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

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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 ineffective 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." I explored other possible theories about this connection, but none seem to be definitively conclusive of the answer. There were two parts to my study: 1) determining the most viable form of ASMR videos to use in the experimental cohort and 2) quantifying changes in bowel motility and enteric 5-HT after scheduled ASMR viewing sessions in responsive individuals, as well as obtaining verbal reports about whether or not they perceived the ASMR to help with their depression. This study is the first of its kind and further research of this methodology would improve our understanding of

depression-related physiology, as well as provide the basis for prospective, non-invasive treatments to suffering individuals.

Keywords: constipation, depression, comorbidity, autonomous sensory meridian response, selective serotonin reuptake inhibitors, serotonin, enteric nervous system, parasympathetic nervous system

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Introduction

Chronic constipation has been implicated as a symptom in both gastrointestinal and neurological comorbid conditions, including diverticulosis, hemorrhoids, cancer, cardiovascular diseases, hypertension, and hypercholesterolemia (Choung et al., 2016, pp. 145-146). 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 gastrointestinal motility dysfunctions (Hosseinzadeh et al., 2011, p. 161). An evident conjoining factor between constipation and depression is serotonin, or 5-hydroxytryptamine (5-HT), which is produced primarily in the enterochromaffin cells of the gastrointestinal tract. The enterochromaffin 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 (Israelyan et al., 2019) has shown to lead to depressive symptoms as well.

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 (Keiles, 2019). 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 (Barratt and Davis, 2015). Despite these limitations, ASMR videos have continued to dramatically rise in popularity since 2012, garnering millions upon millions of views on YouTube (Mooney and Klein, 2016). 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 (Barratt and Davis, 2015). ASMR has also shown reliable, positive changes in physiology, mental state, and neural activity in receptive individuals (Poerio et al., 2018).

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.

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 treatment methods, usually oral or rectal laxatives and anti-depressants, respectively, that solely target symptomatic conditions as opposed to holistic circumstances present in the patient. In contrast to such limited treatment options, 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 must be present linking the conditions, particularly if shared treatment options achieve similarly positive results. 5-HT, found in the extensive protrusions of the raphe nuclei located in the CNS and the enterochromaffin cells of the ENS, is this shared etiological ingredient that is present in both constipation and depression.

The shared connection between constipation and depression was delineated in "Effects of Serotonin and Slow-Release 5-Hydroxytryptophan on Gastrointestinal Motility in a Mouse Model of Depression," in which Israelyan et al. (2019) argued that there must be an etiological connection between comorbid constipation and depression 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). By employing calcium (Ca^{2+}) channel imaging and immunocytochemistry, Israelyan et al. performed quantitative and qualitative analysis of total gastrointestinal transit time, colonic propulsion, gastric emptying, small intestine transit, and in vitro colonic migrating motor complexes (p. 510).

Israelyan et al. 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 the immunocytochemistry and Ca^{2+} channel imaging methods (the latter of which is a parallel activity observed in conjunction with 5-HT activity) 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 gastrointestinal transit time (TGIT), small intestinal transit, and colorectal motility were "significantly slower in TPH2-R439H mice than in WT littermates," with an almost 25% increase *($P < 0.01$)* in TGIT and colorectal motility (pp. 512-514). Upon spatiotemporal mapping of the colonic migrating motor complexes (CMMCs), Israelyan et al. also found that the CCMC velocity in mm/s was approximately 33% lower *($P < 0.05$)* in TPH2-R439H mice than in WT mice (p. 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 gastrointestinal 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. Similar circumstances have been superficially observed by through cohort-based data in humans as well.

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 to find a correlation between occurrences of constipation and depression. Like Israelyan et al. (2019) and Cole et al. (2006), Tahbaz Hosseinzadeh, Poorsaadati, Radkani, and Forootan (2011), in "Psychological Disorders in Patients with Chronic Constipation," claimed that patients suffering from chronic constipation tend to present with symptoms of depression or anxiety disorders at higher percentages than the general population (p. 159). To test this, Tahbaz Hosseinzadeh et al. (2011) recruited 54 constipated patients who had been referred to the Motility Disorder Department of Research Center for Gastroenterology and Liver Diseases, and who had also been screened for psychiatric disorders using the HADS (Hospital Anxiety and Depression Scale) and a MINI (Mini International Neuropsychiatric Interview) (p. 160). Tahbaz Hosseinzadeh et al. found that as many as 33% of constipated patients suffered from major depressive disorder (MDD) (p. 161). Strong empirical and statistical evidence supports the idea that a shared etiology implicating 5-HT is present between 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 number of total number of neurons in myenteric and submucosal plexuses of adult TPH2-R439H mice (p. 516). Israelyan et al. further noted that the numbers of total neurons reached levels equivalent to untreated, normal WT adult mice (p. 516). In addition, Israelyan et al. discovered that 5-HTP SR not only rescued gastric motility and TGIT, but also normalized

intestinal epithelial growth without bringing about any change in already normal WT mice (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.

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 gastrointestinal 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 gastrointestinal 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 understand 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 (Israelyan et al., 2019, p. 508). 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), in "The Brain-Gut-Microbiome Axis," 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 gastrointestinal 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, at minimum, via three interacting channels parallel to each other: the nervous, endocrine, and immune signaling mechanisms (p. 133).

While the individual connections between the gut, brain, and gut microbiota have been or are currently being researched to further the clinical understanding within the scientific community, a combined model has yet to be developed combining the individual aspects into a circuit. Martin et al. proposed this type of novel model of the circuitry 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), in “Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis,” 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). 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 enterochromaffin 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) when 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 cause by lack of gut spore-forming microbiota (p. 265). To further implicate the SPF 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 enterochromaffin cells (p. 266). This data presented by Yano et al. explicitly corroborates the function of gastrointestinal microbiota in host 5-HT modulation, and it 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).

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 gastrointestinal 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). After the mice had grown to the P56 stage, Yano et al. compared gastrointestinal transit times pre- and

post-treatment (p. 268). They found that colonization of GF with gut spore-forming bacteria relieved the host of GF-associated gastrointestinal difficulties, decreased total transit time by almost 100 minutes *(P < 0.01)*, and increased the rate of fecal output by approximately 0.01 pellets/min. *(P < 0.01)* 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 gastrointestinal 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). Martin et al., however, conceded that it is poorly understood if these molecules reach brain sites directly or only induce central responses using long-distance neural signaling by vagal or spinal afferents (p. 135).

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.

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 personal conditions, environmental factors, diseases, or situational conflicts. The cause of depression is often the target of psychotherapy, which differing viewpoints of psychology approach using distinct methods. In a meta-analysis entitled “The Role of 5-HT Receptors in Depression,” Yohn, Gergues, and Samuels (2017)

claimed that major depressive disorder (MDD) is a "polygenic and highly complex psychiatric disorder" that has multiple etiologies, various comorbidities, and overlapping symptomologies that make it exceptionally difficult for modern neurobiology and psychiatry to discern the basis and pathology of its onset (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, Yohn et al. determined through analysis of a report by Akiskal et al. (1973) that SSRIs have continued being prescribed for almost half a century post-development (p. 1). Yohn et al. elaborated that SSRIs gained more legitimacy after clinical observations in the 1950s showed that resperine (which decreases central stores of monoamines such as 5-HT) caused depression in a single cohort of patients (p. 1). Yohn et al. further reported, based on meta-analysis of studies conducted by Leyton et al. (1997) and Delgado (2006), that when tryptophan, a precursor to 5-HT, was depleted within MDD patients, mild depression recurred *if* remission was possible by SSRIs (p. 1). On the basis of relatively inconclusive evidence and mere clinical observations, the *5-HT deficiency theory of depression* was brought forth.

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 of depression* 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), to critically analyze the 5-*HT deficiency theory of depression*, conducted a study using a naturalistic 5-HT deficiency model involving the "Tryptophan Hydroxylase2$^{Arg}439^{His}$ Knockin Mouse" to determine the viability of the 5-HT depression model against the new understanding of 5-HT's role in depression. Jacobsen et al. initially conducted a meta-analysis of multiple studies from previous decades that supported the *5-HT deficiency theory of depression* to determine the reason for the prevalence of this theory and assess its integrity in light of modern and upcoming research (p. 2444). Jacobsen et al. afterwards implemented their own study in a murine model of 5-HT deficiency using "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), similarly to the conclusion reached by Yohn et al. (2017) in their meta-analysis. Jacobsen et al. (2012) digressed, however, that the *5-HT deficiency theory of depression* requires further

analysis and updated alterations to account for the extent to which 5-HT is implicated in depressive symptoms (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 the etiology of depression, determining its pathogenesis is difficult, especially due to the variety of comorbidities present alongside depression.

Israelyan et al. (2019), in their study observing the TPH2-R439H mice and the effect of slow-release 5HTP on gastrointestinal motility and depression, 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 exhibited more depressive behaviors than WT mice, including behaviors that had been observed by Jacobsen et al. (2012), such as increasing immobility time in the tail-suspension test and decreased latency to feed (p. 508). Jacobsen et al. (2012) were directly involved in the study conducted by Israelyan et al. (2019), thereby obtaining validity for the ideas set forth in their [Jacobsen et al.] 2012 study and allowing Israelyan et al. to expand upon the findings from their [Jacobsen et al.] preliminary data.

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), which Israelyan et al. (2019) did in their research by revisiting the role of 5-HT in depleted TPH2-R439H mice.

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 completely discounted in depression etiology, but rather, it should be considered one of *many* possible factors present in depression (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), in "Mice Genetically Depleted of Brain Serotonin do not Display a Depression-like Behavioral Phenotype," 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 (p. 910). Based solely on the data present in their study, Angoa-Perez et al. concluded that 5-HT deficiency is not a neurological basis for depression (p. 915). However, Angoa-Perez et al. conceded that *mild* 5-HT fluctuations may play a greater role in depression compared to the extreme of total gene alteration as seen in this study (p. 915).

While Jacobsen et al. (2012) and Israelyan et al. (2019) both genetically altered mice to have a TPH2-R439H gene, leading to deficiency in the biosynthesis of 5-HT, Angoa-Perez et al. (2014) *completely* removed the TPH2 factor from mice, causing their genotype to be $TPH2^{-/-}$ (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. A $TPH2^{-/-}$ mouse with no 5-HT is representative of a theoretically extreme (likely impossible) condition in depressed humans.

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 (Penn and Tracy, 2012, p. 179). By supplementing clinically prescribed methods, treatments, and drugs targeting depression with newer, unique forms of therapy, depressed individuals may benefit both emotionally and psychologically, especially if those individuals perceive more subjectively relaxing stimuli.

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. Keiles reported that 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. Jennifer Allen, the creator of this group, coined this odd sensation as "ASMR" (Keiles, 2019). 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" (Keiles, 2019). These triggers included specific characteristics such as whispering, direct interaction with the viewer, and satisfying object manipulation (Keiles, 2019). ASMR viewers reported feeling relaxed, calmed, or even relieved while experiencing ASMR (Keiles, 2019). However, the sensation was not universal. Keiles (2019), in her interview with Jennifer Allen, quickly learned that the ASMR that Allen and her fellow subscribers felt was unique to a subset of individuals who were "ASMR-responsive" or "ASMR-sensitive." A specific set of circumstances or factors present in an individual that might contribute to ASMR sensitivity, while not specifically determined, have been investigated.

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 in the comments that individuals gave in the online discussion groups. Barratt and Davis (2015) found that other communities, specifically on platforms such as Reddit and YouTube, had popularized discussion about this unusual experience and turned it into the cultural phenomenon of "ASMR" today (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 Jennifer 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, which is the production of a sense impression on one part of the body in response to stimulation in another part of the body (p. 1). Barratt and Davis also found that certain distinct triggers were present in each ASMR video on YouTube, and oftentimes, the effectiveness of the video depended on the trigger that was employed (p. 2).

Keiles (2019), in "How A.S.M.R. Became a Sensation," noticed that general triggers such as whispering, tapping, and role-playing interaction appeared the most frequently in YouTube ASMR videos, but the specific triggers employed in each video were extremely varied, and oftentimes, they changed according to trends. Keiles stated that these trends were often established by YouTubers who "tested out" novel ASMR triggers in their videos, and if something become popular among the viewers, other "ASMRtists," would reinforce that trigger in their own videos. Keiles contended that ASMR triggers are fleeting and often change in response to viewership, but the general factors present in each video tend to be similar.

To determine the factors that were more commonly present in ASMR videos, Barratt and Davis (2015) observed that popular videos by YouTube channels such as *MassageASMR*, *GentleWhispering*, and *WhisperTalkStudios*, 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). To quantitatively determine which triggers elicited the strongest responses in the largest percentage of participants, Barratt and Davis conducted an online questionnaire with 475 individuals who had volunteered based on an online advertisement (p. 3). The participants ranged from ages 18 to 54 (mean = 24.6 years, standard deviation = 7 years), hailed from all across the globe, particularly the United States and Western Europe, and universally reported having experienced ASMR and watching ASMR-dedicated videos or audio clips regularly (p. 3). Barratt and Davis found from survey responses gathered from all participants entering into the study that whispering, personal attention, crisp sounds such as tapping fingernails, and slow movements all elicited ASMR in more than 50% of individuals, with whispering being the highest at 83% (p. 6).

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 almost 98% of individuals sought out ASMR as an opportunity for relaxation, while 82% of individuals used ASMR to help them sleep, and 70% it to deal with stress (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, about 84%, disagreed with this notion (p. 5).

Similarly, Mervosh (2019), in "A.S.M.R. Videos Give People the Tingles (No, Not That Way)," 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 who has published a book on ASMR and created a research-based website titled "ASMR University." According to Mervosh, both of the interviewees stated that ASMR is not in and of itself a sexual response unless perceived so by the viewer. Mervosh argued that ASMR has been reported by viewers to reduce heart rate, which is the opposite of what would happen during sexual stimulation.

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 as time progressed over the course of three hours post-viewing, the effect waned off (p. 7). Barratt and Davis noticed that participants who had been classified as depressed based on the Beck Depression Inventory (BDI) experienced a more rapid decline in mood compared to non-depressed participants (p. 8). However, the depressed participants also had the greatest increase in mood (mean improvement = 38.75) during the ASMR video compared to those who were not depressed (mean improvement = 21.33) on a scale ranging from 0 to 100 (p. 8). This markedly greater improvement while experiencing ASMR in responsive individuals, particularly those suffering from conditions such as depression and chronic pain, suggests that ASMR could be used as a way to uplift mood, practice mindfulness, and induce 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 (World Health Organization [WHO], 2009, p. 11). 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 the negative symptoms associated with their particular disorders. 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.

A Potential Study: Determining the Qualities of an Optimal Therapeutic Form of ASMR and Measuring Patient Feedback in Relation to Constipation-Depression Symptoms

Because individuals report specific ASMR triggers as being the most common or strongest causes of tingling, a prospective study of ASMR's effects on the constipation-

depression comorbidity would involve determining which qualities should be included in the therapeutic ASMR video to elicit the strongest response in those who are ASMR-sensitive.

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.

A similar setup was utilized by Barratt and Davis (2015) to determine which factors are commonly present across ASMR videos. Barratt and Davis surveyed 475 participants, all of whom self-reported experiencing ASMR, regarding the triggers that evoked the strongest tingling response (p. 6). Among the participants, 75% reported feeling triggered by whispering, 69% by personal attention, 64% by crisps sounds, 53% by slow movements, and 36% by repetitive movements (p. 6). Barratt and Davis (2015) also incorporated uncommon triggers into the study as control factors to confirm that response to the most common triggers were consistent across ASMR viewers (p. 6). These uncommon triggers included vacuum cleaner noises, laughing, airplane noises, and smiling (p. 6). Barratt and Davis (2015) reported that less than 3% of individuals were triggered by the first three uncommon triggers, and only 13% of individuals were triggered by smiling (p. 6). Smiling might elicit a decent response rate because smiling ASMRtists commonly accompany strong triggers such as role-playing.

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, similar to

how Barratt and Davis (2015) utilized a preliminary 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), in "Sensory Determinants of the Autonomous Sensory Meridian Response (ASMR): Understanding the Triggers," 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 with 91 females, 33 males, 2 transgenders, and 4 non-binary individuals from across the globe (p. 4). The ages ranged from 25 to 65, with the average age being 35 years old (standard deviation = 9.2 years) (p. 4). All of the individuals had reported that they experienced ASMR (p. 7). Barratt et al. (2017) studied timing, trigger load, atmosphere, distance from object, visual aspects of triggers, and audio (pp. 5-9).

Barratt et al. (2017) reported 38% of participants responded that 1-5 min. videos were optimal for ASMR, while 30% stated that 6-10 min. videos were better *(N=127)* (p. 5). 47% of participants preferred two triggers in ASMR videos for experiencing the most tingles *(N = 127)* (p. 5). Barratt et al. (2017) also found that individuals preferred a warm, inviting atmosphere to watch ASMR videos (p. 5). In terms of camera distance from object, Barratt et al. (2017) reported that individuals 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)* (p. 7). Barratt et al. (2017) also stated that 51.2% of participants *(N = 127)* rated the visual aspects of the trigger as "extremely important" (p. 7). In terms of audio, Barratt et al. (2017) reported that 77% of participants *(N = 126)* stated the pitch of the sounds in the video affected how strongly they felt tingles, and 56% reported feeling stronger tingles from lower-pitched trigger sounds (p. 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 in a potential research study. 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). Lochte et al. initially recruited 25 individuals from online forums who responded to an advertisement for ASMR-sensitive individuals in the region nearby Dartmouth College (p. 296). Lochte et al. narrowed the cohort of individuals from whom they [Lochte et al.] collected usable data down to 11 individuals who gave sufficient, analyzable results (p. 296). For the purpose of operationalization, Lochte et al. defined ASMR sensitivity as "an ability to consistently report a relaxing and pleasurable tingling sensation multiple times" while watching ASMR videos (p. 296). Lochte et al. used videos that had the most common ASMR stimuli such as whispering,

role-playing, and tapping, but did not include atypical triggers such as black and white film (p. 296).

Lochte et al. (2018) allowed each of the subjects to review five videos and select five seven-minute clips from those videos that [the subjects] stated most strongly induced the ASMR sensation before the study, but afterwards instructed the subjects to refrain from watching any such videos for 48 hours (p. 296). Lochte et al. organized each individual's video clips in a preset sequence, and after each clip, [Lochte et al.] included a 30-second break to return the subjects to their basal brain activity (pp. 296-297).

Lochte et al. instructed the subjects to press one of three buttons at any given moment during the viewing of the ASMR videos: one for baseline brain activity, another for a state of relaxation or pleasant feelings, and the last one for actual moments of pleasurable tingling felt in the back of the neck or the head (p. 297). In order to determine regions of interest and possible causes for ASMR sensation, Lochte et al. proposed possible explanations for ASMR as either having similar responses to musical frission, grooming sensations in primates, or activity in mirror neurons (p. 298). Lochte et al. stated that each of these sensations has specific, documented brain regions that can be compared to ASMR fMRI scans to possibly determine a cause for ASMR sensitivity in humans (p. 298).

Lochte et al. concluded from data analysis that subjects reported pleasurable relaxation 51.36% of the time, baseline sensations 40.47% 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 particular

regions that showed high clusters of activity are highly correlated with emotional arousal and empathy, which might correlate to the ASMR-oxytocin theory proposed earlier. Oxytocin release from the pituitary gland may also show similar regions of fMRI activity, especially during breastfeeding, but due to potential harm to both mother and child, such a test should not be performed.

The external conditions or atmosphere within which individuals participating in the proposed study view ASMR should likely be warm, inviting, calming, and private, as suggested by Barratt et al. (2017). When Barratt and Davis (2015) asked participants in their study if they preferred some specific kind of environmental conditions for viewing ASMR, 52% responded 'yes,' and they almost universally stated that they favored quiet, relaxed conditions, oftentimes with binaural headphones (p. 6). However, Lochte et al. (2018) reported that their subjects viewed the ASMR videos while being imaged inside fMRI scanners, and notably, the ASMR tingling was still perceptible in the presence of the loud noises that could be heard from inside the fMRI apparatus (p. 300). Since the purpose of therapy is to relax the patient and improve his/her mental state, loud conditions would not be idea. But, during the stage when researchers are determining the optimal form of ASMR, using an fMRI scanner might improve the chances of selecting the most advantageous ASMR for use on constipation-depression patients.

Other physiological factors 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. Lochte et al. (2018) suggested that the effects of ASMR triggers on heart rate, blood pressure, respiratory rate, EEG activity, and other indicators of physical/mental changes could help ascertain its role in relaxing the body (pp. 302-303). Along those lines, Poerio, Blakey, Hostler, and Veltri (2018) conducted a study titled

"More than a Feeling: Autonomous Sensory Meridian Response (ASMR) is Characterized by Reliable Changes in Affect and Physiology." Poerio et al. (2018) tested 56 ASMR-responsive and 56 control individuals recruited via social media, university staff and student mailing list, and word-of-mouth (p. 9). Poerio et al. showed each individual three videos: a known, standard ASMR video, a non-ASMR video (control), and a self-selected ASMR video, all of which had been selected based on an analysis of ASMR effectiveness (p. 9). Peorio et al. measured physiological response during tingling episodes using a Comp5 Inifiniti encoder with Biograph Inifiniti software and found that 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).

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-THergic neural projections in the bowel, total GI transit time, colonic propulsion, gastric emptying time, and epithelial straining could also be observed during the proposed study, similar to how Israelyan et al. observed these factors in mice.

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 gastrointestinal structure (villi height and crypt depth) and 5-HT biosynthesis from typtophan) (p. 507). Israelyan et al. stated that 5-HTP SR also restored levels of 5-HT in the CNS and reduced depressive-like behaviors in the altered mice (p. 507). It can be deduced that ENS 5-HT is necessary for normal epithelial growth, and so villus height and crypt depth will be significantly altered in mice expressing a depression phenotype. Israelyan et al. also observed that the relative densities of the enterochromaffin cells were significantly lower in depression phenotype mice compared to WT mice, but after the administration of 5-HTP SR, the relative density of the enterochromaffin 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. In "How to Increase Serotonin in the Human Brain without Drugs," 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.

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 explanations about the effects that ASMR displays.

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 methods of treatment. 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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