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Body Focused Repetitive Behavior Disorders: Behavioral Models and Neurobiological Mechanisms

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ABSTRACT

Objective: Body Focused Repetitive Behaviors (BFRB) is an umbrella term for undesirable, repetitive motor activities such as Trichotillomania (TTM), Skin Picking Disorder (SPD), nail biting, cheek chewing, lip biting, finger sucking, finger cracking and teeth grinding. Such behaviors are engaged in to eliminate a part of the body and may result in impaired functionality.

The frequency of presentation to clinicians is low since BFRB are defined as harmless, although the number of studies on this condition has increased rapidly recently, including those making a clear determination of epidemiological data, those investigating the etiopathogenesis and those providing treatment guidelines, although they remain inadequate. The present study provides a review of studies investigating the etiology of BFRB to date.

Methods: Articles published between 1992 and 2021 stored in the Pubmed, Medline, Scopus and Web of Science databases were reviewed, and the prominent research studies of the condition identified were included in the evaluation.

Results: Studies investigating the etiopathogenesis of BFRB were found in most cases to investigate adult populations, and were hampered by such confounding factors as clinical heterogeneity, high rates of comorbid psychiatric diseases and small sample sizes. The identified studies reveal that attempts have been made to explain BFRB based on behavioral models, and that the condition is inherited at a high rate. Treatment planning is mostly associated with monoamine systems (especially glutamate and dopamine) and interventions were directed to addiction elements. Furthermore, cognitive flexibility and motor inhibition defects in neurocognitive area and cortico-striato-thalamo-cortical cycle abnormalities in neuroimaging studies have been reported.

Conclusion: Studies investigating the clinical features, incidence, etiopathogenesis and treatment of BFRB, which holds a controversial place in psychiatric classification systems, would contribute to a better understanding of the disease and a more appropriate definition of the condition.

Keywords: Body focused repetitive behavior disorders, trichotillomania, skin picking disorder, behavior models, neurobiology, neuroimaging

INTRODUCTION

Body focused repetitive behaviors (BFRB) is an umbrella term for undesirable, repetitive motor activities that may result in functional impairment. They are engaged in to eliminate a part of body and may result in impaired functionality. Behaviors such as trichotillomania (TTM), Skin Picking Disorder (SPD), nail biting, cheek chewing, lip biting, finger sucking, finger cracking and teeth grinding are described as BFRB in literature (Stein et al. 2006, (85) Snorrason et al. 2010). There is frequent common covariance among BFRB, and one person may display more than one behavior (Odlaug and Grant 2008). In addition, the phenomenological, neurological and psychosocial similarities between such behaviors suggests that the similar underlying mechanisms of these behaviors may display differently in clinical settings (Snorrason et al. 2012). The marked difficulty in impulse control, the presence of compulsive behavior with the aim of regulating anxiety or emotions, and the high rate of Obsessive Compulsive Disease (OCD) in such patients and their first-degree relatives have led some authors to suggest that OCD and BFRB have a common genetic background (Stein et al. 2016, Murphy et al. 2016).

BFRB has been introduced to the psychiatric classification system with diagnoses of TTM under the heading of Impulse Control Disorder, together with DSM-III. TTM and SPD are now categorized under "Obsessive Compulsive and Related Disorders" following the latest changes to the DSM,

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while no other disorder category is available for BFRB. The ICD-10, on the other hand, classifies TTM under "habit and impulse disorders," although a specific classification of SPD is absent in this grouping. TTM and SPD are classified as "Obsessive Compulsive and Related Disorders" under the subheading "Body Focused Repetitive Behavioral Disorders" in the IDC-11, while no category of disorders is present for other BFRB (Grant and Stein 2014, Stein et al. 2016).

The prevalence of clinically meaningful BFRB has been found to vary between 0.5% and 4.4% in studies (Duke et al. 2009, Grant et al. 2010, Odlaug et al. 2010). The prevalence of clinically meaningful BFRB among university students has been determined to be 22%, although it has been emphasized that the prevalence may be far higher than the ratio presented in the manuscript, since it is considered "harmless", and the number of sufferers seeking help is generally low (Siddiqui et al. 2012). The most common behaviors are reported as cheek chewing and skin picking, which were subclinical and clinically encountered, respectively, in a study of 4,435 participants aged 18–44 years (Houghton et al. 2018). Nail biting was found to account for 37% of the totals in another study of 281 individuals aged 3–21 years, and has been reported as the most commonly reported BFRBs in pediatric and adolescent samples (Winebrake et al. 2018). Risk factors defined for BFRB are advanced age, female gender, family history of BFRB, OCD, history of Alcohol/Substance Abuse, loose family bonds and not particularly favoring one's expression of his/her emotions, history of traumatic life events, impulsive personalities, and high rates of neuroticism and low rates of extroversion (Grant et al. 2011, Panza et al. 2013, Yalçın et al. 2014, Redden et al. 2016, Ricketts et al. 2018, Peris et al. 2019, Grant et al. 2021).

An evaluation of body literature reveals that society-based large-scale studies are insufficient for determining the prevalence of BFRB, and most of the studies performed to date have been of the adult population. BFRB entered psychiatric classification systems relatively late, although it has been addressed in medical literature for more than a century. Investigations of the phenomenology, etiopathology and treatment of these behaviors have witnessed a recent increase, especially over the last decade, although information remains limited, especially from pediatric and adolescent samples. This study aims to provide a review of studies investigating the etiology of BFRB.

METHOD

In the present study, an electronic search was made of the databases of Pubmed, Medline, Scopus and Web of Science for manuscripts published between 1992 and 2021 primarily focusing on research and review studies. The keywords used in the search were "body focused repetitive behavior disorders," "trichotillomania," "skin picking disorder," "behavior models," "neurobiology" and "neuroimaging."

Behavioral Modeling Studies

Behavioral models provide us information about the etiopathogenesis of a behavior by considering the function of BFRB. Many behavioral models have been developed in an attempt to explain the emergence and continuity of BFRB, focusing on studies referring to stimulus regulation models, sensorial processing, emotion regulation, prevented action and behavioral addiction. The scope of the subheading "behavioral addiction" was elaborated as extensively as possible due to the increasing interest in the association between behavioral addiction and BFRB. The biological aspects of behavioral addiction and psychopharmacological treatment approaches have also been mentioned.

According to the stimulus regulation model, BFRB is an effort to regulate an internal sensory imbalance externally. Penzel defines BFRB as a behavioral model expressed by the individuals to distract themselves when overstimulated, or to stimulate themselves when understimulated. The possible contributory factors to BFRB development according to Penzel are that the hair, skin and nails are easily accessible and present in ample amounts; that the body parts affected by the behavior are rich in nerve endings and so are a good source of stimulus; that the hair, skin and nails are quite sensitive to touch; that such behaviors are part of an evolutionary process as a genetic remnant of "grooming"; and that there is a and there is a pleasant/rewarding aspect to such behaviors (Penzel 2002).

Dunn's Sensory processing model , on the other hand, emphasizes that the interaction between the neurological threshold and behavioral response generates behavioral patterns (Dunn 1997). People with a low neurological threshold (sensory sensitivity) recognize and respond to sensory stimuli easily and quickly, while those with a high neurological threshold (low enrollment) require longer to respond to existing stimuli or miss the stimuli altogether. In opposite behaviors (sensory avoidance or sensory seeking), the person reacts in opposition to their neurological threshold. Increased interoceptive sensations, sensorial intolerance, and perceptional and tactical sensitivity have been reported in individuals with BFRB in a number of studies based on Dunn's sensory processing models (Houghton et al. 2018, Houghton et al. 2019). Hair pulling, skin picking and similar behaviors serve both to strengthen pleasant sensorial stimuli and detract from uncomfortable sensorial conditions such as stress and tension. This contradictory situation can be explained by the addiction model. Initially, individuals act to achieve a specific sensation as a positive reinforcer, while more frequent and intensive behaviors subsequently gain the function of refraining from uncomfortable sensations and act as negative reinforcers (Houghton et al. 2018).

There has been a recent increase in the number of studies reporting an association between difficulties in emotion regulation and BFRB. Emotion regulation is conceptualized as “decreasing negative emotions and decreasing stimulation by control” by some authors, or as “experiencing all emotions, differentiating and reacting to them” by others. The main function of BFRB has thus been reported to be to alleviate negative emotions or complete avoidance, while the resulting comfort strengthens the behavior and results in its continuation (Roberts et al. 2013). Incompatible emotional reactivity and difficulties in recognizing, understanding or accepting emotions is at the forefront in individuals with BFRB (Gratz and Roomer 2004). In another study, a higher level of incompatible emotional reactivity and experiential refrain was reported by individuals with BFRB than in the healthy control group, and thus emotion regulation difficulties were suggested to be a central compound of BFRB (Alexander et al. 2018). A combination of chronic emotional reactivity and emotion regulation difficulty has been reported to cause incompatible emotional regulation strategies such as BFRB (Snorrason et al. 2010). In another study, difficulties in recognition and understanding emotions were reported to be an important predictor of the severity of TTM (Ruffer et al. 2014).

According to the “Frustrated Action Model” developed by O’Connor et al., perfectionism and a tendency for self-criticism and the sense of embarrassment play important roles in the development and maintenance of BFRB (O’Connor et al. 2003, Dunkley et al. 2006). Individuals who exhibit BFRB have a tendency to experience such uncomfortable sensations as boredom, eagerness, disappointment and unhappiness as a result of mismatch between unrealistic expectations and personal standards (Duke et al. 2010). Sensation of embarrassment and incompatible emotion regulation strategies have been found to predict the severity of BFRB substantially, and to mediate the association of the emotion of embarrassment with perfectionism and BFRB (Houazene et al. 2020). Studies of incompatible emotion regulation strategies and the effects of perfectionism and sensation of embarrassment may contribute to the development of more effective cognitive behavioral treatment methods.

The continuation of a behavior as repetitive and compulsive, craving prior to the behavior, feelings of excitement and pleasure during the behavior, and the high rates of alcohol and substance abuse in the first degree relatives of individuals who were diagnosed to have especially TTM and SPD all suggest that BFRB should be conceptualized as “behavioral addiction “(Konkan et al. 2011). Award processing has been accepted as an important neural mechanism in the cognitive and behavioral processes associated with addiction. Dopaminergic neurons extending from the ventral tegmental area (VTA) to the ventral striatum (VS) and frontostriatal neural cycle, including such areas of the brain as the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC) and orbitofrontal cortex (OFC) play important roles in award processing (Berridge and Kringelbach 2008), and the authors suggest that changes occurring during the award processing processes play an important role in the development and continuation of addictive behaviors. In this context, one of the theories used to explain addiction behavior is the “incentive sensitization model,” where emphasis is on the learned clues that might lead to a differentiation between liking/wanting and craving. “Wanting” is a process that underlies the motivation of award seeking, and is closely associated with such expectational emotions as craving, while being modulated by the dopamine-dependent neuronal circuits, including the mesocorticolimbic pathway (Berridge and Robinson 2016). On the other hand, “Liking” expresses a hedonic response to the receipt of awards, and is regulated by non-dopamine dependent neuronal circuits, including the nucleus accumbens (NAcc) and Ventral Pallidum (VP) (Berridge and Kringelbach 2015). “Pathological wanting” has been closely associated with substance abuse, addiction to gambling and binge eating disorder (Berridge et al. 2010, Linnet 2014). “ Wanting” was found to be positively correlated with the severity of TTM, impulsivity, psychiatric signs and sleep disorders in a study comparing the effects of “desire” and “like” compounds in TTM (Snorrason et al. 2019). Supporting this study, the “Wanting” subscale was closely associated with impulse, clue reactivity and routines/habits associated with picking behavior in a study assessing the validity and safety of the Skin Picking Award Scale (Snorrason et al. 2015). In reward deficiency syndrome, on the other hand, a specific desensitization in the circuits that play role in award processing is present. This desensitization provides the basis for the development of addictive behaviors by leading one to search for pleasant sensations or novelties (Yao et al. 2020). Similarly, in a study evaluating the functional bonds during award processing and resting in TTM, a significant weakening was detected in the functional bonds between abnormal NAcc activation (relatively decreased NAcc activation when an award was expected, relative NAcc hyperactivation according to the results of gains and losses), dorsal ACC-NAcc and basolateral amigdala-NAcc. It has been suggested that the role of irregular award processing and low mediator input from the dorsal ACC and basolateral amigdala to NAcc on the TTM pathophysiology should be evaluated (White et al. 2013). Adolescence, on the other hand, is a period of development that is characterized by increased impulsivity and award-focused behaviors, independent of psychopathology. Considering the increased incidence of BFRBH in adolescence, it is still unclear to what degree these theories are associated with certain addiction-causing behavioral patterns.

Increased number of interventions directed at the addiction-related aspects during the planning of BFRB treatments is significant. In this context, the most commonly evaluated psychopharmacologic treatment modality involves the opioid receptor antagonists playing a role in the modulation of the dopamine dependent mesocorticolimbic pathway (especially naltrexone). In an open label study involving 14 children with

TTM, more than 50% decrease was reported in the severity of the symptoms in 11 patients after the use of naltrexone at 100mg/day for 10 weeks (De Sousa 2008). In a case report, a 13 year-old boy was treated with naltrexone 50mg/day for one month and a complete reduction in SPD symptoms was reported (Banga and Connor 2012). The variability in the underlying neural mechanisms, clinical homogeneity, the absence of an adequate number of randomized controlled studies, and the fact that previous studies have involved only adult cases suggest a need for larger number of studies to confirm present findings.

Genetic Studies

Data obtained from studies of families and twins suggest the presence of a significant genetic component of BFRB. It has been determined that monozygotic twins have higher rates of concordance than dizygotic twins (Novak et al. 2009). Genetic factors were found to be effective in 40% of cases in another study of twins with SPD in which unshared environmental factors were included in the analysis (Monzani et al. 2012). The rate of total phenotypic variance attributed to genetic effects was found to be 66% in males and 50% in females for finger sucking, and 50% in both males and females for nail biting (Ooki 2005). It was also found in family studies that the first degree relatives of people diagnosed with TTM have a higher rate of TTM and OCD than healthy controls (Keuthen et al. 2014). Another study evaluating the effect of family history on BFRB, at least one first degree relative was detected to have been diagnosed with TTM or SPD in 29.1% of cases, and "Substance Use Disorder" in 22.3%, while another study reported that pulling and picking behaviors may be a self-regulation mechanism in response to the emotional chaos in families in which substance abuse is present (Redden et al. 2016). Cases of TTM, SPD, nail biting and acne excoriation have been reported in four generations in one family (Khumalo et al. 2016), although it is still uncertain whether specific symptoms are associated with family history, as well as responses to treatment.

The number of studies supporting the hypothesis that abnormal and intense grooming behaviors mimic OCD spectrum disorders, which are characterized by an over repetition of behavioral actions (Zike et al. 2017). Grooming is an important evolutionary behavior that is seen in many animal taxa. Although the primary driver of grooming is hygiene, it also has other functions, such as thermoregulation, social interaction, chemical communication, arousal and stress reduction (Spruijt et al. 1992). Studies of grooming behaviors seen in animals provide significant information about the organization of complex behaviors within the brain and the factors affecting these behaviors. The determination of the neural circuits, molecular pathways and candidate genes associated with grooming behavior would facilitate the understanding of neuropsychiatric diseases that manifest with repetitive behaviors (Kalueff et al. 2007). Candidate genes with the highest level of evidence associated with BFRB and its possible equivalent abnormal grooming behavior are SAPAP3 and HOXb8. SLITRK1, SLITRK5, while other genes that have been studied include serotonergic (especially 5HT-2A) and dopaminergic (like DRD1) genes (Hemmings et al. 2006, Zuchner et al. 2006, Shmelkov et al. 2010). The SAPAP3 gene is expressed primarily in the striatum and plays role in the signal modulation of ionotropic glutamate receptors in the postsynaptic region (Wan et al. 2014). Anxiety-like behaviors increased with increased grooming behaviors in rodents with SAPAP3 deletion, and were noted to decrease with repeated fluoxetine injections (Welch et al. 2007). The human equivalent of the SAPAP3 gene is DLGAP3 gene and functions in the multi neuronal processes including changing the power of stimulant synapses (Wu et al. 2012). DLGAP1-4 has been associated with various psychiatric diseases, including TTM and OCD (Rasmussen et al. 2017). A decrease in grooming behaviors was detected in rats with SAPAP3 deletion following the autogenetic mediated repetitive stimulation of the medial OFC (Burguiere et al. 2013). The SLITRK1 protein, on the other hand, is a transmembrane protein that is involved in neuronal growth and extracellular signal transduction. Increased levels of neurochemicals, such as noradrenalin and its metabolite 3-metoxy -4-hydroxyfenylglycol (MHPG), has been detected in addition to anxiety-like behaviors in rats with SLITRK1 deletion. It has been reported that SLITRK1 dysfunction may play a role in the pathogenesis of neuropsychiatric diseases such as TTM and Tourette's syndrome (Katayama et al. 2010). HOXb8 is a growth-related transcription factor that has been found to be increased in grooming behaviors in mutant rats in animal studies (Chen et al. 2010). In a recent study, increased grooming behaviors and marked decreases in impulse control have been demonstrated in rats with plexinA1 deletion (PlxnA1- a transmembrane receptor for the semaphorins, being a large protein family leading axonal growth during the development of the nervous system. The authors reported that rats with PlxnA1 deletion may be valuable model for the evaluation of the repetitive behaviors and deficiencies of information processing seen in many neurodevelopmental and psychiatric disorders (Jahan et al. 2020).

Neurochemical Findings

The "serotonin dysfunction" hypothesis has been the focus of studies investigating the pathophysiology of body-focused repetitive behaviors, and was developed as a result of the successful outcomes achieved through the use of clomipramine and selective serotonin reuptake inhibitors (SSRI) for the treatment of OCD. On the other hand, different systems that may play a role in etiopathogenesis have been evaluated since SSRIs and clomipramine were shown to bring an inadequate improvement to symptoms, and to have potential side effects. Studies focused on glutamatergic and dopaminergic system abnormalities and neurochemical symptoms were seen to develop as a response to psychopharmacological treatment in majority of cases (Barroso et al. 2017, Kara and Akaltun 2018).

The imbalance in the stimulating and inhibitor signalization in the cortico-striato-thalamo-cortical (CSTC) circuits regulated by Glutamate and γ-aminobutiric acid (GABA) is a frequently analyzed subject. The glutamatergic hyperreactivity associated with the over activity of the direct pathway has been suggested to cause such imbalance (Wu et al. 2012). In compliance with this information, a study involving children and adolescents diagnosed with TTM analyzed the association between glutamate and GABA levels in the brain regions associated with TTM, the severity of symptoms and the response to the reversal of habit treatment. The authors concluded that elevated glutamate levels in the pregenual ACC (pACC) region and thalamus were associated with a significant increase in TTM. Furthermore, GABA levels in the putamen after reversal of habit treatments have been found significantly elevated when compared to pre-treatment levels, and high glutamate levels in more than one brain region (caudate, putamen, thalamus and pACC) were found to offer a good prediction of response to treatment. The authors reported the increased stimulant signalization in pACC and thalamus as an important element of the TTM pathophysiology, and those behavioral treatments led to an improvement of the symptoms by inhibiting direct pathway activity in the CSTC circuit (Peris et al 2020). A significant increase was observed in the grooming behaviors and stereotypical movements of astrocyte rats following the deletion of the glutamate transporter protein (GLT-1), which is responsible for glutamate clearance (Jia et al. 2021). The successful use of the glutamatergic agent N-Acetyl Cysteine (NAC) in many psychodermatological diseases, and the demonstration of the induction of stereotypical behavior in rodents by agents such as NMDA receptor antagonist phencyclidine (PCP) supports the "glutamate dysfunction" model (Williams et al. 2006). On the other hand, patients with OCD and accompanying SPD have been found to have significantly lower glutamate levels in pregenual ACC compared to patients without SPD or to healthy controls, and this was suggested to be the biomarker of a different OCD subcluster (Zheng et al. 2020). Considering the confounding factors and studies directed toward the direct measurement of biomarker levels is important for the generalization of results.

Dopamine, as an important modulator of nigrostriatal and mesolimbic systems, plays a critical role in locomotor functions, grooming and compulsive behaviors. In animal models, haloperidol – a dopamine D2 receptor antagonist – was seen to prevent sequential super stereotypes induced by a D1 agonist drug (Berridge et al. 2005). In another study, asymmetry was seen in grooming behaviors in unilateral dopaminergic neuron damage which was resolved following L-Dopa injection (Pelosi et al. 2015). Similar to animal studies, successful results have been reported in the treatment of various dopamine receptor blockers, mainly olanzapine and aripiprazole, involving clinical samples in the treatment of BFRB (Turner et al. 2014, Okumus and Hocaoglu 2018).

Many recent studies to date evaluated the role of the endocannabinoid system in the pathophysiology of TTM. Cannabinoid receptors (especially CB1) are found intensely in the basal ganglia, such as globus pallidus and substantia nigra pars reticularis, and this suggests that it plays a key role in the regulation of motor activity. Cannabinoid conduction acts as a modulator in the basal ganglia and increases GABAergic conduction, decreases glutamate secretion and regulates dopamine intake in cells. Considering the success of pharmacotherapies targeting excess glutamatergic activity, such as the CB-1 receptor agonist droabinol and glutamate dysfunction model, there is clear evidence of an association between TTM and the endocannabinoid system (Grant et al. 2015).

During the present study, two research studies drawing attention to the role of immune dysregulation in the etiology of repetitive behavior were encountered. In one study, a lower level of inflammatory cytokines was detected in the saliva of patients with TTM than in the healthy controls. It was suggested that this finding may serve as a possible guide for the differentiation of OCD, schizophrenia and depression, which are typically associated with increased inflammation and TTM (Grant and Chamberlain 2017). In another study involving 77 cases with TTM aged 2–18 years, the proinflammatory cytokine levels of the TTM group were found elevated (TNF-α, IL-6, IL-17) (Kutuk et al. 2020). Considering the effects of cytokines on neural development and differentiation, synapse development and neural plasticity, in addition to their role in the immune system, the "immune dysregulation" theory may be a promising field of research for the development of new treatments.

Neurochemical findings associated with BFRB have been generally associated with the monoamine system in studies conducted to date. Repeating the results, studying BFRB other than TTM, evaluating the different systems that may be related with the etiopathogenesis and carrying out studies including clinical sampling would contribute to the current findings in literature.

Neurocognitive Findings

Studies evaluating the neurocognitive processes behind body-focused repetitive behaviors place more emphasis on cognitive flexibility and inhibitor motor control inadequacy. Cognitive flexibility is defined as the ability of behaviors of organisms to undergo rapid changes in order to minimize their behaviour-related losses against environmental circumstances and to optimize their achievements (Izquierdo and Jentsch 2012, Izquierdo et al. 2017). The most commonly used criteria in cognitive flexibility is "reversal learning." Many neurocognitive areas, including cognitive flexibility, working memory, attention sliding, planning and organization were evaluated in a study involving young adults with BFRB, and cognitive flexibility was found to be the source of the statistically significant difference between groups (Flessner et al. 2015). Only one study of reversal learning in child and adolescent samples was found in the literature. An impairment in executive functions, such as reversal learning, planning and organization, was detected in the group with TTM when compared to the healthy controls (Flessner et al. 2016). On the other hand, no statistically significant association was found between cognitive flexibility and compulsive behavior in either group in a reversal learning task performed on patients with OCD and on rats with SAPAP3 deletion, while certain subgroups were emphasized to possibly have problems in cognitive flexibility (Benzina et al. 2021). Future studies directed at the detection of clinical subgroups and neurocognitive defects specific to these subgroups would enlighten psychopharmacological and psychosocial treatment approaches. Another form of conceptualization in reversal learning relates to the difficulty in abandoning a continuing behavior after an unexpected status change, compulsive reaction tendency. Compatible with this information, perseverative reactions to previously awarded responses were seen in rodents with OFC lesions due to impairment in reversal learning, and the nonflexible reaction in reverse learning was associated with impulsivity (Man et al. 2008, Fineberg et al. 2010).

Impaired response inhibition, on the other hand, is defined as an insufficiency in top-down inhibitor motor control. The literature review revealed two studies with controversial results evaluating insufficient motor response inhibition in a child and adolescent samples. In one study, the TTM group was found to perform better in the stop signal reaction time than the healthy controls, and the authors reported that response inhibition deficits may be associated with adult onset cases, although they also reported that the use of only the stop signal reaction time for the evaluation of motor inhibition may be a significant limitation of the study (2016). On the other hand, considering that one of the key signs of attention deficit hyperactivity disorder (ADHD) is "failure to stop impulsive behavior," it is possible that including patients with ADHD might be a confounding factor.

The other study evaluated the efficacy of a training activity of the computerized response inhibition in eight sessions involving 22 cases with TTM aged 9–17 years. Symptom severity was found to decrease significantly in the group who underwent training when compared to the group on the waiting list (Lee et al. 2018). The norepinephrine system facilitates the modulation of motor control-related neural circuits. Compatible with this information, an improvement was reported in stop signal reaction times following the application of atomoxetine, a selective noradrenalin reuptake inhibitor, while serotonergic agents were demonstrated to be inefficient in this area (ByMaster et al. 2002). A large number of studies are required to evaluate the effects of neurochemical modulation in the frontostriatal circuits and of pharmacological/psychosocial treatments in individuals exhibiting BFRB on inhibitor motor control.

Recently, studies have used "delay discounting" to measure impulsivity in those exhibiting BFRB. In delay discounting, an award loses its value subjectively when its presentation is delayed, while impulsive selection is defined as the acceptance of a small award (Chamberlain and Sahakian 2007). In a study of young adults exhibiting subclinical BFRB (nail biting, skin picking and comorbid nail biting and skin picking), multiple BFRB were associated with impaired response inhibition, and a powerful association was reported between the severity of nail biting behavior and delay discounting. The authors concluded that delay discounting may be more important than response inhibition, and so warranted further evaluation (Murphy and Flessner 2016).

When the neurocognitive studies of BFRB are evaluated, it is seen that they are few in number, and the results are controversial, preventing generalizability. As such, a repetition of results through studies including large samples and with no confounding factors are needed. Different neurocognitive specifications, mainly delay discounting, should be evaluated.

Imaging Studies

Neuroimaging studies in BFRB draw attention to fronto-cortico-striatal circuit abnormalities. Although the results of the study are quite complex, and far from generalizable, the prefrontal cortex, basal ganglion, amygdala and parietal lobe are the brain regions that come to the fore.

The OFC is a key center for such executive functions as decision-making and planning, and plays a critical role in mediating aim-directed behaviors (Torregrossa et al. 2008). In a study, the response inhibition, the OFC associated with the monitorization of movement and the development of habits, and hypoactivation in right frontal areas, ACC and striatum, were detected in patients diagnosed with SPD (Schienle et al. 2018a, Schienle et al. 2018b). In another study, decreased gray matter was noted in OFC in the SPD group (Schienle et al. 2018c). The results of studies investigating patients with TTM are controversial. Excess cortical thickness was found in the right inferior frontal gyrus of patients diagnosed with TTM, and this finding was reported to possibly play an important role in the etiopathogenesis of TTM (Chamberlain et al. 2018). Impairment in white matter integrity between ACC and OFC, in addition to increased gray matter in ACC, have been suggested to play a key role in the patophysiology of TTM in some studies (Chamberlain et al. 2008, Chamberlain et al. 2010). Also, no structural or functional difference was detected in OFC and ACC in some studies (Roos et al. 2013). Putamen is a basic component of motor control, and plays an important role in response inhibition. The caudate nucleus has gained prominence in directed learning, such as in complicated planning or flexible learning (Grahn et al. 2008). A significant volume decrease was identified in the left putamen and the right amygdala in patients with TTM when compared to healthy controls, which was attributed to the change in the setup to counter significantly impaired response inhibition and relatively protected executive functions (Isobe et al. 2018). In a recent study, a significant increase was noted in gray matter volumes in the parahippocampal gyrus and the cerebellum, independent of disease severity or duration in patients with TTM. The volumetric changes in these structures were associated with the decreased ability to control hair picking behaviors (Uhlmann et al. 2020). On the other hand, no significant difference was noted in the volumes of the subcortical structures between the TTM and healthy control groups (Chamberlain et al. 2008). In another study of patients with SPD, no significant difference was found in the caudate nucleus and putamen volumes (Harries et al. 2017), although difficulty in imaging subcortical structures, which play a well-known role in emotion regulation and behavior control, has been reported in literature due to variable signal intensity. Neuroimaging methods have been reported to be designed for the definition of cortical areas rather than subcortical structures.

Recent studies have focused on the role of amygdala in stimulation, attention, value representation and decision-making processes. A weakness was noted between the right basolateral amygdala in particular and the OFC connection in patients with TTM in a study (White et al. 2013). In another study, more gray matter density was found in the left amygdala in a TTM sampling when compared to the healthy control group (Chamberlain et al. 2008). Impairments in the white matter integrity in the left primary somatosensorial cortex and increased cortical thickness in precuneus have been detected (Grant et al. 2014). In a study of patients with SPD, weakness in the SMA-angular gyrus connection were associated with symptom severity, and the angular gyrus was reported to play role in the association of emotional information (tactic) with motor movement during skin picking behaviors (Huggins et al. 2020).

CONCLUSION

Body focused repetitive behaviors include chronic behavior associated with a significant damaging in functioning area and since they are defined as "harmless" and due to inadequate awareness, presentation to the clinicians is rare, although the disorder is more frequent than thought. Studies to determine the epidemiological data clearly, to enlighten the etiopathogenesis of the disorder and to develop treatment guidelines have gained great pace however their insufficiency lingers. Most of the research in literature are seen performed on adult sampling. Repetition is necessary since most of the results are controversial.

Due to the limited and controversial results in the etiopathogenesis of body focused repetitive behaviors, the place of the disease in the psychiatric classification systems is debatable. Some authors classify these behavior under "impulse control disorders" due to various reasons such as presence of irresistible impulses directed at hair pulling/skin picking and the resulting sensation of tension, relief following the exhibition of the behavior or report of pleasure and high rates of alcohol/substance abuse in the family (Spiegel et Finklea 2009). Some authors on the other hand classify these behaviors among "Obsessive Compulsive and Associated Disorders" due to phenomenological (relief of anxiety and relaxation of the overstimulation state, repetitive and ritualistic properties) and neurobiological (frontostriatal circuit abnormalities and inhibitor motor cortex insufficiencies similarities (Stein et al. 2016). On the other hand, contradictory to OCD, BFRB is known to include emotional experiences instead of cognitive phenomenon as behavior precursors such as entrance thoughts, obsessions and mental occupation. At the same time, response to treatment with SSRI is relatively low in BFRB and glutamatergic modulators and dopamine receptors come to forefront during treatment. Therefore, authors suggest that these behaviors should be classified under "Body Focused Repetitive Behavior Disorders," under "Obsessive Compulsive and Associated Disorders" (Grant and Stein 2014). Some authors suggest that TTM is even more closely associated with tic disorders compared to OCD and therefore TTM may be conceptualized as "complex tics" (Lamothe et al. 2020). Studies on the clinical properties, prevalence, etiopathogenesis and treatment of BFRB will contribute to the proper definition of the disease and also to a better understanding of it.

Studies evaluating the neurocognitive processes in body focused repetitive behaviors mainly establish cognitive flexibility and inhibitor motor control insufficiencies, while neuroimaging studies point out to the importance of fronto-cortico-striatal circuits in the pathophysiology of the disease. The prominent question here is whether or not "different pathophysiological mechanisms result in same behavioral expression" or "if there a single pathophysiological abnormality resulting in different behavioral expressions and classified as different diseases." Understanding the functional anatomy of BFRD will contribute to the answers of these questions and to enlighten the etiopathogenesis of the disease.

Studies to shed further light on the etiopathogenesis of body focused repetitive behavior disorders will guide to the development of evidence-based treatment strategies. Dopaminergic and serotonergic dysfunction, and mainly glutamate plays an important role in the pathophysiology of compulsive disorders. Therefore, the efficacy of serotonergic agents such as clomipramine and SSRI, glutamatergic modulators such as NAC, and dopamine receptor blockers, mainly olanzapine and aripiprazole in the treatment of the disease have been evaluated in studies performed previously. In the light of data obtained in such studies, possible drugs with a highest level of evidence to be used in the treatment of BFRB are NAC, clomipramine and olanzapine (Sani et al. 2019). Drugs that increase the GABAergic tonus such as benzodiazepines and allopregnanolone, generally not in sedative doses, have been demonstrated to cause decreased grooming behavior in rodents (Nin et al. 2012). Considering that the GABAergic system is an important regulator of behaviors related with stress and anxiety, use of drugs that increase the GABAergic efficacy as an enhancing agent in the treatment of BFRB may be beneficial. On the other hand, the higher efficacy of cognitive behavioral therapy compared to pharmacological treatment, in a way establishing the importance of neurocognitive mechanisms especially in children and adolescents, should be kept in mind. Also family focused interventions including areas such as encouragement of warmth and commitment among family members, problem solving in the family based on collaboration, constructive and coherent expression of emotions and development of appropriate emotion regulation strategies are potentially effective strategies (Woods and Houghton 2016).

In conclusion, although structural and functional properties of various different areas of the brain associated with the etiology of BFRB have been evaluated, sample size is generally low and many confounding factors are seen to be ignored. Small sample size causes a limited statistical power and increases the risk of false positive findings. Large sample size studies taking into account the comorbidities and performed especially in children and adolescents are needed for generalized results.

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