the processing of social sensory information. [63, 64] The essential role of the vmPFC in the effortful control of avoidance responses during social interactions was recently revealed by a study that used continuous theta bursts with TMS to non-invasively inhibit the activity of the vmPFC in subjects during an approach-avoidance task.[25] They found that subjects whose vmPFC was selectively inhibited committed more errors when they had to override automatic avoidance tendencies in order to apply rule-based responses.

The errors coincided with an upregulation in the activity of the insula and amygdala, two regions downstream of the vmPFC implicated in automatic processing.

It is likely that the vmPFC executes adaptive social behavioral decisions by computing valence and personal relevance of social stimuli and integrating this high-level multisensory information with the activity of subcortical limbic and brainstem structures, which control other elementary aspects of emotions such as autonomic and motor responses.[65, 66] Among the downstream regions controlled by the vmPFC are the nucleus accumbens and amygdala, as well mesencephalic and pontine monoaminergic nuclei containing dopamine and serotonin producing neurons. The following sections of this review focus on the circuitry underlying the reciprocal interaction of serotonin systems and the vmPFC during social interaction.

Serotonin influences on social behaviors

Serotonin (5-HT) is a phylogenetically ancient neuromodulator that exerts a wide range of influences on physiology and behavior through its action on 15 different receptors.[67] One of the most consistent roles attributed to 5-HT based on human and animal behavioral data relates to its influence on the expression of behaviors along the affiliative-aggressive axis. In humans, depleting 5-HT by reducing the dietary source of its precursor L-tryptophan, or boosting 5-HT via administration of selective serotonin reuptake inhibitors has respectively been shown to induce negative and positive shifts in social perception (Table 2).[68–73] Variants of genes that control 5-HT synaptic availability, such as the serotonin transporter (5-HTT)[74–76] and the 5-HT synthesizing enzyme tryptophan hydroxylase (TPH) [77, 78] have also been associated with alterations in socioemotional behaviors, such as differential sensitivity to the rewarding properties of social cues or reactivity to unfairness.[79] Differential corticolimbic responses to these cues have also been reported in carriers of these polymorphisms.[76–78] The effect of 5-HT on social behavior is likely to be mediated in part by its effects on neurons from the frontal cortex, as this area is one of the most enriched in serotonergic axons and 5-HT receptors. 5-HT modulates the excitability of cortical neurons and their discharge rate through the activation of several receptor subtypes, of which the 5-$HT1_A$, 5-$HT1_B$, 5-$HT2_A$, and 5-HT3 play major roles.[80–82]

The primary serotonergic nuclei that innervate the prefrontal cortex in mammals are the median and dorsal raphe nucleus (MRN, DRN), two brainstem structures that provide the bulk of serotonergic afferents to the forebrain. Though the DRN and MRN are the two largest serotonergic cell groups, imaging them *in vivo* in humans remains a challenge due to their relatively small size and deep location in the brainstem.[83, 84] Only with the most recent advances in imaging methods has it become possible to visualize individual raphe nuclei in awake subjects and conduct probabilistic tractographic analyses of major fiber tracts to these brainstem nuclei.[85] This is an important issue as tractography indicates that brainstem nuclei are among key downstream regions likely to mediate the effects of vmPFC neurostimulation for the treatment of MDD.[86] Imaging studies together with postmortem investigations indicate that the distribution of raphe nuclei cell clusters and the architecture of the frontopontine fiber tract are well conserved across mammals.[87, 88] A small number of studies have begun identifying volumetric alterations and structural abnormalities in

brainstem fiber tracts that connect the raphe with the frontolimbic systems in MDD patients, although abnormalities in functional connectivity have yet to be reported.[89, 90] Nevertheless, combined use of PET and fMRI in healthy subjects have provided evidence for negative correlations between the density of 5-HT_{1A} receptors in the DRN and amygdala reactivity to threats, suggesting that the capacity for DRN neuron autoinhibition predicts cotricolimbic reactivity.[91] Histological studies of the DRN in post-mortem tissues of MDD and suicide victims have revealed differences in levels of certain 5-HT-specific markers such as 5-HT_{1A} and 5-HT_{2A} receptors,[92, 93] TPH[94–96] and certain transcription factors controlling gene expression in 5-HT neurons.[97–100] However, evidence directly linking alterations of serotonergic systems with symptoms of mood disorders remains limited and confirmation will require replications in larger cohorts.[86, 90] The fact that over half of the DRN cell population is comprised of non-serotonergic cells[101, 102] including glutamatergic,[103] GABAergic,[104] and dopaminergic neurons[105] that in some cases exert opposite effects on behavior and connectivity complicates the interpretation of human data derived from imaging or tissue homogenates.[106, 107] Because studies in many different organisms ranging from insects and fishes [108–111] to rodents and primates have shown that altering levels of 5-HT influences the expression of affiliative-aggressive behaviors,[112] researchers have turned to these simpler models to more finely dissect the DRN microcircuit and its interaction with corticolimbic systems during socioaffective behaviors.

Dissecting the cellular architecture of the vmPFC-DRN pathways in animals

There is strong evidence dating from the 1990's that the vmPFC is connected with the DRN via reciprocal monosynaptic projections, however the methods used to characterize these circuits have left areas of uncertainty regarding the cellular architecture of the pathway. Within the last few years, recent advances in mouse transgenics, viral tracing and connectomics methods have allowed for exponential progress in the characterization of this pathway. The first efforts to trace the vmPFC-DRN pathway relied on conventional retrograde and anterograde tracers such as biotinylated dextran amine and horseradish peroxidase.[87, 113–120] Most of these studies were conducted in the rat or non-human primates and in a few instances, combined tracing with ultrastructural methods or *in vivo* electrophysiology to test functional connectivity. These studies showed that the vmPFC sends robust direct afferents to the DRN, however the majority of axons anterogradely traced in the DRN represented fibers of passage and only 6% of traced axons formed synaptic contacts.[115, 121] Electron microscopy analysis of dual labeling in the DRN for mPFC afferents and *Tph2* (5-HT neurons) or GABA revealed a greater frequency of mPFC terminals synapsing on GABA-labeled dendrites versus *Tph2*-labeled dendrites.[115] This suggested the existence of a disynaptic microcircuit mediating the inhibitory influence of the cortex on 5-HT neurons (Figure 2). Electrophysiological evidence supported this hypothetical organization when electrical stimulation of the rat mPFC caused a predominant reduction in the firing rates of DRN 5-HT neurons *in vivo* that was blocked by GABA antagonists.[114, 122] However, these earlier studies provided little information about the actual topographical organization of these cellular ensembles.

To overcome these limitations, our group recently generated two lines of transgenic mice and with fluorescently labeled GABA (*GAD2-tdTomato*) or 5-HT (*Pet1-tdTomato*)

neurons.[123] Using these mice, we mapped the relative distribution of GABA versus 5-HT cell types in the DRN and defined for the first time the morphological and electrophysiological signatures of genetically identified GABA neurons in the DRN.[123] We found little overlap between the areas occupied by 5-HT and GABA neurons in the DRN (Figure 2). Serotonergic neurons sit in the midline portion of the nucleus, whereas GABAergic neurons were found primarily at paramedial locations such as the lateral wings and ventrolateral periaqueductal grey (PAG). We also determined that GABA neurons are of smaller size than serotonergic neurons, have a greater excitability, and are often spontaneously active in slice preparations, while 5-HT neurons are silent [104, 124] Using optogenetics in these mice we demonstrated that DRN GABA neurons inhibit 5-HT neurons concentrated in the midline in the same slice. To examine the relative distribution of vmPFC afferents with regard to GABA and 5-HT cells, we developed a viral vector system to selectively express a fluorescent Synaptophysin-GFP (*SynP-GFP*) fusion protein in excitatory neurons of the vmPFC.[125] Because this protein is targeted to presynaptic densities, it acts as an anterograde tracer that labels synaptic contacts while excluding fibers of passage. Using this vector we found that synapses formed by vmPFC axons in the DRN are topographically distributed and follow a rostrocaudal gradient (Figure 2). In the rostral DRN, most vmPFC synapses were found in the lateral wings area overlapping with GABA neurons clusters. In contrast, vmPFC synapses were concentrated in the midline in the caudal DRN and overlapped with 5-HT neurons. This gradient suggests that vmPFC inputs are likely to disynaptically inhibit serotonergic output from the rostral DRN, but monosynaptically stimulate serotonergic output from the caudal DRN.[125] Because rostral and caudal DRN 5-HT neurons project to distinct forebrain targets, this hypothetical microcircuit places the DRN GABA population in a critical position to gate top-down influence from vmPFC on a key subset of mood-regulating rostral 5-HT neurons.[126–128]

Our results showing regional overlap between *SynP-GFP*-labeled vmPFC axonal boutons and GABA or 5-HT neurons suggest the existence of synaptic contacts, but do not provide functional evidence for this connectivity. A number of approaches have been used to address this question. One takes advantage of the retrograde transsynaptic properties of genetically modified rabies viruses to map synaptic connections between identified cell-types in a network. Weissbourd *et al*. and Pollak Dorocic *et al*. recently used this type of rabies virus-based approach in combination with *in situ* hybridization and brain slice electrophysiology to comprehensively map and quantitate the origin of synaptic inputs to DRN serotonergic and GABAergic neurons.[127, 128] They utilized *GAD2-Cre* and *SERT-Cre* transgenic drivers to target GABA and 5-HT neurons respectively and employed two different forms of an avian virus receptor (TVA) to optimize their anatomical tracing of either long-range or local intra-DRN connectivity. Their results show that prefrontocortical inputs amount to roughly 15% of the total synaptic input received by DRN neurons. This suggests that the functional influence of cortical inputs on the DRN is likely to be weaker than certain subcortical inputs such as the hypothalamus (30% of input). Surprisingly, retrograde labeling of cortical neurons was denser when starter cells were DRN 5-HT neurons rather than GABA neurons, indicating, in contrast with our data, that the PFC preferentially innervates DRN 5-HT cells (10%) over GABA neurons (5%). *In situ* hybridization results showed that virtually all of these cortical inputs were glutamatergic, in agreement with previous tracing studies showing

that most DRN-projecting cortical neurons are localized in layer V,[117, 118] a typical location for subcortically projecting pyramidal neurons.[57, 129, 130] Approximately 2% of DRN inputs identified by Weissbourd *et al.* originated from the prelimbic cortex (PL) and less than 0.5% were from the infralimbic cortex (IL), two regions whose combination corresponds to the human vmPFC. These results are in line with earlier tracing studies showing that the PL is the predominant source of vmPFC inputs to the DRN.[113, 116, 118] Unexpectedly though, among all prefrontocortical areas, the insular cortex (3%) proved to be the major source of inputs to the DRN.

To test the functional architecture of the PFC-DRN pathway, several groups including our own have conducted *Channelrhopsin2*-assisted circuit mapping (CRACM). This analysis uses optogenetically evoked EPSCs as an index of functional connectivity between 2 regions. Our group was the first to report this type of analysis between the vmPFC and DRN.[125] We expressed *Channelrhodopsin2* (*ChR2*) in vmPFC pyramidal neurons using an AAV virus driven by the *CaMKIIA* promoter and recorded from identified serotonergic and GABAergic neurons in the DRN of *tdTomato* reporter lines. Optogenetically activating vmPFC terminals reliably triggered *cFos* expression and laser-locked EPSCs in GABAergic neurons of the lateral wings, but not in midline 5-HT cells, suggesting that the former are the preferential functional targets of vmPFC projections.[123] In contrast, using similar approaches, Weissbourd *et al.* and Pollak Dorocic *et al.*[127] found that cortical axon photoactivation was twice as efficient at triggering EPSCs in 5-HT neurons than in GABA neurons.

Given the gradient described above, inconsistencies between the results from ours and other's CRACM experiments investigating the PFC-DRN pathway might reflect distinctions in the rostrocaudal localization of the DRN cells selected for recording, as well as in the cortical areas targeted by viral injections (vmPFC in our study versus anterior cingulate in Weissbourd *et al*. versus anterior PFC in Pollak Dorocic *et al*.). In addition, differences may also be explained by technical factors such as differences in the viral vectors used to express *ChR2* (i.e. AAV serotypes and promoters) or strategies used to identify cells for recording (e.g. viral versus transgenic expression of *tdTomato; Pet1-Cre* versus *SERT-Cre* to identify 5-HT neurons). Although our understanding of the architecture of the vmPFC-DRN could still be improved by an even greater refinement in the definition of various cellular subsets in the DRN, the recent studies described above provide detailed groundwork to start examining the function and plasticity of these circuits *in vivo* and test their influence on socioaffective behaviors.

Chronic Social Defeat Stress (CSDS): an animal model of socioemotional bias?

Modeling psychiatric disorders in animals poses major challenges,[131] however a number of animal procedures offer opportunities to isolate specific dimensions or endophenotypes of diseases in order to probe their underlying neurobiology. Chronic social defeat stress (CSDS) takes advantage of ethologically relevant threats in mice (i.e. dyadic aggressive interactions) to precipitate a multidimensional stress-induced syndrome that resembles certain features of clinical depression and comorbid anxiety disorders, including circadian

disruption, HPA axis dysregulation, anhedonia, and socioaffective deficits, each of which occur with distinct temporal dynamics.[132–136] The primary behavioral endpoint of the CSDS model is altered social approach-avoidance behavior. This variable is tested in a social interaction task where experimental mice must confront an unfamiliar social target contained in a wire mesh box and are evaluated for their decisions to approach or avoid the target (Figure 1). In many ways this task provides an animal parallel to the approach-avoidance laboratory task used in humans and described above. To induce avoidance, mice in the "defeat" experimental group are subjected to brief experiences of physical aggression from trained CD1 aggressors followed by continuous protected sensory contact with the aggressor (Figure 3). In contrast, control mice are housed peacefully among dyads of the same strain and live under sensory contact conditions replicating those of the defeated mice. For naïve mice, unfamiliar social targets appear positively valenced as virtually all undefeated control mice make the rapid choice to approach the unfamiliar target during the social interaction task and remain engaged in social interaction during the entire duration of the test. In contrast, most defeated mice (roughly 70%, termed vulnerable) develop a social aversion, characterized by a delayed latency to start investigating the target followed by vigorous retreat and persistent immobility in the corners of the arena (Figure 1).

Our experiments have determined that the avoidance response is a "learned behavior" and its encoding depends critically on the daily sensory contact period that follows each episode of physical defeat.[123] We determined that 20 minutes of post-defeat sensory exposure each day is necessary and sufficient to trigger a maximal avoidance response. This is suggestive of an associative process that occurs during the early phase of the post defeat sensory exposure and leads to the consolidation of the social avoidance response. During the social interaction test, the expression of the avoidance behavior is triggered by social cues emitted by the behaviorally active social target. This was deduced from the observation that defeated mice do not avoid an inanimate novel object or an anesthetized social target.[137] However the avoidance response is not conditioned to cues that are specific of the aggressors, as avoidance generalizes to any unfamiliar social target, including mice from a different strain and devoid of territorial aggression.[137] The exact nature of these sensory cues is currently unknown, but could involve a combination of visual, olfactory and ultrasonic cues.[138] The avoidance response is long lasting and does not extinguish upon repeated testing. [137, 139, 140] CSDS-induced avoidance can thus be conceptualized as a learned aversive response to socioemotional cues that is overgeneralized and overconsolidated. The reliance of CSDS on this learned socioemotional response instead of a response to an innately aversive stimulus (i.e. shock or forced water immersion used in other antidepressant screens) is a major distinguishing feature of the model. This difference implies that the brain systems and plasticity mechanisms engaged by CSDS are likely to differ considerably from those at play in other models of depression, such as the learned helplessness paradigm, the tail suspension test or the forced swim test.[141, 142] The CSDS model does not respond to acute administration of benzodiazepine anxiolytics, but is responsive to SSRIs, tricyclic antidepressants, ketamine and DBS with clinically relevant time-courses.[137, 143]

The primary sensory modalities humans and rodents rely on to execute rapid approach-avoidance decisions are very likely to differ. Vision is predominant in humans while olfaction is likely to be the primary sensory process at play in the murine test. However, it is

reasonable to draw a translational parallel regarding the executive processes at play. A subpopulation in each cohort of defeated mice (roughly 30%, termed resilient) will maintain social approach despite experiencing similar level of aggression. Like in the human approach-avoidance task, the sustained approach behavior of these resilient mice can be interpreted as an ability to actively overcome automatic avoidance responses triggered by the ambiguous social target.[125] The comparison of cohorts stratified into resilient and susceptible subpopulations (Figure 1) allows the dissection of the neurobiological mechanisms underlying active adaptation versus vulnerability to the effects of psychosocial stress.

Since our original description of the CSDS model, the work from several groups applying innovative approaches such as optogenetics and multiregion *in vivo* recording has contributed to an increased molecular and circuit-level understanding of the mechanisms underlying resilient and vulnerable phenotypes (Table 2). In parallel with the human literature on the role of stress hormones in the development of socioaffective bias,[144] glucocorticoids have been shown to mediate the development of social avoidance, in part by acting on adult-born neurons[145] as well as dopaminergic and serotonergic systems.[146–148] Tph2 knockin mice with a mutation analogous to the rare human R441H variant of the *TPH2* gene, which leads to an 80% reduction in 5-HT levels, have corticolimbic hypersynchrony and increased vulnerability to various stressors including social defeat.[149] This genetic effect can be mimicked by pharmacological depletion of 5-HT,[150, 151] an effect that resembles the influence of tryptophan depletion in approach-avoidance tests and socioemotional processing in human subjects.[22, 68, 152] High frequency electrical stimulation of the vmPFC, a treatment that enhances 5-HT release in the forebrain,[153] has been shown to restore social approach behavior in defeated mice.[154] This effect replicates the action of vmPFC DBS on negative bias and mood related symptoms in MDD patients.[155, 156]

In all, these results underlie the striking cross-species parallels that exist regarding the roles of the vmPFC and serotonergic systems in socioemotional responses. This supports the hypothesis that the plasticity of the vmPFC-DRN pathway that links these two systems may contribute to the encoding or expression of social avoidance across species.

Social-experience-induced structural and functional plasticity of the vmPFC-DRN microcircuits

We have reported that exposure to CSDS followed by protected sensory contact with an aggressor induces the accumulation of *cFos* and Δ*FosB* in the DRN.[123, 157] These markers of activity-dependent neuroplasticity were expressed specifically by a cluster of GABA cells in the lateral wings of the DRN, the area that receives the densest axonal input from the vmPFC. This suggests that neuroplastic changes occur in DRN GABA neurons might be driven by vmPFC inputs and facilitate in encoding a shift in social valence after social defeat. To test this hypothesis we examined whether the electrical and morphological properties of serotonergic and GABAergic neurons were altered in the DRN after CSDS in a manner that correlates with the expression of social avoidance. After stratifying mice as resilient or susceptible after 10 days of CSDS, we performed whole-cell recordings on fluorescently tagged 5-HT or GABA neurons from transgenic mice to unambiguously

identify the cellular populations. In susceptible mice that developed social avoidance, we found that DRN GABAergic neurons in the lateral wings were hyperexcitable and had increased glutamatergic input compared to controls, whereas serotonergic neurons showed opposite changes, namely, a reduced intrinsic excitability and increased GABAergic input (Figure 4).[123] Furthermore, morphological analysis of filled 5-HT neurons revealed an increase in size and complexity of the proximal dendrites in vulnerable mice. [146] Lastly, we also observed a drastic reduction in the number and density of *SynP-GFP* labeled varicosities along serotonergic axons, a sensitive index of presynaptic plasticity and release efficacy.[154] None of these electrophysiological or structural changes were observed in resilient mice.

Given our previous observations that DRN GABA neurons receive synaptic contacts from the vmPFC and inhibit nearby 5-HT neurons, the results summarized above suggest that CSDS may lead to maladaptive sensitization of the disynaptic inhibition of 5-HT cells while simultaneously depressing the intrinsic excitability of 5-HT neurons.[123] In line with this prediction, microdialysis experiments ongoing in our lab indicate that CSDS-resilient mice respond to sensory re-exposure to an aggressor with a dramatic increase in 5-HT release in the vmPFC whereas vulnerable mice do not show this response. This suggests that activation of serotonergic neurons and 5-HT release in the PFC and possibly other regions may contribute to the ability of resilient mice to maintain social approach after CSDS (Figure 5). This mechanism would be in line with recent evidence that the firing of certain subsets of serotonergic neurons tonically increases *in vivo* during expectation of a reward[158, 159] and mediates social reward signals through release of 5-HT and activation of 5-HT1_B receptors on corticostriatal axon terminals in the nucleus accumbens (NAc).[160] Several recent studies have also implicated subsets of ventral tegmental area (VTA) projecting DRN serotonergic and glutamatergic neurons in the encoding of reward.[161] These findings provide mechanistic bases to understand the reduced social motivation and negative shifts in social perception observed after depleting 5-HT (Table 2).[22, 73, 95]

To determine whether vmPFC-driven disynaptic inhibition of 5-HT neurons was sufficient to promote social avoidance we performed *in vivo* photoactivation of glutamatergic vmPFC terminals in the DRN of mice that were exposed only to sensory contact with a CD1 aggressor through a plexiglass partition. Even in the absence of physical aggression, photoactivation resulted in the development of subsequent avoidance responses that recapitulated the behavior of defeated mice.[125] To test whether this circuit mechanism was necessary for the development of social avoidance, we photoinhibited either the vmPFC inputs to the DRN or DRN GABA neurons during the daily post-defeat sensory contact period. Under these conditions we found that mice exposed to CSDS did not become avoidant, confirming the causal role of the vmPFC-DRN disynaptic circuit in the encoding of social avoidance.[123, 125] Interestingly, in contrast with this key role in the associative process leading to avoidance, altering the top-down inhibitory control of raphe circuits by the vmPFC did not appear to affect the expression of a previously learned avoidance response. Indeed, acute optogenetic inhibition of vmPFC inputs to the DRN or silencing DRN GABAergic neurons during the social interaction task did not inhibit avoidance of mice previously defeated without stimulation.[123, 125] On the other hand, chronic treatment

with vmPFC DBS, when applied for 5 hours daily over a week, did restore approach behaviors of mice previously characterized as vulnerable. This effect was obtained using parameters that replicated clinically used stimulation conditions and was associated with a desensitization of DRN GABA neurons and a restoration of the intrinsic excitability and morphology of 5-HT neurons.[154] Furthermore, DBS potentiated the direct glutamatergic drive of 5-HT cells, as revealed by an enhanced frequency of mEPSCs and increased density of PSD95 puncta on 5-HT dendrites above baseline. Surprisingly, DBS also restored the density of 5-HT axonal boutons in a projection-specific manner, leading to a greater serotonin release capacity in the vmPFC. The fact that high frequency stimulation of the vmPFC by DBS can restore social approach once avoidance has already been stabilized, but not local bidirectional optogenetic modulation of vmPFC axons in the DRN, suggests that this therapeutic effect may require the combined activation of several downstream targets of the vmPFC, which in turn may converge on the DRN.

Altogether our results thus confirm the hypothesis that CSDS sensitizes vmPFC driven disynaptic inhibition of 5-HT neurons, thereby reducing 5-HT output in innervated regions to alter the affective impact of an adverse social experience and promoting generalized social aversion in vulnerable mice (Figure 4). Although the mechanism whereby resilient mice are protected from the effects of CSDS and evade sensitization of vmPFC-DRN pathway remains unclear, it is possible to formulate hypotheses based on recent studies using the same model. The Dzirasa group recently combined optogenetics and *in vivo* multiregion recordings in mice to show that stimulation of the vmPFC resulted in evoked potentials in numerous subcortical and limbic structures, including the amygdala and NAc as well as in aminergic neuromodulatory centers like the DRN and VTA.[162] Surprisingly, vmPFC evoked responses occurred significantly faster in the DRN that in limbic regions despite this structure being more anatomically distal from the vnPFC. This faster transmission velocity in the vmPFC-DRN pathway places the DRN in a position to modulate threat sensitivity by acting as a closed-loop regulator that can synchronize or desynchronize corticolimbic networks by independently controlling excitability of the hub (i.e. vmPFC) and its distributed downstream targets. Further work by the Dzirasa laboratory has also shown that naturally occurring differences in corticolimbic synchrony correlates with trait vulnerability to CSDS, with greater phase locking between the PFC and amygdala predicting increased vulnerability.[163] Interestingly, as mentioned above, animal and human studies have shown that 5-HT is a major regulator of vmPFC-amygdala coupling and reducing 5-HT using genetic mouse models of 5-HT deficiency or pharmacological treatments has been shown to favor cortico-amygdala hypersynchrony and enhance vulnerability to social defeat (Figure 5).[164]

Concluding remarks

Evidence grows to suggest that biased socioemotional processing is a core cognitive component of MDD that contributes to interpersonal deficits in this disorder. Socioemotional processing is under key control by the prefrontal cortex and serotonergic systems in part via a direct vmPFC-DRN circuit whose plasticity is targeted by long-term antidepressant treatment and DBS. Relying on translationally meaningful models for the recapitulation of socioaffective symptoms of MDD, studies from our lab and others

summarized in this review have started establishing a cellular blueprint for the organization of this pathway and identifying key neuroplastic events that mediate normal and pathological regulation of socioaffective function. An important next step for future studies will be to define how vmPFC-driven neuroplastic adaptations of specific subsets of serotonergic neurons translate into modifications of corticolimbic circuit dynamics. A further goal will be to delve deeper into the molecular mechanisms that underlie the synaptic adaptations of DRN neurons. Our hope is that these approaches will offer new insights into more efficacious pharmacological or circuit-based therapeutics that target the socioemotional aspects of depressive symptomology.

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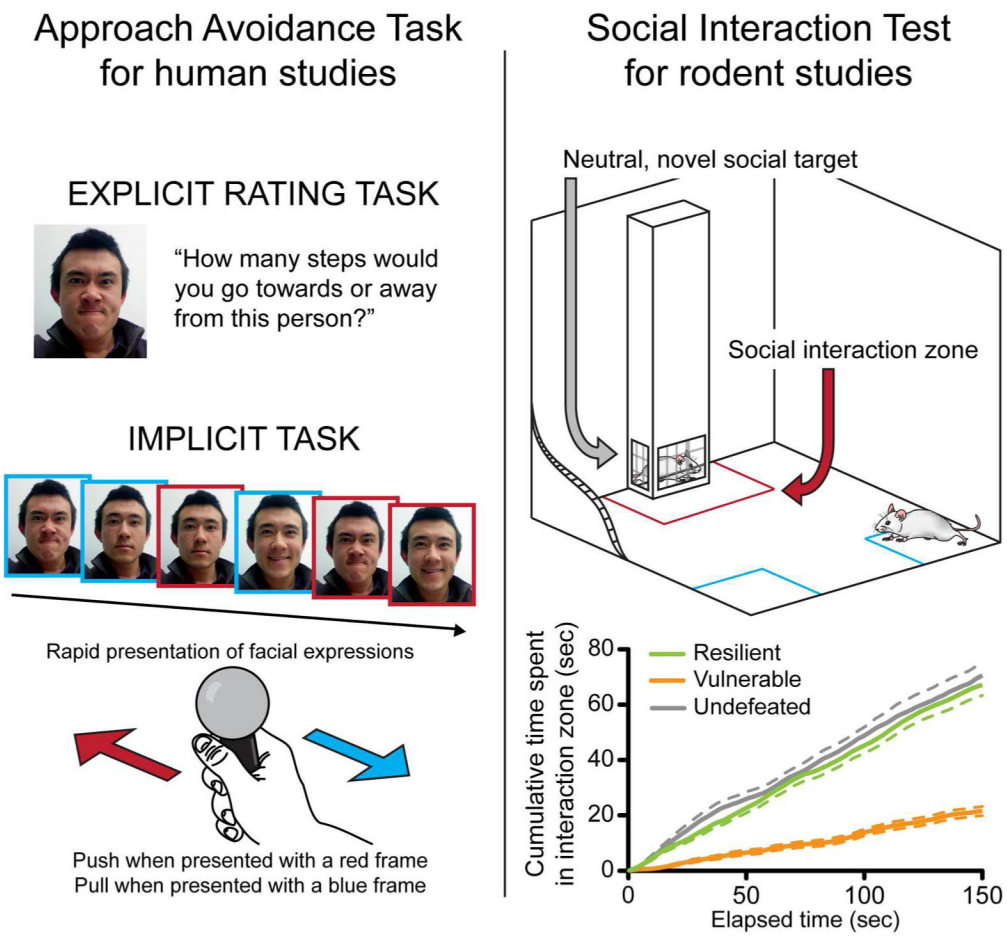

Figure 1. Behavioral tasks used to probe social approach/avoidance behaviors

In the Approach Avoidance task for humans, approach or avoidant behaviors are quantified using two tasks. In the explicit task, individuals are asked to define how close they would approach the subject on the picture or rate properties associated with its social valence, such as safety or trustworthiness. In the implicit task, automatic processing and tendencies are assessed. Pictures of faces with different emotions (i.e. happy, neutral, angry) are presented for short durations (50ms). A colored frame surrounds these pictures and subjects are instructed to pull or push a joystick according to the color of the frame presented. Even in the absence of conscious perception, subjects are faster at avoiding threatening faces.

In the social interaction test for mice, experimental subjects are placed in the corner of an open field arena with a caged off unfamiliar social target on the opposite side. Mice are free to explore the arena while movement is recorded using video tracking software. Undefeated control mice unconditionally approach the target within seconds. One subset of defeated mice display strong avoidance tendencies (vulnerable) while the other will maintain social approach and interaction (resilient).

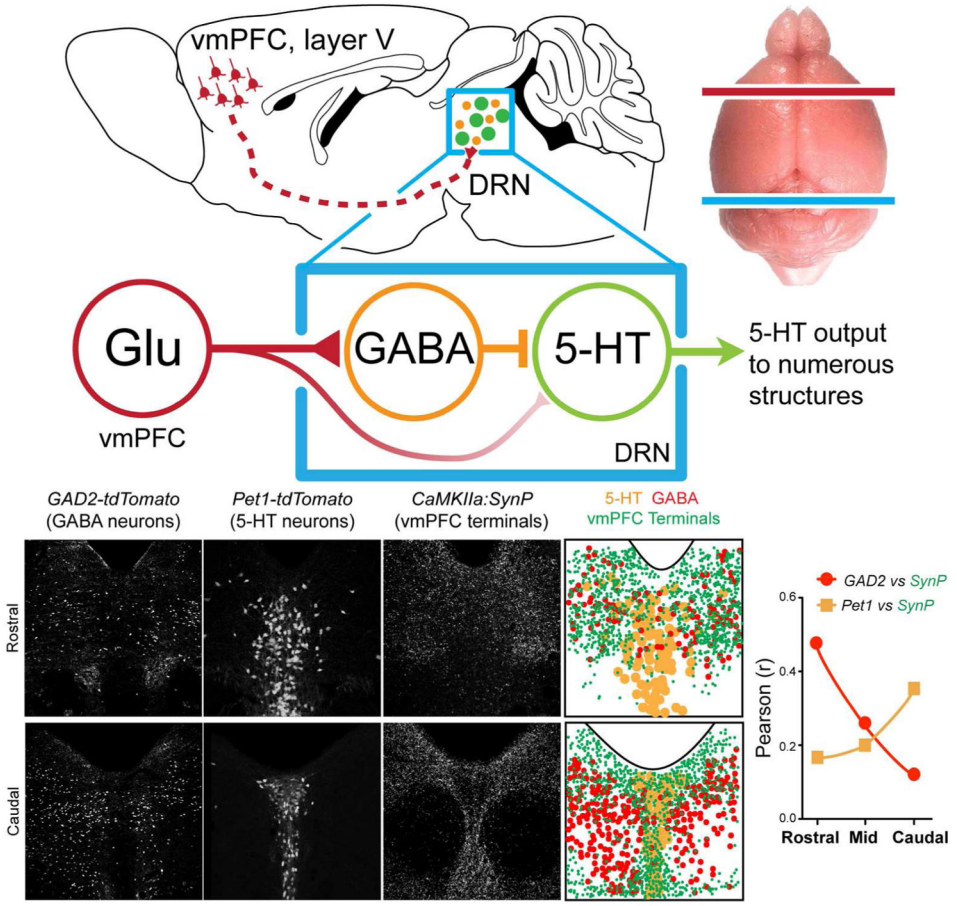

Figure 2. Overview of vmPFC-DRN circuitry

Based on data from previous tracing studies, glutamatergic layer V vmPFC neurons send afferents to the DRN that preferentially synapse on GABA interneurons, which then locally inhibit 5-HT neurons and gate serotonergic output. Representative confocal images depict typical localization of GABAergic (*GAD2-tdTomato*), serotonergic (*Pet1-tdTomato*) and vmPFC terminals (*CaMKIIA*-driven *SynP-GFP*) in the rostral and caudal DRN. Analysis reveals higher correlation of vmPFC terminals with GABA neurons in the rostral DRN and with 5-HT neurons in the caudal DRN.

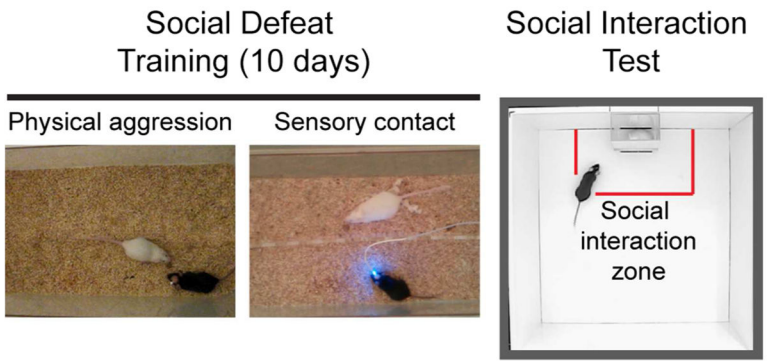

Figure 3. Chronic social defeat stress paradigm

In CSDS, mice are first exposed to social defeat training, which involves physical aggression from a trained CD-1 mouse followed by sensory contact protected by a plexiglass divider. After 10 days of defeat with exposure to novel aggressor each day, social behaviors are characterized in the social interaction test (described in Figure 1). Depicted here is photomanipulation of the subject mouse during the sensory contact period.

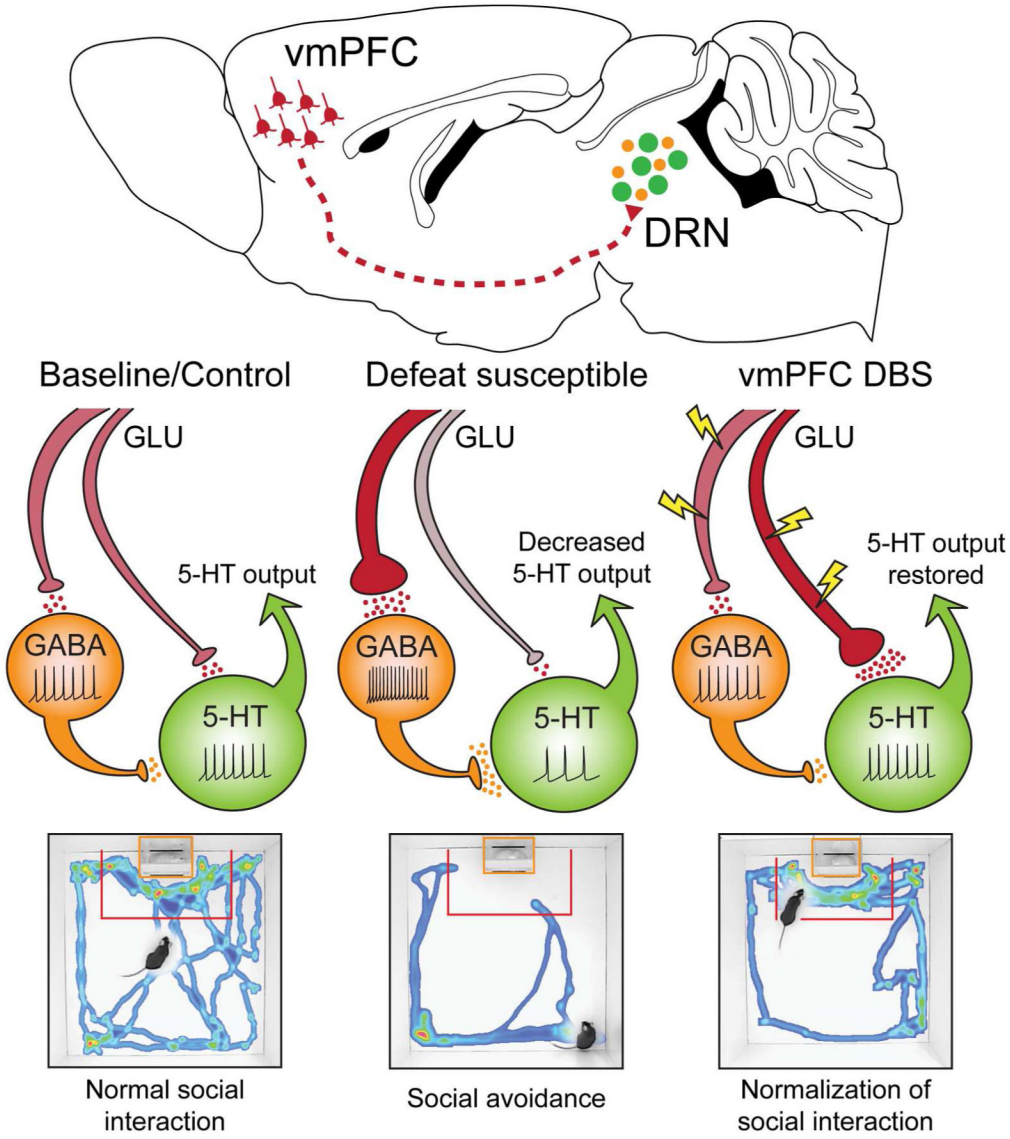

Figure 4. Hypothesized adaptations in the vmPFC-DRN microcircuit associated with defeat-induced avoidance and its normalization by vmPFC DBS

Schematic summarizing the differential neuroplastic adaptations in the vmPFC-DRN microcircuit and hypothesized effect on 5-HT output. Depicted are changes in intrinsic cellular excitability, synaptic activity (EPSC, IPSC) and corresponding social approach/avoidance behavior profiles (shown as video tracking heat maps). Compared to controls, in susceptible mice we observed hyperexcitable GABA neurons that had increased glutamatergic input and hypoexcitable 5-HT neurons that had increased GABAergic input. After chronic vmPFC DBS, there was a neuroplastic remodeling of DRN microcircuitry that normalized GABA-mediated hyperinhibition of 5-HT neurons and facilitated a direct excitatory synaptic drive of 5-HT neurons. Though the direct source of synaptic adaptations was not causally determined in this work, our mapping studies provide strong evidence for this circuit and adaptive mechanisms.

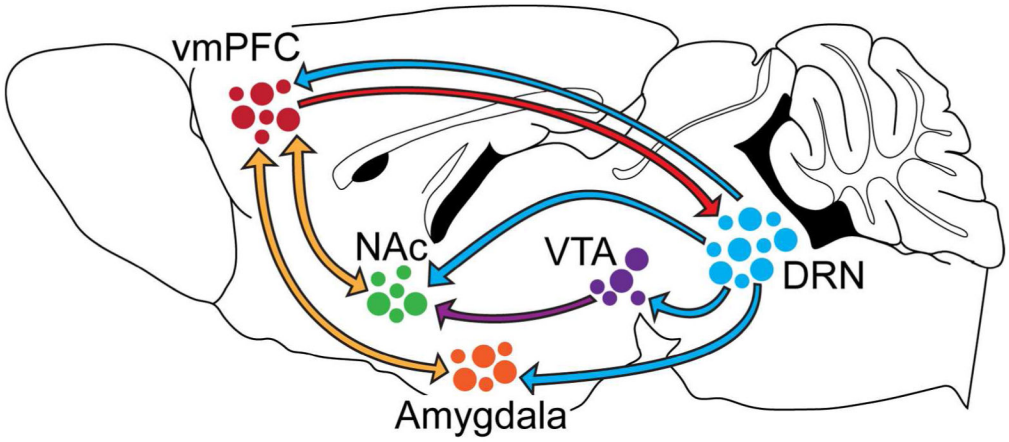

Figure 5. Neuronal targets downstream of the vmPFC-DRN pathway in socioaffective behaviors

Schematic depicts vmPFC control of the DRN and the structures likely to be affected by modulated DRN serotonergic projections in socioaffective behavior. Reciprocal projections to the vmPFC have been implicated in impulsivity and negative affective bias, 5-HT activity in the amygdala has been linked to fear and threat processing, and projections to the pathway between the VTA and NAc have been shown to affect reward behaviors.

Table 1

Symptoms associated with MDD.

Psychological symptoms*	Physical symptoms*	Social symptoms
• Guilt, self-doubt or loss of self-esteem • Lack of interest, pleasure or enthusiasm • Concentration or attention span is reduced • Recurring thoughts of death or suicide	• Disturbances in sleep – insomnia or hypersomnia • Abnormal psychomotor activity • Fatigue or loss of energy • Impaired appetite resulting in weight loss or gain	• Poor performance at work or school • Interpersonal difficulties at home or with family • Social withdrawal • Neglecting hobbies or interests

In addition to depressed mood and sadness, listed are the core symptoms associated with MDD. It is important to note that only symptoms in the categories marked with an asterisk are used to clinically diagnose MDD.

Table 2

Parallel human and animal studies on socioaffective behaviors

	Human studies	Animal studies
Stress hormones	• Cortisol administration increased attention to social threat especially in social anxiety patients[144]	• CORT administration facilitated social avoidance after CSDS[146]; blocking CORT release via adrenalectomy prevented avoidance[147,148]
Mood disorders	• Patients clinically diagnosed with MDD reacted differently to emotional faces, rated ambiguous social expression more negatively and displayed stronger avoidance tendencies in the explicit condition of the AAT, whereas social withdrawal was less pronounced in the implicit condition [31, 32]	• CSDS[125] and LH[165] models of depression result in long lasting social withdrawal and avoidant behavioral tendencies
Genetic models	• Subjects with the short allele of 5-HTTLPR polymorphism displayed stronger social avoidance[166] and increased attention to negative social stimuli[167–169]	• In macaques, pictures of high status male were rewarding and induced risk seeking behaviors in 5-HTTLPR long allele carriers, while the opposite was observed in short allele carriers[170] • SERT −/− mice displayed increased vulnerability to social stress[171] and decreased social dominance[172,173] • Humanized TPH2 (R439H) knock-in (*Tph2KI*) mice displayed increased social avoidance after social defeat[174]
Decreased serotonin	• ATD decreased positive appraisal of happy faces[152] or evaluation of social relationships of intimate couples[68] and increased attention towards threatening cues[22]	• TRP depletion[151] or 5,7-DHT administration[150] decreased sociability in mice
Increased serotonin	• TRP supplementation increased recognition of happiness[175] and decreased quarrelsome behaviors[176] • Citalopram administration increased recognition of happy[50] or fearful[177] faces and increased rating of ambiguous faces as positively valenced[71] • MDMA administration enhanced prosocial behaviors[178] and decreased depressive tendencies in social gatherings[179]	• TRP administration improved sociability[151] • Citalopram[180] or fluoxetine[137] administration following CSDS restored social approach • MDMA administration decreased aggression and increased social interaction duration[181,182]
Corticolimbic synchrony	• Enhanced prefrontal-amygdala coupling was associated with negatively biased evaluation of socioemotional cues in healthy subjects and avoidance tendencies in depressed patients; coupling was reduced by increased serotonin[72]	• Enhanced cortico-amygdala synchrony predicted vulnerability to CSDS-induced avoidance[163] and is increased in TPH2 −/− mice[164]
vmPFC manipulation	• cTBS of the aPFC increased emotional dysfunction during social interaction[76] • DBS of the SCG normalized negative self bias[183] and resulted in social reintegration and lowered social dysfunction[155,156]	• High frequency (>100 Hz) electrical[154] or optogenetic[184] stimulation of the vmPFC reverses avoidance after social defeat • Elevating excitatory/inhibitory balance via 80Hz optogenetic activation induced social deficits[185]

Abbreviations: 5-HTTLPR – serotonin transporter linked polymorphic region, AAT – approach avoidance task, aPFC – anterior prefrontal cortex, ATD – acute tryptophan depletion, CORT – corticosterone, CSDS – chronic social defeat stress, cTBS – chronic theta burst stimulation, DBS – deep brain stimulation, LH – learned helplessness, MDD – major depressive disorder, MDMA – methylenedioxymethamphetamine, SCG – subcallosal cingulate, SERT – serotonin transporter, TRP – tryptophan, TPH – tryptophan hydroxylase, vmPFC – ventromedial prefrontal cortex