Understanding Differential Responses to Social Anxiety Disorder (SAD) Therapies

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Abstract

This paper provides an overview of the epidemiology and prominent emotional and physical clinical symptoms of social anxiety. We review two neurotransmitter systems commonly implicated in the condition: dopamine and serotonin. We then look at pharmacological interventions that address the deficiencies in these systems. Finally, we discuss how Cognitive Behavioral Therapy works from computational and behavioral perspectives, discuss its shortcomings, and suggest novel approaches to address these concerns.

Introduction

Social anxiety disorder (SAD) or social phobia is a common chronic mental health condition in which everyday social interactions, such as working in groups, going to a party, and talking to new people, induce irrational levels of stress, embarrassment, and fear of rejection and judgment (Schneier, 2019; NIH, 2017). The Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-V) categorizes SAD into two subtypes: generalized and non-generalized (Jorstad-Stein et al., 2009; SAMHSA, 2016). General social phobia causes patients to develop a fear of most social situations and is thus more debilitating than non-generalized social phobia, which involves the fear of any public performance such as public speaking (SAMHSA, 2016).

Epidemiology

Globally, social phobia ranks as the third most prevalent psychiatric disorder. Interestingly, prevalence rates vary across different cultures, potentially because social fears hinge on the cultural environment in which one grows up and lives. For example, the degree of a community's focus on individualism versus collectivism can shape a person's perception of social norms, which may lead to a phobia if the individual's personality does not conform or if the person moves to a different cultural context (Thomas, 2018; Stein et al., 2017). The disorder affects about 13% of the American population, with similar rates in other Western and South American countries (Thomas, 2018). By contrast, collectivist societies such as those in Asian countries tend to promote more reserved behaviors, which may explain the extremely low social phobia rates of 0.6%, 0.2%, and 0.8% in Korea, China, and Japan, respectively (Thomas, 2018).

Behavioral presentations

Behavioral presentations vary based on the severity (mild to moderate to severe) and subtype of social phobia. Overall, however, patients with SAD commonly experience physiological symptoms such as nausea, dizziness, muscle tension, and trembling voice and hands during social interactions (Leichsenring & Leweke, 2017). Such fight or flight reactions occur when patients perceive the interaction to be threatening or emotionally dangerous to them. After a social encounter, SAD patients tend to replay past interactions

repeatedly, hoping to optimize the situation in their minds to determine what they could have said or done to avoid embarrassment and guilt (Leichsenring & Leweke, 2017). More often than not, patients ultimately resort to cancelling events and avoiding social interactions altogether to avoid any future public embarrassment that may or may not occur (Leichsenring & Leweke, 2017).

Around 70% to 80% of those with SAD also have comorbid general anxiety and depression that exacerbate social anxiety symptoms greatly and complicate treatment modalities (Schneier, 2019).

Neurotransmitter systems in SAD

Dopamine plays an important role in fear processing, as well as human social and avoidance behaviors (Skuse et al., 2009). To assess dopamine levels in SAD, studies have looked at dopamine binding potentials (BP_{ND}) using single photon emission tomography (PET); prior work has shown that the levels of a neurotransmitter is positively correlated with its binding potential levels (Berry et al., 2018).

One pioneer study, conducted on ten individuals with social phobia without any signs of comorbidity and ten healthy individuals as controls, explored D_2 receptors (D_2R) binding levels in the brain (Schneier et al., 2000). It was observed that the group of individuals with social phobia had significantly lower D_2R binding potential than the control group. The Liebowtiz Social Anxiety Scale was used to test the differences in severity of social anxiety between the two cohorts, and the scale showed nonsignificant correlation of binding potentials. Thus, while this pioneer study established the prevalence of reduced dopamine levels in the SAD brain, it did not elucidate how differential amounts of dopamine affected the severity of social anxiety in patients. Additionally, this study was done in the striatum, and the results from the extrastriatal region, such as the amygdala and prefrontal areas, vastly differ from those of the striatal regions.

Previous studies on neural activation from blood flow using functional magnetic resonance imaging (fMRI) indicate that extrastriatal regions − namely the amygdala, anterior cingulate, insula, orbitofrontal cortex (OFC) and medial frontal cortex (MFC) − play a key role in social phobia (Freitas-Ferrari et al., 2010; Brühl et al., 2014). As a result, a 2017 recent study by Plavén-Sigray and colleagues used PET scans and high-affinity D_2 radioligand [^{11}C] FLB457 to test for D_2R availability in extrastriatal regions of SAD patients (Plavén-Sigray et al., 2017). This experiment illustrated statistically significant differences in elevated levels of D_2R binding potential in bilateral OFC and right dorsolateral prefrontal cortex (DLPFC) voxels between SAD and control individuals. Plavén-Sigray and colleagues were the first to show that the extrastriatal region played a role in SAD, specifically due to greater D_2R availability in the OFC and DLPFC. The OFC processes sensory stimuli to make predictions about the future which it sends to the DLPFC where prediction errors emerge. Thus, higher D_2R availability in these two regions may explain the orchestration of anxiety

and inflated prediction of threats, which leads to avoidance desires in expectation-result mismatches during social interactions.

To further understand the role of dopamine in social phobia therapeutic modalities, a study by Warwick and colleagues looked at the availability of transporters, proteins that bring neurotransmitters back to presynaptic neurons. The researchers posit that serotonin and dopamine may be interlinked in SAD as they observed an increase in dopamine transporter (DAT) availability when SAD patients were treated with escitalopram, a selective serotonin reuptake inhibitor (SSRI) which increases serotonin levels (Warwick et al., 2012). To explore Warwick's findings further, Hjorth and colleagues tested the expression of serotonin transporter binding potential (SERT BP_{ND}) and dopamine transporter protein binding potential (DAT BP_{ND}) using PET scans. The study showed higher SERT BP_{ND} availability in the nucleus accumbens of SAD individuals compared to control individuals (Fig. 1C). While no difference in DAT BP_{ND} availability was observed between controls and SAD patients (Fig. 1G), DAT BP_{ND} availability in the amygdala, hippocampus, and putamen was positively correlated with higher symptom severity *within* the SAD cohort (Fig. 1H). The study also showed a higher *co-expression* of SERT BP_{ND} and DAT BP_{ND} in the amygdala, nucleus accumbens, caudate, putamen, and posterior ventral thalamus (Fig. 2). By exploring this potential connection between the serotonin and dopamine systems in social anxiety, Hjorth et al. have begun to unpack how SSRIs may be mitigating social anxiety.

Therapeutic modalities

Our knowledge of the role of dopamine and serotonin systems has helped inform psychotherapies used to treat SAD. Such therapies are usually also shaped by patients' comorbidities, idiosyncrasies, cultural and medical backgrounds, and past adverse reactions to medication.

The current literature suggests that different psychotherapies target various specific regions of the brain as shown in Figure 3 (Papalini et al., 2020). For instance, exposure therapy first tries to maximize prediction errors in the striatum to minimize negative expectations (step 1 in Fig. 3). These dopamine-based prediction errors mostly occur in the nucleus accumbens and ventral tegmental area (mesolimbic brain regions). Secondly, error-based learning techniques help dopaminergic signals drive the acquisition of safer memories that are not connected to any negative stimuli (step 2 in Fig. 3). Specifically, dopaminergic transmissions from midbrain to prefrontal regions aid in updating negative expectations of threat and fear extinction memories. These phasic dopamine signals generally utilize D_2 receptors to interact with tonic dopamine processes in the brain. To target more signals, more studies are now investigating D_2R and dopamine-based interventions that may promote fear extinction retrieval. These interventions can serve as a promising addition to exposure therapy and working memory (WM) training, a technique that helps patients use their WM rationally (step 3 in Fig. 3) (Papalini et al., 2020).

These approaches to therapy are some of the many techniques used on SAD patients, and they provide broad ideas of how such modalities can tackle different cognitive irregularities in specific regions associated with SAD. In our review, however, we will only focus on two commonly used therapies, namely pharmacotherapy and cognitive behavioral therapy (CBT), and one novel technique called attention bias modification (ABM) training.

Pharmacotherapy

Pharmacotherapy is one of the most common treatment options for social phobia and targets symptoms by addressing supposed neurotransmitter deficiencies in the SAD brain. Several categories of medications are often prescribed including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), beta blockers, and benzodiazepines (Mayo-Wilson et al., 2014; Stein, 2008). Today, SSRIs and SNRIs serve as first-line pharmacological agents because they have the least significant side effects (Mayo-Wilson et al., 2014). Effexor, an SNRI, targets serotonin and norepinephrine, the latter of which regulates fear conditioning and stress responses such as the fight or flight response (Mayo-Wilson et al., 2014). SSRIs such as Celexa, Paxil, and Zoloft slow down the reabsorption of serotonin and dopamine by binding to SERT molecules and blocking their normal activity (Swanson, 2013). By doing so, more of these "feel good," mood-regulatory neurotransmitters remain in the interneuronal spaces and participate in increased neuronal signaling and communication (Swanson, 2013). However, exactly how this biochemistry then works against social anxiety symptoms still remains unclear (Swanson, 2013).

Both groups of inhibitors work to make the patients feel less physiologically aroused so that they can feel less of their stress symptoms such as sweating and rapid heart rates, calm down, and begin to think rationally about the actually neutral but negatively perceived stimuli in their environments (Mayo-Wilson et al., 2014). Although only one in three studies show Prozac, a popular SSRI, works better than placebo, most other SSRIs and SNRIs are highly and nearly equally effective in alleviating generalized social anxiety symptoms in 50% to 80% of patients (Mayo-Wilson et al., 2014). Differences in the exact medication and dose prescribed to a patient depend on the person's medical history and comorbidities.

One of the biggest disadvantages of SSRIs involves the slow uptake of the medication into the brain. The process by which SSRIs establish a consistently greater supply of available neurotransmitters in the brains of SAD patients takes a very long time. In fact, within the first two weeks of starting SSRI therapy, SAD symptoms actually tend to worsen, potentially because of the incongruous timing of side effects against the benefits (Mayo-Wilson et al., 2014). The side effects of the medications, such as lethargy and more severe depression and anxiety, are observed before the benefits can be reaped. Significant therapeutic benefits are first noted at usually around four to six weeks, and the full range of benefits can take up to 12 weeks (Mayo-Wilson et al., 2014).

Given the lengthy uptake time, possibility of inefficacy, and lack of clarity as to *why* SSRIs often do work, a popular controversy shrouds SSRIs: To what extent are these medications

merely a placebo effect? One PET study explored this question, focusing on the amygdala which is a target region for SSRIs (Faria et al., 2012). The study had four groups of patients: SAD patients or "responders" who were expected to respond to medication and "nonresponder" control individuals who were not expected to perform differently to medication. The two cohorts were further subdivided and given SSRIs and placebos. While both placebo responders and SSRI responders had strong responses in the bilateral amygdala in a public speaking task, both groups of nonresponders did not, suggesting that expectations may play a significant role in symptom alleviation. Knowing they have social anxiety, responders most likely expected to feel at least somewhat better when given a pill. Nonresponders, on the other hand, did not expect to feel any better or worse since they knew they did not have social anxiety. Further work remains to be done to understand how SSRIs truly alter our brain biochemistry and what role expectation plays in attenuating behavioral responses.

By contrast, beta blockers and benzodiazepines are fast-acting, suppressing social anxiety symptoms typically within an hour (Mayo-Wilson et al., 2014). Although beta blockers are typically used to treat heart conditions, they can be useful in lowering the heart rates and blood pressure of SAD patients as well by blocking the effects of epinephrine. Benzodiazepines increase GABA activity, an inhibitory neurotransmitter, to obstruct heightened rates of neural signaling in anxious patients (Mayo-Wilson et al., 2014). By doing so, benzodiazepines reduce the neuronal processing of anxious thoughts. Unfortunately, beta blockers and benzodiazepines are highly addictive and cause a plethora of harmful side effects such as liver damage (Mayo-Wilson et al., 2014). As such, they serve as last lines of therapy for coping with generalized social anxiety but have been shown to be more useful for specific social phobias such as public speaking.

Cognitive behavioral therapy (CBT)

Cognitive behavioral therapy (CBT) is currently considered to be the first-line psychotherapy for social anxiety disorder (SAD) (Narr and Teachman, 2018). CBT aims to reduce anxiety symptoms by correcting maladaptive beliefs and reducing avoidance behaviors through exposure to social situations (Beck et al., 2005). But despite its status as the gold standard treatment, its efficacy is limited especially in everyday mental health practice with a recovery rate ranging from 14% to 48% (Parker and Waller, 2015). In order to explain such large variance in outcomes following CBT among SAD patients, we must understand the mechanism of action by which CBT targets different aspects of SAD.

A study by Moutoussis et al. (2018) provides potential explanations for why CBT sometimes fails from a computational perspective. In SAD patients, the maladaptive belief that they will be humiliated in social settings is maintained through avoidance behaviors that have been developed to mitigate this perceived risk (Moscovitch, 2009). The exposure component of CBT specifically targets this defect by encouraging exploration of social situations and opening up a window for the negative values associated with such situations to be updated. The effect of exposure on avoidance behavior was modelled with a variant of the temporal difference learning model (Moutoussis et al., 2008). In this simulation, negative state values were established by exposing agents to shocks while avoidance was

restricted. When this restriction was lifted, avoidance behavior increased and was sustained, though no more shocks were delivered. The agent then underwent an exposure therapy equivalent where avoidance was again restricted, but shocks were omitted. Most critically, the simulation demonstrated that the exposure session only had to reverse the aversive value partially to reduce subsequent avoidance behavior (Moutoussis et al., 2008). This model predicts that even after the conclusion of therapy, SAD patients will start engaging in social situations more, which would in turn drive further learning through a positive feedback mechanism.

If this were true, a few sessions of CBT should cure SAD. But this is not the case in many patients. To explain why, we must clarify exactly what CBT is encouraging the exploration of. In social anxiety, it is not just the failure to explore social situations per se that prevents the extinction of maladaptive beliefs, but also the lack of exploring the entire hypothesis space regarding social feedback. Exposing patients to social situations addresses the first issue, but not necessarily the latter issue. An example of this is near-miss inference, where patients believe that a disaster almost happened, though nothing really happened (Moutoussis et al., 2018). These patients may then update the state values counterfactually, treating the "near-miss disaster" as an actual aversive stimulus. This can stall the extinction of the negative value associated with social situations. This phenomenon can be explained in Bayesian terms via the following equation (Moutoussis et al., 2018):

$$p(C_b|r_b) = \frac{p(r_b|C_b)p(C_b)}{p(r_b|C_b)p(C_b) + p(r_b|C_h)p(C_h)} = \frac{p(C_b)}{p(C_b) + p(r_b|C_h)(1 - p(C_b))}$$

where C_b and C_h are benign and harmful situations respectively, and r_b and r_h are benign and harmful feedback. Note that the first equation simplifies to the second because the agent fully expects a positive feedback given that the situation is benign ($p(r_b|C_b) = 1$). During exposure therapy, if patients are convinced that the situation is benign, $p(C_b)$ is close to 1, and the posterior belief, $p(C_b|r_b)$, that the situation is benign given a positive feedback would be close to 1. But with near-miss inference, patients are not convinced that the situation during exposure is really safe. Then, $p(C_b)$ will be lower, and consequently, the posterior will be lower. In other words, the patient will continue to believe that the situation is unsafe even when provided with positive social feedback, rendering exposure ineffective.

This exaggerated and pessimistic evaluation of social situations can be informed by patients' own anxiety symptoms (Moutoussis et al., 2018). A related preposition is that patients tend to focus their cognitive resources on threat, failing to consider the alternative hypothesis that the situation is safe (Moutoussis et al., 2018). In fact, it has been shown that SAD patients are overly sensitive to negative feedback and consequently tend to update their beliefs more to negative relative to positive social cues (Khdour et al., 2016). But it remains unknown how much of this biased appraisal is driven by physiological hyperarousal or maladaptive cognitive reasoning. The cognitive component of CBT, such as psychoeducation and cognitive restructuring, can identify maladaptive beliefs and modify them to get patients to evaluate social situations more rationally, but it is naturally difficult

to change someone's mind, especially when there is pathology involved. For instance, SAD patients showed reduced ability to engage in flexible model-based learning compared to controls, with greater reduction predicting poorer CBT response among patients (Alvares et al., 2014). The consequent bias towards inflexible model-free control over actions could reduce their sensitivity to changes in state values during both cognitive therapy and behavioral exposure. This could also explain the variance in CBT efficacy among patients. Combinatorial therapy with anxiolytics can help alleviate the physiological symptoms of anxiety, reducing their influence on near-miss inference. This can help enhance the efficacy of exposure, especially in pessimistic agents.

Furthermore, classical CBT methods remain ineffective in decreasing anxiety symptoms in one third of SAD patients due to another disease mechanism that may be driving biased appraisal towards negative social cues (Davidson et al., 2004). The current literature reports that attentional bias directed toward threat can occur in several forms: facilitation of directing attention toward the threat, difficulty in detaching attention from the threat, and avoidance of threat by attention (Fistikci et al., 2015; Koster et al., 2006). Facilitated attention is directing attention toward a threat stimulus more easily or faster. When one experiences difficulty in detaching attention from the threat, attention is trapped by threat and cannot be directed toward another (more productive and realistic) direction. In attentional avoidance, attention is directed in the opposite direction of the threatening stimulus in fear.

Attentional bias modification (ABM) training strives to correct the bias to negative social cues prominent in social phobia patients. Whereas CBT *explicitly* teaches patients to change their distorted cognitions and avoidant behavior through practice, attention bias modification (ABM) training *implicitly* trains patients to divert attention from threats (Lazarov et al., 2018). Because the two therapies target different mechanisms, exposing patients to both in tandem can theoretically be very effective at targeting root causes of social phobia. In ABM training sessions, the dot-probe paradigm is most frequently used such that a probe always appears after neutral stimuli (e.g., a neutral face) (Lazarov et al., 2018). By forcing their attention onto the probe, patients learn over many trials to disengage their attention away from threatening stimuli (e.g., an angry face) and direct it toward non-threatening ones. The probe frequency after the neutral stimuli is increased, and the patient's attention toward the neutral stimulus is reinforced (Lazarov et al., 2018). In doing so, patients see neutral stimuli as truly neutral, thereby decreasing the threat inflation from the OFC (Amir et al., 2009). In a 2009 study, 50% of participants with SAD who were trained under the ABM paradigm no longer met clinical psychiatric criteria for social anxiety after training, compared to only 14% of control participants; this study had a large effect size and the positive results were maintained at three months followup (Lazarov et al., 2018). These findings are also consistent with many other studies and provide a very promising option for SAD treatments.

However, even if a therapist is able to address these issues and a patient shows improvement, a process called overaccommodation can lead to relapse (Moutoussis et al., 2018). This has been used to explain why fear responses sometimes come back in a different setting after extinction. The idea is that a different latent cause gets associated

with the same stimulus in different settings (Gershman and Niv, 2010) so that learning in one setting fails to generalize. In terms of SAD, the therapy and the real-life setting may become associated with separate latent causes. Consequently, patients may learn that social situations chosen by the therapists to conduct exposure are safe but continue to believe that things may go wrong in real-life situations.

To minimize relapse due to overaccommodation, in-vivo exposure in realistic settings where patients normally experience anxiety could be better than imaginary or VR exposure therapies, which are sometimes used due to their relative convenience and higher patient compliance. But the trade-off is that the latter exposure methods may feel safer to patients, reducing near-miss inference. Generalizability of learning can be maximized if exposure is conducted in multiple settings (de Jong et al., 2019). This could be done by varying the CS itself (different social activities), the external context (different physical locations), or the internal context (different emotional or physiological states). Varying the interpersonal context, such as conducting exposure with and without a therapist, can also reduce the patients' reliance on their therapists for affirmations of safety (Craske et al., 2014). Retrieval cues that will help activate the latent cause associated with clinical setting can also potentially augment therapy (de Jong et al., 2019). This can be an external cue like a bracelet that is worn during and after therapy or an internal cue such as active mental recall of treatment context.

A final method to prevent relapse is occasional reinforced extinction (ORE) (Craske, 2015). In this procedure, an agent occasionally receives CS-US pairings during extinction learning. This is similar to the gradual extinction procedure in which occasional shocks gradually decrease in frequency (Gershman et al., 2013). This was effective for reducing the return of fear responses after extinction. Applied to social anxiety, this would involve occasionally exposing patients to social rejections. The patients incorporate these negative feedback as part of the therapeutic context (Krompinger et al., 2018). Thus, in real-life situations, if they receive negative feedback, they are less likely to say "bad things are happening because real life is different from therapy." Instead, they would say "bad things can sometimes happen, but only occasionally." This would theoretically reduce the chance of relapse.

There are, however, potential caveats to applying this method to SAD patients. There may be ethical issues with intentionally exposing patients to negative social feedback. Even if it is allowed, fewer patients are likely to commit themselves to such "risky" exposures. It is also unknown whether the procedure will benefit SAD patients. This method may be especially poor for patients who engage in near-miss inference. The occasional negative feedback would give them more reason to believe that something bad almost happened. In these patients, their response to negative feedback is amplified (Khdour et al., 2016). Thus, even an occasional negative feedback can be extremely traumatizing, worsening the anxiety symptoms.

Conclusion

The current literature on SAD highlights many confounding results in terms of how therapeutic modalities affect the brain. Here, we reviewed the modulation of key neurotransmitters implicated in SAD: dopamine and serotonin. According to recent research, dopamine and serotonin may have interrelated effects on a SAD patient as seen by the co-expression of SERT and DAT in the amygdala, nucleus accumbens, caudate, putamen, and posterior ventral thalamus. The relationship between dopamine and serotonin may explain why SSRIs and SNRIs are some of the leading pharmacological agents used to alleviate the symptoms of social phobia with high efficacy rates. Although the exact reasons for how SSRIs affect neurotransmitter levels in the brain still remain under question, studies have shown that the amygdala might be one of the key targets of SSRIs. Interestingly, while SSRIs and SNRIs strive to increase neuronal signaling to boost realistic evaluation of stimuli, benzodiazepines suppress signaling to reduce transmission of anxious thoughts. CBT, despite being the first-line psychotherapy, is limited in efficacy. From a computational perspective, this limitation may stem from exaggerated negative appraisal of social situations driven by near-miss inference and attentional bias towards threat cues that maintain aversive unconditioned stimulus during exposure therapy. This prevents extinction of negative values associated with social situations, maintaining avoidance behavior. Combination therapy with pharmacological agents and ABM procedures could potentially address these issues. However, a pitfall is that overaccommodation can prevent learning in therapy settings from being generalized to real-life settings, leading to relapse despite initial improvement. Pioneers in the field are finding ways to extinguish such caveats using methods such as exposure in various settings, retrieval cues, and occasional reinforced extinction to augment CBT and minimize relapse. But these options are not without their own disadvantages, and the appropriate treatment plan should be tailored to each patient's idiosyncratic pathology. Comorbidities, which are common in SAD, further complicate treatment. In our review, we have addressed that much of what happens in the brain during these therapies remains unknown and it seems as if most psychotherapies and pharmacological methods only occur by "chance." There is no "one-size-fits-all" approach to treating SAD, and future studies should seek to further uncover the effects of treatments on brain and behavior to inform optimal treatment decisions.

Appendix

Figures

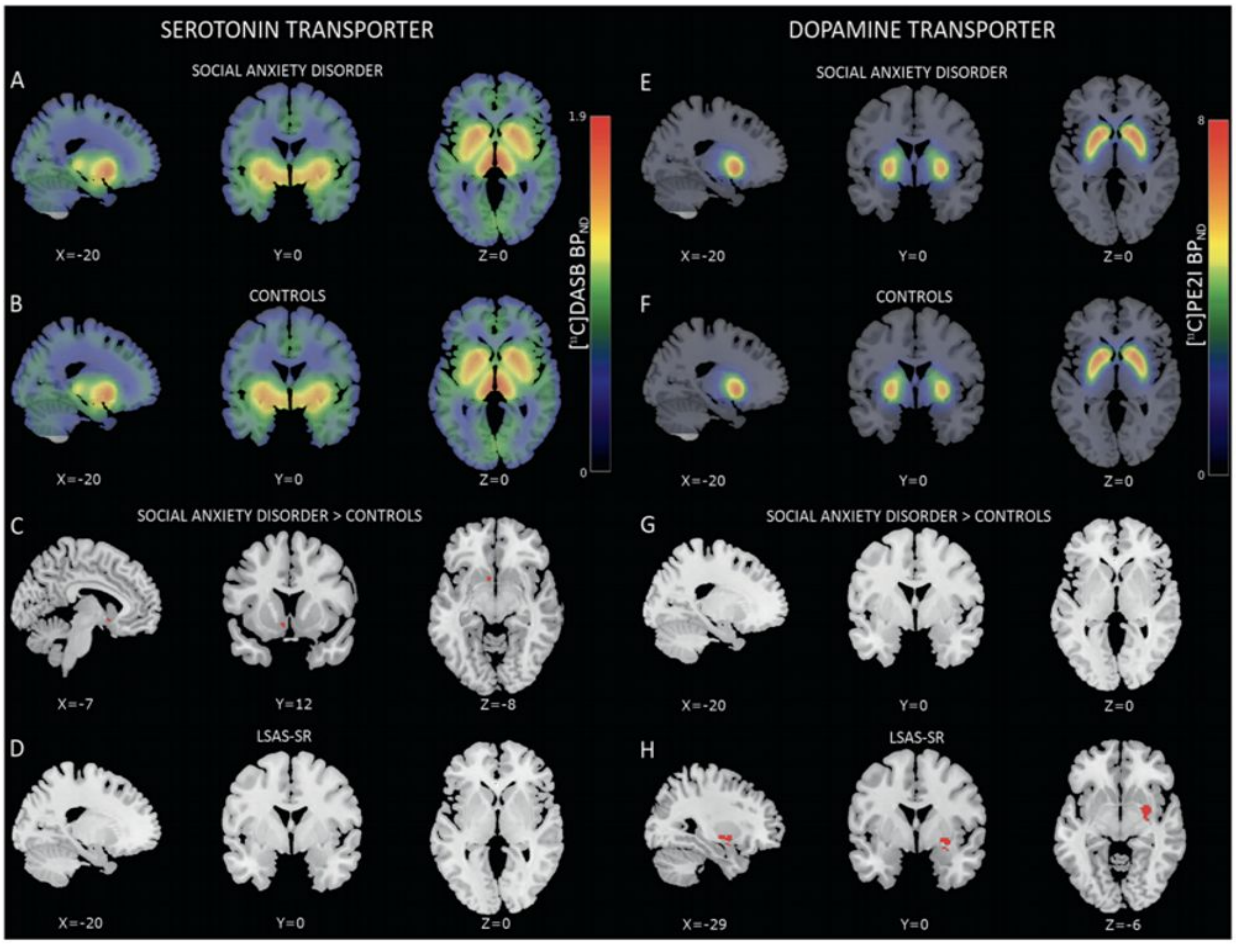

Figure 1:

(left) Elevated seretonin transporter binding potential (SERT BP_{ND}) availability in Nucleus Accumbens in SAD patients (panel C)

(right) No difference in dopamine transporter binding potential (DAT BP_{ND}) availability between controls and SAD patients (panel G)

Significant positive correlation between DAT BP_{ND} availability and symptom severity in amygdala, hippocampus, pallidum and putamen (panel H)

(figure adapted from Hjorth et al., 2019)

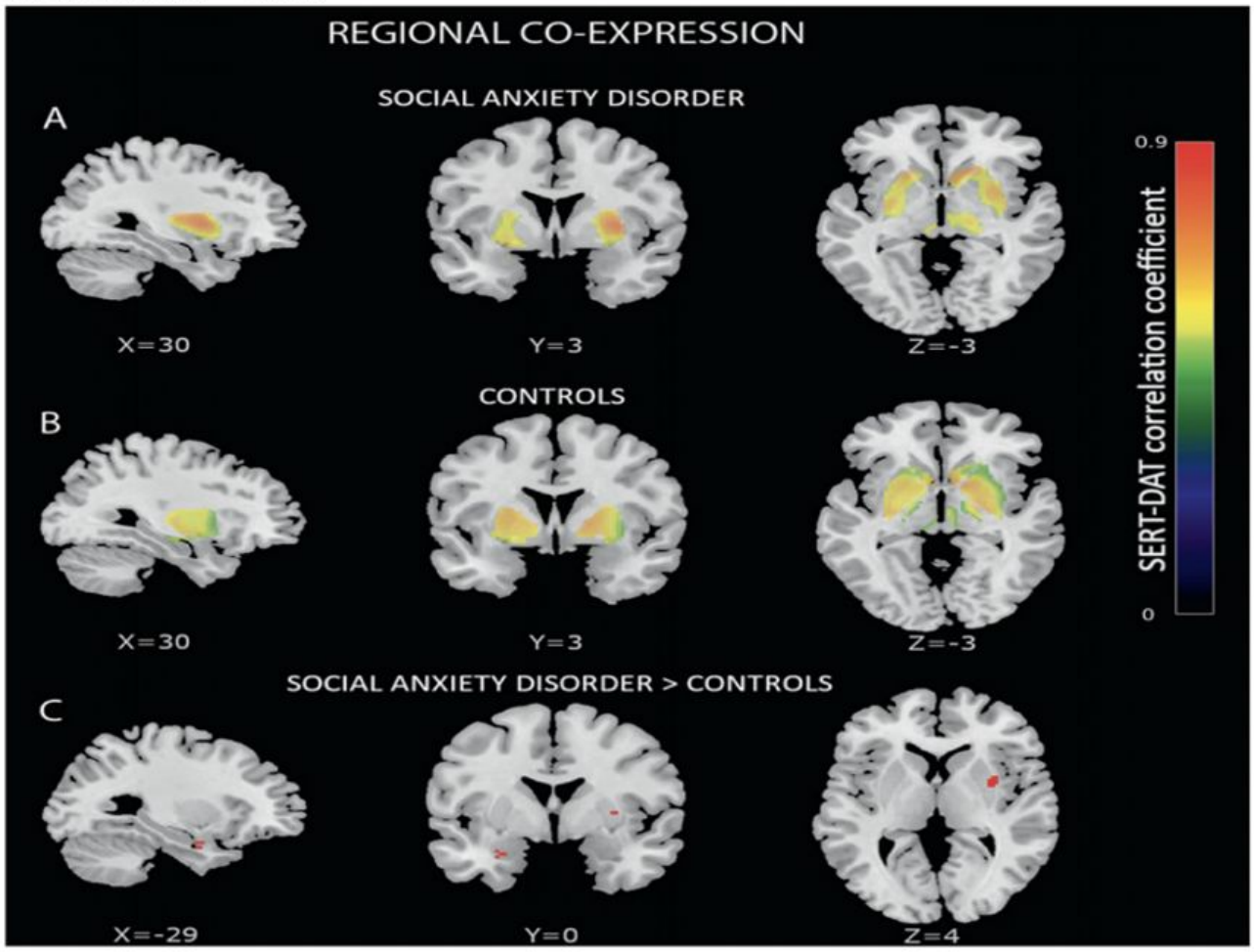

Figure 2: Seretonin transporter binding potential (SERT BP_{ND}) and dopamine transporter binding potential (DAT BP_{ND}) co-expression in amygdala, caudate, putamen, nucleus accumbens, and thalamus

(figure adapted from Hjorth et al., 2019)

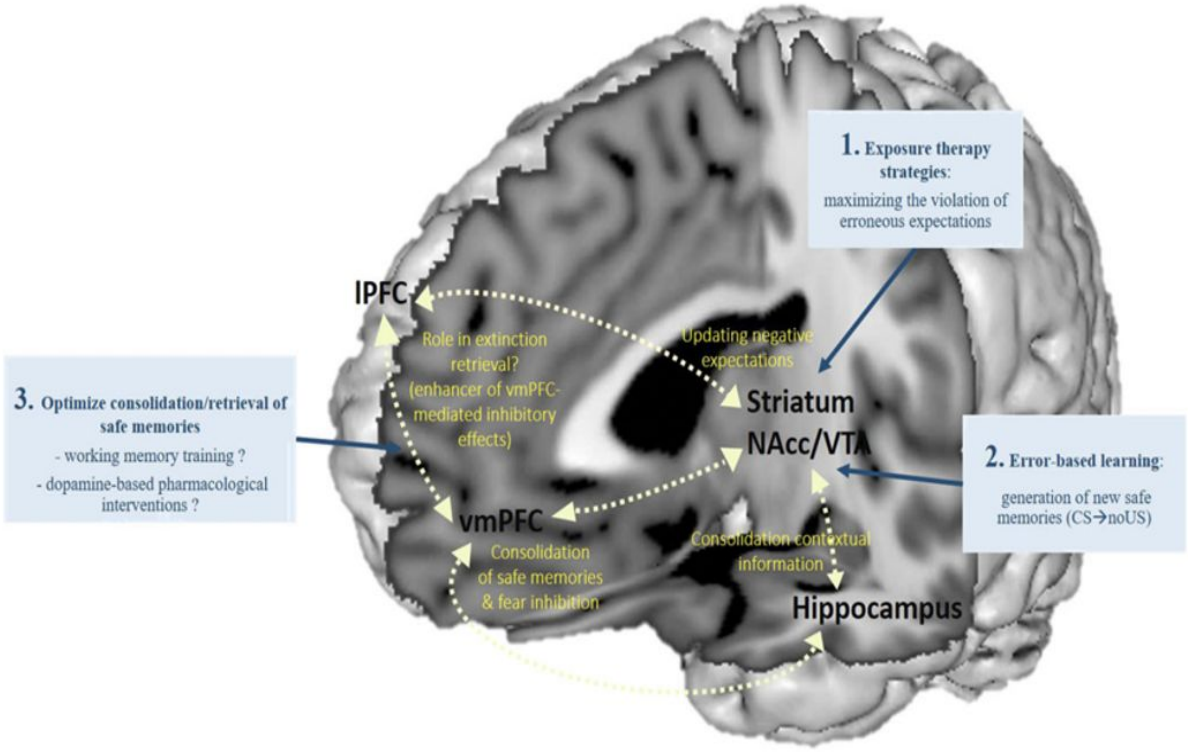

Figure 3: Illustration of various strategies targetting various regions of the brain (figure adapted from Papalini et al., 2020)

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