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Novel Method of Supplementing Current Depression Treatments: Using Autonomous Sensory Meridian Response-Centered Therapy to Improve Constipation-Associated Comorbidity of Depression

Shivam S. Patel
The Honors College
Virginia Commonwealth University
Richmond, VA 23220 USA

Faculty Advisor: Mary Boyes

Abstract

One-third of individuals struggling with constipation also suffer chronically from comorbid depression. While both conditions have been extensively explored separately, the evidently shared etiology that connects these two has been relatively unresearched. By examining depression from a biopsychological perspective, incorporating both gastroenterology and neuropsychology, more operational information will become available regarding prospective treatments for individuals suffering from these specific comorbidities. This proposed study aims to analyze the role played by ASMR (autonomous sensory meridian response), a newly recorded neural phenomenon that causes relaxing "tingles" from unique "triggers" in a specific subset of individuals, in altering serotonin (5-HT) levels within the enteric nervous system to aid with both depression and constipation. In depressed individuals, reduced 5-HT has been clinically accepted as a key symptom and is frequently treated with prescription SSRIs. Possible alternative methods of treatment, such as ASMR, would not only aid in cost-reduction, but also help explain the role of external influences on internal, measurable 5-HT levels within the gut. 5-HT additionally plays a key role in promoting gut motility, and researchers have posited a connection between the gastrointestinal microbiome and the brain along a "gut-brain axis." Other possible theories about this connection do not seem to be definitively conclusive of the answer. A prospective study would use this paper as a blueprint for: 1) determining the most viable form of ASMR videos to use in the experimental cohort, 2) devising a way to collect quantitative changes in bowel motility and enteric 5-HT after scheduled ASMR viewing sessions in responsive individuals and 3) deciding how to collect qualitative verbal reports about the perceived role of ASMR in assuaging their depression. Such a prospective study would be the first of its kind and will improve understanding of depression-related physiology and provide the basis for non-invasive treatments to suffering individuals.

Keywords: Constipation-Depression Comorbidity, ASMR, Enteric 5-HT

1. Introduction

Chronic constipation has been implicated as a symptom in both gastrointestinal (GI) and neurological comorbid conditions, including diverticulosis, hemorrhoids, cancer, cardiovascular diseases, hypertension, and hypercholesterolemia (pp. 145-146).[4] A comorbidity worth noting, however, is depression, which has been shown to accompany constipation in as many as one-third of patients suffering from any form of GI motility dysfunctions (p. 161).[16] An evident conjoining factor between constipation and depression is serotonin, or 5-hydroxytryptamine (5-HT), which is produced primarily in the enterochromaffin (EC) cells of the GI tract. The EC cells constitute a principal mechanism within the enteric nervous system (ENS), a network of neurons that governs the functionality of the digestive tract. The ENS, or "second brain," is a component of the autonomic nervous system (ANS) and can be influenced by the sympathetic and parasympathetic nervous systems via communication from the vagus nerve.

The etiology of depression also implicates imbalances in 5-HT, according to the prevalent *5-HT deficiency theory of depression*. Subscription to this theory has been prominent among clinicians, especially due to the efficacy of selective serotonin reuptake inhibitors (SSRIs). These anti-depressant drugs, marketed until popular names such as Paxil (paroxetine), Prozac (fluoxetine), and Lexapro (escitalopram), have become the most prescribed SSRIs for depressive symptoms and have shown positive effects in remission among patients, starting four to six weeks after initiating treatment. Artificially induced 5-HT deficiency in mice has shown to lead to depressive symptoms as well.[7]

While the *5-HT deficiency theory of depression* has not yet been formally established as a comprehensive explanation for depression, it has provided a logical starting point for conversation and research into the true etiology underlying depressive symptoms. It would be amiss if the seemingly shared etiology present between chronic constipation and depression were not exploited to find a possible therapy method aiding in the alleviation of constipation-derived depression.

The answer might lie in the autonomous sensory meridian response (ASMR), a recently documented phenomenon that individuals on online forums describe as a tingling feeling down the scalp and spine.[9] ASMR is experienced by specific visual and auditory "triggers" that are often purposefully induced in YouTube videos. Not all individuals feel this sensation, and some only feel it when presented with certain triggers.[2] Despite these limitations, ASMR videos have continued to dramatically rise in popularity since 2012, garnering millions upon millions of views on YouTube.[13] Thousands of viewers have commented that ASMR aids them in dealing with depression, insomnia, anxiety, stress, and some have even stated that it helps them gain focus or relaxation.[2] ASMR has also shown reliable, positive changes in physiology, mental state, and neural activity in receptive individuals.[15]

Because of the efficacy that ASMR presents as a potential method of aiding in depression, an experimental design could be formulated studying ASMR-responsive patients who are undergoing treatment for chronic constipation and depression. Such a study would require 1) determining the optimal, most-responsive ASMR trigger(s) to use and 2) studying the effects of systematic exposure to pre-developed "ASMR video supplemental therapy" on subjective symptoms of depression, ENS-derived 5-HT levels, and gut motility.

2. Comorbidity of Constipation-Associated Depression

Because constipation and depression have similar etiological ingredients involving 5-HT and its biosynthesis in the central nervous system (CNS) and ENS via TPH2 (tryptophan hydroxylase 2), current research has hypothesized a manifest link between the two conditions.

Constipation and depression are addressed clinically through separate pharmacological treatments, usually oral or rectal laxatives and anti-depressants, respectively, that solely target symptomatic conditions as opposed to holistic circumstances present in the patient. Since more comprehensive lifestyle changes such as alterations in diet, exercise routine, and sleep cycle lead to independent improvements in mood and constipation symptoms, an innate, relatively unexplored commonality may be present linking the two conditions. 5-HT, found in the extensive protrusions of the raphe nuclei located in the CNS and the EC cells of the ENS, is this shared etiological ingredient.

The relationship between constipation and depression was delineated in a study by Israelyan et al. (2019), in which they argued that there must be an etiological connection modulated through the production and activity of 5-HT, within both the CNS and the ENS (p. 507). Israelyan et al. claimed that an alternative form of tryptophan hydroxylase 2 (TPH2), the rate-limiting enzyme which normally functions in 5-HT biosynthesis, called TPH2-R441H, has been found in individuals expressing phenotypic symptoms of depression (p. 508).

In order to quantitatively and visually document this phenomenon, Israelyan et al. studied the analogous version of this mutation in a murine model called TPH2-R439H (p. 507). They conducted a two-part experiment: the first part involved observing mice with the TPH2-R439H gene alteration for changes in gut motility, tail suspension, gut 5-HT levels in the ENS, and phenotypic depressive behaviors compared to wild-type (WT) control mice, while the second part involved administering slow-release 5-hydroxytryptophan (5-HTP SR) into the gut of TPH2-R439H and WT mice to determine its effectiveness as a recovery mechanism for 5-HT depleted mice (p. 507).

While conducting the first part of the experiment, Israelyan et al. found a 60% to 80% decrease in 5-HT levels within the CNS of TPH2-R439H mice, as well as phenotypical behaviors indicative of depression, such as increased immobility time for tail suspension, particularly when compared to normal WT mice (p. 508). Israelyan et al. observed via related cellular and chemical processes that TPH2-R439H mice had "significantly fewer 5-HT-immunoreactive nerve cell bodies," when compared to WT mice belonging to the same litter (p. 510).

In terms of the colonic effects caused by depleted 5-HT reserves, Israelyan et al. observed in that total GI transit time (TGIT), small intestinal transit, and colorectal motility were "significantly slower in TPH2-R439H mice than in

WT littermates," with ~25% increase *(P < 0.01)* in TGIT and colorectal motility, and 33% lower *(P < 0.05)* colonic migrating motor complex velocity in TPH2-R439H mice compared to WT mice (pp. 512-514).

By inducing the depletion of 5-HT in TPH2-R439H mice, Israelyan et al. obtained results that were sufficient enough to equate a murine model to a human model without any dissention as to the function of 5-HT in GI motility. The depressive phenotypes seen in the mice struggling with TGIT also distinctly implicated both 5-HT deficiency and constipation symptoms as an etiological basis for comorbid depression.

Cole, Rothman, Cabral, Zhang, and Farraye (2006), similar to Israelyan et al. (2019), in "Migraine, Fibromyalgia, and Depression Among People with IBS: A Prevalence Study," found that in a cohort of 97,593 individuals, 128 per 1,000 people had insurance claims for both depression and irritable bowel syndrome (IBS) through their health insurance plan between January 1, 1996 and June 30, 2002 (p. 4). Cole et al. (2006) statistically determined through percentage ratios that three disorders frequently appeared alongside IBS: depression, fibromyalgia, and migraines (p. 4). By analyzing comparative prevalence ratios, Cole et al. (2006) found that individuals with depression who were also part of the IBS cohort had 40% higher odds of reporting depressive symptoms through insurance claims than those individuals in the non-IBS cohort (pp. 4-5). More human studies have utilized statistical evidence based on already present qualitative data and surveys as well to find a correlation between occurrences of constipation and depression. Patients suffering from chronic constipation tend to present with symptoms of depression or anxiety disorders at higher percentages than the general population.[16] Strong empirical and statistical evidence outside of the above sources also support the idea of a shared etiology implicating 5-HT in constipation and depression.

A restoration of colonic 5-HT, especially in a manipulatable murine model, should essentially show improvements in both constipation and depression according to the previously presented theory suggesting linked etiologies. To determine this, Israelyan et al. (2019), in the second part of their experiment, administered 1 g/kg/d of 5-HTP SR, a precursor in the biosynthesis of 5-HT, in the chow of both TPH2-R439H and WT mice over the course of four weeks (p. 516). Israelyan et al. found that this form of oral administration led to observable increases in the total number of neurons in myenteric and submucosal plexuses of adult TPH2-R439H mice (equivalent to untreated, normal WT adult mice), as well as recovery of gastric motility, TGIT, and normal intestinal epithelial growth (p. 516).

Conclusive evidence from the depletion and restoration of 5-HT reserves in the colon in the murine model of depression is suggestive of the undeniably shared etiology shared by both constipation and depression. Both conditions, in countless instances, occur concurrently, and further understanding in the role that 5-HT individually inhabits within each condition may give more insight in the shared etiology. This combined etiology can then be taken advantage of as a pathway towards novel medical treatments targeting both conditions simultaneously.

3. ENS-Derived 5-HT and the Gut-Brain Axis

Because almost 95% of the body's 5-HT is produced in the ENS located in the gut, but effects of these 5-HT level alternations are seen in the brain, there must be a shared correlation between 5-HT levels in the GI tract and the brain that is currently being explored via the mechanisms that constitute the gut-brain axis.

While studying a murine model of depression, Israelyan et al. (2019) implicated 5-HT as the common factor between mood disorders, such as depression, and GI motility disorders, such as constipation (p. 507). 5-HT, which works in both the CNS and the ENS, regulates activity in both domains. However, the other roles of 5-HT within the body are currently being explored, and as more information comes to the forefront of scientific literature, further understanding of 5-HT will makes its role clearer in the general physiology of the human body. The rate-limiting enzyme TPH2, a precursor to 5-HT biosynthesis, metabolizes tryptophan into serotonin through a series of metabolic processes involving multiple enzymatic breakdown stages. TPH2 is found in the neuronal regions *and* the enteric regions, further supporting the theory that it performs shared functions in both divisions of the nervous system. Neuronal 5-HT metabolized from the TPH2 found in the brain and raphe nuclei is essential to neuron development in the ENS, GI motility, and mucosal development in the intestine (p. 508).[7] So, depletion of 5-HT in the CNS resulting from subjective experiences of depressive symptoms will inadvertently affect the gut motility and ENS 5-HT activity.

Jacobsen, Medvedev, and Caron (2012), like Israelyan et al. (2019), claimed that TPH2 is a common factor between CNS-derived 5-HT and ENS-derived 5-HT due to the fact that both forms of 5-HT must process tryptophan through this same rate-limiting enzyme (p. 2453). Jacobsen et al. (2012), while studying the *5-HT deficiency theory of depression* (discussed extensively in the forthcoming section) in a murine model involving the "Tryptophan Hydroxylase2$^{Arg}439^{His}$ Knockin Mouse," very briefly correlated the etiologies of depression and gut 5-HT (p. 2446). In the remaining majority of the study, Jacobsen et al. explored how 5-HT correlates to depression in light of modern research arguing *against* the involvement of 5-HT in depression. The "Tryptophan Hydroxylase2$^{Arg}439^{His}$ Knockin

Mice," which had been genetically altered to have decreased 5-HT biosynthesis, presented with depression-type behaviors such as increased tail immobility, aggression, amplified stress response, and decreased sucrose desire, implicating ENS-metabolized 5-HT in behavioral changes modulated through the nervous system (p. 2454).

To further understand the connection between CNS-derived 5-HT and ENS-derived 5-HT, Martin, Osadchiy, Kalani, and Mayer (2018) conducted a meta-analysis examining the theorized connection between the brain, gut, and gut microbiome, particularly because this connection has recently been implicated in both GI and mood disorders. Martin et al. (2018) also outlined a possible pathway detailing the cyclic nature and synergism of the posited gut-brain axis (p. 140). Martin et al. found through their meta-analysis that interactions to and from the brain-gut-microbiome axis exist between both regions, suggesting that a dysfunction in the individual interactions at any stage could affect the axis circuitry as a whole (p. 133). Martin et al. also theorized that gut microbes communicate to the CNS via at least three interacting channels parallel to each other: the nervous, endocrine, and immune signaling mechanisms (p. 133).

The individual connections between the gut, brain, and gut microbiota are currently being researched to further clinical understanding and develop a combined model. Martin et al. proposed this type of novel circuitry model and first implicated the gut microbiota community as the primary effector species to ANS activity modulated by the brain and the CNS (p. 133). This gut microbiota, Martin et al. suggested, modulates regional gut motility, intestinal transit, gut permeability, and luminal secretion of hormones that directly modulate gene expression in gut microbiota (p. 133). Upon these basic premises, Martin et al. built their model, showing interconnected communication loops (p. 140).

Understanding of gut microbiome is a fairly neoteric subject within the field of gastroenterology, and future research shows promise of unique therapy forms utilizing the indwelling bacteria of a host. Initial studies conducted by Yano et al. (2015) stated that the mechanisms regulating the 5-HT biosynthesis in the gut are unclear, but microbiota unequivocally play a role in regulating critical levels of host 5-HT (p. 264), similar to what had been suggested by Martin et al. (2018).[18] Yano et al. claimed that indigenous spore-forming bacteria from the mouse and human microbiota assist in 5-HT biosynthesis, specifically in the metabolism of 5-HT precursors originating from colonic EC cells (p. 264). Yano et al. also stated that this microbiota-aided 5-HT is supplied to the lumen, mucosal layers, and circulating platelets (p. 264). Yano et al. utilized a murine model to study how alteration in gut microbiota could alter 5-HT levels in the host's lumen and fecal matter (p. 265). The murine model that Yano et al. utilized consisted of germ-free (GF) mice, which were genetically depleted of all gut microbiota, and spore-forming (SPF) mice, which had normal levels of gut microbiota.

Yano et al., using stained colon images and quantitative 5-HT measurements in colonic epithelial tissue, observed that GF mice presented with significantly decreased levels of colonic and fecal 5-HT and increased buildup of unmetabolized tryptophan (Trp) compared to mice with spore-forming bacteria (p. 265). Similar to how Israelyan et al. (2019) administered 5-HTP SR in TPH2-R439H mice, Yano et al. (2015) found that oral supplementation of TPH-product 5-HTP mitigates the negative effects caused by lack of gut SPF microbiota (p. 265). To further implicate the spore-forming bacteria in 5-HT biosynthesis, Yano et al. recolonized postnatal GF mice with gut microbiota and found that 5-HT levels rebounded, particularly at the EC cells (p. 266). This data explicitly corroborates the function of GI microbiota in host 5-HT modulation and also supports the theory proposed by Martin et al. (2018) that gut microbiota contribute to the peripheral availability of Trp for synthesis of 5-HT in the CNS (p. 136).[18]

Among the general population, the use of probiotic yogurts as a method of constipation or bowel obstruction relief has also become increasingly prominent, enforcing the role of gut microbiota in GI health. Yano et al. also observed similar results in their murine model when they colonized adult (P42) GF mice with spore-forming bacteria (p. 268). Post-P56 stage growth in the mice, Yano et al. compared GI transit times pre- and post-treatment and found that colonization of GF with gut spore-forming bacteria relieved the host of GF-associated GI difficulties, decreased total transit time, and increased the rate of fecal output under controlled conditions (p. 269). This confirms both the role of 5-HT-associated spore-forming gut microbiota in constipation and the connection between the gut and gut microbiota proposed by Martin et al. in their circuit-based brain-gut-microbiome axis (2018).

The remaining factor in the Martin et al. (2018) axis is the brain and how it communicates with the gut and gut microbiota to send and receive necessary feedback. Currently, no firm theory has been established or accepted within the scientific community as to the complex nature of the brain-gut communication. However, current understanding of the ANS provides *some* insight into the physiology of brain-gut axis. A division of the ANS, the parasympathetic nervous system, relaxes the body, inhibits the release of stress hormones, promotes salivation and hunger, stimulates intestinal peristalsis, and relaxes the muscles, including the rectum. The ANS communicates with the GI system via the vagus nerve, accounting for the top-down processing that constitutes one aspect of this communication pathway. However, the mechanism of bottom-up processing has only been hypothesized.

One theory, outlined by Martin et al. (2018), suggests that bottom-up modulation of the CNS occurs through neuroendocrine and neuroimmune mechanisms via the same vagus nerve that was implicated in top-down processing (p. 135). Martin et al. argued that microbially derived molecules, including short-chain fatty acids (SCFAs), secondary

bile acids (2BAs), and tryptophan metabolites, could be the missing link in understanding this brain-gut communication. Similarly, Yano et al. (2015) had also observed that host spore-forming bacteria produced metabolites that were crucial to the modulation of 5-HT biosynthesis in the murine colon (pp. 268-270). Martin et al. claimed that these metabolites could send secondary signals by crossing the intestinal barrier, entering systemic circulation, and transecting the blood-brain barrier (p. 135). It is poorly understood, however, if these molecules reach brain sites directly or only induce central responses using long-distance neural signaling by vagal or spinal afferents (p. 135).[11]

ENS-derived 5-HT has been critically analyzed in comprehensive studies over the course of the previous decade, and the anatomy and physiology have begun to be slowly understood. Martin et al. stated that preclinical observations are currently focusing on alterations in the brain-gut-microbiome communication in order to understand the pathogenesis and general pathophysiology of conditions such as irritable bowel syndrome, psychiatric diseases, and neurologic disorders (p. 133). Gut 5-HT has been strongly implicated in constipation, and while the communication between the gut and brain is still vaguely understood, a gut-brain axis model could explain why depression, a disorder manifesting initially through the brain, affects gut motility and vice-versa.

4. The Basis and Evidence for the 5-HT Deficiency Theory of Depression

Because studies conducted in the past decades have implicated serotonin deficiency as a neuropathological cause of depression and prescribed SSRIs have shown improvement (albeit delayed) in depressive symptoms, clinical practitioners have accepted the prevailing 5-HT deficiency theory of depression.

Depression, by itself, can arise in response to a myriad of personal and external conditions. The cause of depression is often the target of psychotherapy, which differing viewpoints of psychology approach using distinct methods. In a meta-analysis, Yohn, Gergues, and Samuels (2017) claimed that major depressive disorder (MDD) is a "polygenic and highly complex psychiatric disorder" that has multiple etiologies, comorbidities, and symptomologies (p. 1).

Yohn et al. (2017) further stated that SSRIs have been prescribed primarily since the 1980s for MDD (p. 1). SSRIs prevent the reuptake of 5-HT into the axons of raphe nuclei neurons in the brain stem, thereby simulating the effects that would result from increased levels of 5-HT. Yohn et al. added that chronic SSRI treatment over the course of multiple years leads to higher levels of 5-HT present in the patient's synaptic gap, which can activate potential signals down the neural pathway and lead to decreased symptoms of depression (p. 1). Due to their generally positive effects in depression patients and biochemical abilities, SSRIs have continued being prescribed for almost half a century post-development, thus giving birth to a still-developing *5-HT deficiency theory of depression* (p. 1).[19]

Among the general population, and even clinicians, 5-HT has become a major assumed cause of depression. Jacobsen et al. (2012) claimed that the *5-HT deficiency theory* has become too widely accepted as the sole cause of depression, and they suggested the truth of the pathogenesis is rather heterogeneous and multi-faceted. Jacobsen et al. (2012) critically analyzed the viability of the 5-HT depression model against the new understanding of 5-HT's role in depression, and then compared their findings to their "Tph2 His^{439} Knockin Mice" (p. 2450).

Based on a discovery made previously in their own laboratory, Jacobsen et al. found that the gene alteration of Arg^{441} to His^{441} TPH2 was present in a cohort of geriatric Eastern US depression patients (p. 2448). Jacobsen et al. bred mice with the analogous substitution containing an alteration on amino acid 439, and these TPH2-KI mice showed a 60% to 80% decrease in 5-HT levels and biosynthesis (p. 2451). The TPH2-KI mice also presented with increased immobility in the tail-suspension test, increased aggression, exaggerated responses to acute stressors, and decreased lever-pressing for sucrose, all of which correlate with depressive behaviors in humans with depression, such as despair, aggression, vulnerability to stress, and anhedonia (p. 2454).

Jacobsen et al. concluded that while 5-HT imbalance or dysfunction may not *exclusively* be the cause of major depression, the evidence collected from TPH2-KI-resultant 5-HT deficient mice certainly points towards the implication of 5-HT deficiency in humans with depression (p. 2453), similar to the conclusion reached by Yohn et al. (2017). Jacobsen et al. (2012) digressed, however, that the *5-HT deficiency theory* still requires further analysis (p. 2453). Both Jacobson et al. (2012) and Yohn et al. (2017) suggested that 5-HT must have a role in depression, but due to the multifactorial nature of its etiology, determining its pathogenesis is difficult.

Israelyan et al. (2019) also noted similar results to what had set forth by Jacobsen et al. (2012). Israelyan et al. (2019) concluded that mice with altered TPH2 presented with severely decreased levels of 5-HT and similar depressive behaviors, such as greater immobility time in the tail-suspension test and decreased latency to feed (p. 508).

Much like the opinions of Jacobsen et al. (2012) and Yohn et al. (2017), Cowen and Browning (2015), in their article refuting the exclusive, relatively undocumented role of serotonin in depression, argued that the *5-HT deficiency theory of depression* is not definitively validated, but has rather become an oversimplified public explanation for depression

over time, largely due to the fact that SSRIs are clinically commonplace antidepressants and have shown positive results in patients (p. 158). Cowen and Browning asserted that outdated models of 5-HT deficiency and its role in depression need to be re-evaluated in light of new and continuing research about the neuropsychology of depression (p. 160). Cowen & Browning (2015) acknowledged, however, that 5-HT *does* aid the brain in responding to external situations, suggesting that it may be implicit in the expression of depression, but likely through a secondary pathway (p. 159). Cowen & Browning concluded that 5-HT is fairly undocumented in terms of CNS chemistry and should not be discounted in depression etiology, but should be considered one of *many* possible factors (p. 160).

Contrary to the research conducted by Yohn et al. (2017), Jacobsen et al. (2012), and Israelyan et al.(2019), Angoa-Pérez et al. (2014) claimed that mice lacking the gene for TPH2 ($TPH2^{-/-}$) did not present with behavioral symptoms of depression (p. 908). Angoa-Perez et al. further claimed that the role of 5-HT is doubtful, considering that it takes anywhere from weeks to months for SSRI effects to manifest (p. 908). Using genetically altered $TPH2^{-/-}$ mice, Angoa-Perez et al. tested the mice in a forced swim test, tail suspension test, and a sucrose preference test (p. 910). Angoa-Perez determined that $TPH2^{-/-}$ mice presented with statistically similar results in these tests compared to the unaltered, wild-type mice, with ~80-85% sucrose preference *($P = 0.005$)* in both groups, and concluded that 5-HT deficiency is not a neurological basis for depression (pp. 910-915). However, Angoa-Perez et al. conceded that *mild* 5-HT fluctuations may play a comparatively greater role in depression (p. 915). While Jacobsen et al. (2012) and Israelyan et al. (2019) both genetically altered mice to have a TPH2-R439H gene, leading to 5-HT biosynthesis deficiency, Angoa-Perez et al. (2014) *completely* removed the TPH2 factor from mice (genotype $TPH2^{-/-}$) (p. 909). Total removal of TPH2 provided different results than mere alternation of TPH2, suggesting that there is a possible homeostasis achieved if TPH2 was never present in the host's system. Most individuals exhibiting depressive phenotypes, however, have deficient levels of 5-HT, which correlates with a TPH2-R439H mouse to a much greater extent.

While the *5-HT deficiency theory of depression* may be incomprehensive in terms of describing the effects of 5-HT in a depressed individual as a whole, 5-HT is certainly one factor that can be targeted to treat depression. SSRIs, while effective, are delayed in taking effect, which can discourage individuals who don't perceive immediate results (p. 179).[14] By supplementing clinically prescribed methods, with newer, unique forms of therapy, depressed individuals may benefit emotionally and psychologically, especially if they perceive more subjectively relaxing stimuli.

5. ASMR: Its Triggers and Its Utilization as a Form of Therapy

Because many individuals online have reported feeling a relaxing tingle from their scalp down through their spine after watching ASMR content on online platforms such as YouTube, ASMR is arbitrarily already being used by many individuals struggling with depression, insomnia, and other mental disorders as a therapeutic mechanism.

Jamie L. Keiles (2019), a New York Times reporter, conducted wide-ranging research on the origins of the online ASMR phenomenon, the rise in popularity of ASMR across the younger demographic, the components that constitute an ASMR video, and the current scientific understand that has been attained. A discussion group on Facebook dating back to 2010 had first initiated dialogue about an odd tingling experience that some individuals had been experiencing, especially when they saw specific things or heard specific sounds.[9] Jennifer Allen, the creator of this group, coined this odd sensation as "ASMR".[9] Keiles (2019) stated that individuals in the group described ASMR as a tingling feeling spreading across the scalp, similar to "goosebumps," and sometimes extending down the back of the neck. Unlike "goosebumps," the temporary chills felt by these ASMR-responsive individuals were intentionally stimulated by sounds or visuals, referred to as "triggers".[9] These triggers included specific characteristics such as whispering, direct interaction with the viewer, and satisfying object manipulation.[9] ASMR viewers reported feeling relaxed, calmed, or even relieved while experiencing ASMR.[9] However, the sensation was not universal, and the ASMR that Allen and her fellow subscribers felt was unique to a subset of individuals who were ASMR-responsive.[9]

In "Autonomous Sensory Meridian Response (ASMR): A Flow-Like Mental State," Barratt and Davis (2015) stated that ASMR is a previously unstudied sensory experience that involves individuals feeling tingling sensations across the scalp, the back of the neck, and sometimes in extended areas while viewing or experiencing a "trigger" (p. 1). This description of the concept of ASMR is similar to what Keiles (2019) observed. Barratt and Davis (2015) found that platforms like Reddit and YouTube had turned this unusual "ASMR" experience into a cultural phenomenon (p. 1).

Barratt and Davis stated that individuals who were responsive to ASMR and viewed it on a regular basis reported feeling increased relaxation and decreased sensation of chronic pain (p. 1), which Keiles (2019) reported was also commonly seen in the comments posted under Allen's Facebook group. In an attempt to link this unknown sensation of ASMR with an already known phenomenon, Barratt and Davis claimed that ASMR-associated tingling and relaxation may follow a similar neural pathway to synesthesia (p. 1). Barratt and Davis also found that distinct triggers

were used in each ASMR YouTube video, and the effectiveness depended on the *particular* trigger (p. 2). Popular ASMR YouTube videos involved role-play situations in virtual proximity between the ASMRtist and the viewer, point of view recordings with attention directly to the viewer, focus towards a distinct object, and discrete, pronounced sounds that were emphasized by tapping or rubbing (p. 2).[2] Triggers such as whispering, personal attention, crisp sounds, and slow movements were shown to elicit ASMR in >50% of individuals, with whispering being the highest at 83% (p. 6).[2] Keiles (2019) similarly noted that general triggers such as whispering, tapping, and role-playing interaction appeared the most frequently in YouTube ASMR videos, but found that they could also be extremely varied and change according to internet viewership and popularity trends.

ASMR content has become widespread as a method of achieving temporary relaxation, peacefulness, or state of personal meditation while engaging the senses in a single sensation present in the video. Using Likert style questions on their questionnaire, Barratt and Davis discovered that ~98% of individuals used ASMR for relaxation, 82% for sleep, and 70% for stress relief (p. 5). Barratt and Davis also found that 5% of individuals reported using ASMR media for sexual stimulation, but the vast majority of survey participants, ~84%, disagreed with this notion (p. 5). Similarly, Mervosh (2019) stated that ASMRtists and viewers reported they do not watch ASMR in a sexual connotation. Mervosh interviewed a popular ASMRtist, Sharon Dubois, as well as Craig Richard, a professor at Shenandoah University in Virginia and creator of a research-based website titled "ASMR University." Both of the interviewees stated that ASMR is not in and of itself a sexual response unless perceived so by the viewer.[12] ASMR has also been reported by viewers to reduce heart rate, which is the opposite of what would happen during sexual stimulation.[12]

ASMR is not solely a sensory experience, but rather a distinct combination of emotional, neurological, and sensory experiences. To understand the effect of ASMR on mood levels, Barratt and Davis (2015) found that ASMR had a positive effect on 80% of the 475 participants *($P < 0.0005$)*, but effect waned off after three hours post-viewing (p. 7). Barratt and Davis noticed that participants who had been classified as depressed based on the BDI experienced a more rapid decline in mood on a scale ranging from 0 to 100 compared to non-depressed participants, but had the greatest increase in mood during the ASMR video (mean increase $^{\text{depressed}} = 38.75$ compared to mean increase $^{\text{non-depressed}} = 21.33$) (p. 8). This markedly greater improvement while experiencing ASMR in responsive individuals suffering from depression or chronic pain suggests that ASMR could be used to uplift mood, mindfulness, and temporary relief.

A reason as to why ASMR might produce such comforting experiences in ASMR-sensitive individuals might lie in oxytocin. Oxytocin is secreted by the posterior lobe of the pituitary gland during breastfeeding, and this hormone helps form an emotional connection between the mother and child (p. 11).[17] The child becomes accustomed to the mother and is comforted by her touch, especially while breastfeeding. ASMR may be an evolutionary remainder from this instinctual habit that all children develop. By simulating direct, one-on-one touch with the viewer, ASMRtists, the majority of whom *are* women, may, in theory, be increasing the oxytocin levels in the viewer.

While the general population of ASMR viewers may find watching ASMR to be simply a leisure activity, those individuals struggling with mental or emotional conditions (e.g. depression, insomnia, and generalized anxiety disorders) may turn to ASMR as a form of therapy to curb their negative symptoms. In a sense, ASMR could give these suffering individuals a mental "high," which could, in turn, stimulate positive emotional activity within the limbic system. The mechanisms within the limbic system, particularly the hippocampus, amygdala, and hypothalamus, would then influence the ANS and endocrine system. The parasympathetic nervous system would then be activated, causing relaxation of the bowels and ENS-derived 5-HT production via the communication between the brain-gut-microbiome axis. Concurrently, the endocrine system and ANS would stimulate activity within the 5-HT specific raphe nuclei, and the "happiness neurotransmitters," including 5-HT, would be released into the synaptic gap. This form of a positive feedback loop would simultaneously improve the conditions of constipation and comorbid depression, especially if the individual is already undergoing some form of clinician-prescribed treatment.

6. Past Blueprints for Finding Optimal Therapeutic ASMR and Observing Alterations

Because individuals report specific ASMR triggers as being the most common, strongest causes of tingling, a prospective study of ASMR's effects on the constipation-depression comorbidity would involve determining the qualities necessary for therapeutic ASMR videos to elicit the most effective response in ASMR-sensitive individuals.

The first step in creating an experimental design would involve determining the type, quality, and specific factors of ASMR that should be involved in the videos that will be utilized in the depressed constipation patients during the next segment of the experiment. Multiple trial videos would have to be created, some with known ASMR triggers, and others with triggers that are unlikely to elicit a strong response from a large proportion of the participants.

Barratt and Davis (2015) utilized a similar setup to determine which factors are commonly present across ASMR videos, and 75% of participants felt triggered by direct whispering (p. 6). Although less common, smiling might elicit a decent response rate because smiling ASMRtists commonly accompany strong triggers such as role-playing.[2]

Individuals for a potential experimental design would be recruited via online forums or university announcements, and general health conditions, medication usage, lifestyle, age, gender, country of origin, etc. would need to be recorded via an entrance questionnaire to understand the general demographic of study participants.

A collection of at least 15 to 20 ASMR videos, each containing different, testable factors, should be made by the researchers in conjunction with a willing, popular ASMRtist(s). Barratt, Spence, and Davis (2017) conducted a follow-up study to understand if changes to certain factors already present in ASMR altered the rate of response to those triggers (p. 1). Barratt et al. (2017) obtained a total of 130 participants and observed timing, trigger load, atmosphere, distance from object, visual aspects of triggers, and audio (pp. 5-9). 38% of participants responded that 1-5 min. videos were optimal for ASMR, 30% stated that 6-10 min. videos were better, and 47% preferred two triggers in ASMR videos for experiencing the most tingles *(N = 127)* (p. 5).[3] Individuals preferred a warm, inviting atmosphere to watch ASMR videos, and in terms of camera distance from object, they preferred smaller trigger objects to be 60 cm or closer, while larger objects were preferred at a distance of 60 cm to 1 m from the camera *(N = 125)* (pp. 5-7). 51.2% of participants *(N = 127)* rated the visual aspects of the trigger as "extremely important," and 77% of participants *(N = 126)* stated the pitch of the video sounds affected how strongly they felt tingles (56% reported stronger tingles from lower-pitched sounds) (pp. 7-8). Each of these factors can be tested in the individual videos, along with "placebo" videos contained pre-determined non-triggers, viewed by study participants. This process could determine which video qualities are ideal to use on constipation-depression patients.

Other physiological changes in an individual while experiencing ASMR must also be taken into account when determining an optimal form of use as a therapeutic supplement. In order to scientifically investigate some of ASMR's physiological bases, Lochte, Guillory, Richard, and Kelley (2018), in "An fMRI Investigation of the Neural Correlates Underlying the Autonomous Sensory Meridian Response (ASMR)," used fMRI technology to analyze changes in neural activity within specific brain regions of ASMR-responsive individuals while viewing ASMR and found definitive changes in neural blood flow activity during self-reported tingle-events (p. 295).

Lochte et al. (2018) chose to study regions/structures of the brain that had been theoretically determined to be actively involved in ASMR sensation, including the medial prefrontal cortex (mPFC), nucleus accumbens (NAcc), and supplementary motor areas (SMA) (p. 298). In order to determine these regions of interest and possible causes for ASMR sensation, Lochte et al. proposed ASMR as either having similar responses to musical frission, grooming sensations in primates, or activity in mirror neurons (p. 298). These sensations have specific, documented brain regions that can be compared to ASMR fMRI scans to possibly determine a cause for ASMR sensitivity in humans (p. 298).[10]

Lochte et al. found from their study of 11 individuals that subjects reported pleasurable relaxation 51.36% of the time and tingling feelings down their neck or across their head 5.90% of the time (p. 299). Lochte et al. stated that significant clusters of activity were noted during tingling in the mPFC, insula, and NAcc (p. 299). Lochte et al. also observed increased activity in the left somatosensory cortex when participants viewed videos based on a touching interaction between the actor and the viewer (p. 300). These regions that showed high clusters of activity are highly correlated with emotional arousal and empathy, which might correlate to the aforementioned ASMR-oxytocin theory.

The external conditions or atmosphere within which study participants view ASMR should likely be warm, inviting, calming, and private, and audio should come through binaural headphones (p. 6).[3] However, Lochte et al. (2018) reported that their subjects viewed the ASMR videos while being imaged inside loud fMRI scanners, and the ASMR tingling was still notably perceptible (p. 300). Loud conditions would not be ideal, however, and are discouraged.

Other physiological factors, such as heart rate, blood pressure, respiratory rate, EEG activity, may also indicate the presence of the ASMR sensation, and potential researchers may opt to study these factors in conjunction with neural activity to determine the most suitable ASMR for therapeutic use (pp. 302-303).[10] Along those lines, Poerio, Blakey, Hostler, and Veltri (2018) conducted a study with 56 ASMR-responsive and 56 control individuals to measure physiological response during tingling episodes. ASMR-associated tingling correlated strongly with reduced heart rate and increased skin conductance compared to non-ASMR participants (heart rate average reduction = 3.41 bpm; skin conductance average increase = 0.30 μS) (p. 13).[15]

By creating a comprehensive plan incorporating ASMR trigger studies, neural activity data, physiologic response, and subjective participant input, potential researchers will be able to determine the ideal form of ASMR to use for individuals pre-screened for constipation-associated depression. If optimal factors for eliciting the strongest ASMR are present in each of the videos viewed by individuals suffering from the constipation-depression comorbidity, then both objective and subjective effects in patients will be increasingly positive.

To study the effect of this optimized form of ASMR on constipation, a variety of pre-determined or novel factors could be examined to document the effects (if any) that the ASMR might have on gut motility. Israelyan et al. (2019),

using a murine model of study, stated that enteric 5-HTergic neurons had sizeable projections within the bowel, which thus allowed them to use computer-assisted imaging techniques to determine the proportional presence of 5-HT-immunoreactive neurites to total neurites within the myenteric plexus of the ENS (p. 510). Israelyan et al. also discovered that the average intensity of fluorescent 5-HT neurites was "significantly less in TPH2-R439H mice than in WT mice," suggesting that a polymorphism is indeed a key factor in the receding levels of 5-HT within the ENS (p. 510). Along with 5-HTergic neural projections in the bowel, total GI transit time, colonic propulsion, gastric emptying time, and epithelial straining could be observed, similar to the murine responses observed by Israelyan et al.

Anatomical changes may also be seen in individuals suffering from a constipation-depression comorbidity. Israelyan et al. found that an increase in ENS 5-HT using slow-release 5-HTP in TPH2-R439H mice correlated with fewer-depressive like symptoms, as well as restoration of GI structure (villi height and crypt depth) and 5-HT biosynthesis from typtophan (p. 507). Since the 5-HTP SR also restored levels of 5-HT in the CNS and reduced depressive-like behaviors in the altered mice, it can be deduced that ENS 5-HT is necessary for normal epithelial growth. Israelyan et al. also observed that the relative densities of the EC cells were significantly lower in depression phenotype mice compared to WT mice, but post-5-HTP SR administration, the relative density of the EC cells increased significantly in TPH2-R439H mice (p. 516). Studying the anatomical changes as described here pre- and post-study may prove beneficial to understanding if ASMR leads to similar effects. If such effects *are* seen, the implication of 5-HT in ASMR may also be deduced.

While 5-HT is present naturally in the body, the external factors that increase 5-HT have not yet been determined. Young (2007) conducted a meta-analysis of previously available studies and proposed four possible solutions as to how 5-HT can be increased in the brain: mood improvement, exposure to bright light, increased exercise, and improved diet (pp. 394-396). Young recognized an association between 5-HT and mood, stating that lower platelet 5-HT_2 receptor function was associated with lower mood in a study conducted by Pierson and Heuchert (2000), and conversely, better mood was associated with higher blood 5-HT levels in a study by Williams et al. (2006) (p. 395).

Young also determined, similar to the conclusions made by Israelyan et al. (2019), that an increase in dietary Tph would likely increase the levels of 5-HT available in the body and to the brain, although the source from which this 5-HT would originate in the body is disputable. Young et al. surmised that non-pharmacological methods of 5-HT promotion are indeed possible and should be pursued in the interest of both clinical and research applications (p. 397). ASMR might be one of those effective non-pharmacological methods of 5-HT promotion to supplement current treatments. Pursuing such a study could prove to be extremely beneficial in the medical and psychological communities, especially if the study provides positive results. Future pathways and branches to other research studies could also operationalize ASMR for medical use.

7. Conclusion

The shared 5-HT etiology between constipation and depression, the implication of 5-HT in each condition independently, the communication between the gut and brain via a theoretical gut-brain axis, and the presence of 5-HT in both the ENS and CNS all suggest that a 5-HT-targeted therapy is the approach to treating the constipation-depression comorbidity. The subjective reports of ASMR improving depression and the parasympathetic changes that accompany ASMR could pave the way to a novel, specifically-optimized ASMR therapy will likely be effective in aiding individuals suffering from constipation and depression. A successful experiment would also support the hypothesis that external factors effect 5-HT production within the body and provide further knowledge about ASMR.

Conducting this experiment will prove to be extraordinarily beneficial to the medical community, and by understanding the medical applications of frequently overlooked subjective remedies, therapists and researchers may be able access a wide array of unconventional techniques as supplements to contemporary clinical treatments. Ancient methods of psychological therapy, while antiquated or obsolete, employed knowledge from multiple fields of study, not solely a scientific perspective. By understanding and perhaps harnessing the ability of ASMR as a therapeutic, clinicians will become more open-minded to the unique possibilities that are yet to be explored.

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9. References

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