# Genetic and epigenetic underpinnings of bulimia nervosa/bulimia spectrum disorder and comorbid borderline personality disorder: implications for treatment

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## Introduction

Borderline personality disorder (BPD) is comorbid in about 30% of individuals with bulimia nervosa/ bulimia spectrum disorder (BN/BSD) (Zanarini et al., 1997). Individuals with BN/BSD and comorbid BPD (BN/BSD-BPD) experience increased psychopathology, poorer interpersonal relationships, and more frequent hospitalizations compared to those with BN/BSD alone (Kröger et al., 2010). This essay discusses the genetic and epigenetic aspects of BN/BSD-BPD, and argues successful treatment for BN/BSD-BPD will likely differ from treatment for BN/BSD or BDP as individuals with this condition demonstrate unique genetic and epigenetic changes, influencing clinical presentation and response to treatment.

## Defining bulimia nervosa (BN), bulimia spectrum disorder (BSD) and borderline personality disorder (BPD)

BN is a multifaceted ED characterized by an overvaluation of body shape and/or weight on self-image, coupled with recurrent episodes of binge eating and compensatory behaviours in attempts to prevent weight gain (Call et al., 2013). The thoughts and behaviours of those with BN and BSD are the same, the only difference between the two groups is the frequency with which the individual engages in the bulimic behaviours (Steiger & Bruce, 2007). BPD is a complex disorder characterized by affect instability, poor impulse control, impaired interpersonal relationships, and unstable self-image, and is frequently characterized by comorbidity with other psychiatric disorders including EDs (Lieb et al., 2004). Interestingly, individuals affected by BN/BSD and BPD share many of the same affect, impulse, and behavioural regulation traits. Both

groups demonstrate difficulties mentalizing. As defined by Bateman and Fonagy (2004) mentalizing is “the mental process by which an individual implicitly and explicitly interprets the actions of herself and others as meaningful on the basis of intentional mental states such as personal desires, needs, feelings, beliefs, and reasons”. Bateman and Fonagy (2013) propose that early attachment difficulties, followed by trauma has the potential to disrupt one’s ability to mentalize and consequently leads to impaired affect regulation, and indeed, insecure attachment styles are commonly observed in those with BN/BSD (Tasca & Balfour, 2014) as well as those with BPD (Critchfield et al., 2008).

**Genetics and epigenetics of bulimia nervosa/bulimia spectrum disorder and borderline personality disorder**

The similarities observed between BN/BSD and BPD seem to go as deep as genetics and epigenetics. Individuals with BN/BSD-BPD display lower serotonin and MAO activity than those with BN/BSD or healthy controls (HC). Methylation patterns were also seen to differ between individuals with BN/BSD-BPD, BN/BSD, and HC indicating that epigenetic processes contribute.

Central serotonin impacts eating behavior. Both human and animal studies have demonstrated an inverse relationship between serotonin neurotransmitter activity and food consumption (Steiger, 2004). Further, a significant negative correlation between serotonin transporter levels and illness duration in observed in the BN/BSD population ($p = 0.042$) (Tauscher et al., 2001). The serotonin system is also implicated in mood regulation, social behaviour, and impulsivity-all characteristics of BPD (Steiger & Bruce, 2007). The 5-hydroxytrypramine [5-HT] transporter gene (5-HTTLPR) is correlated with low transcription of the serotonin transporter protein, increased depression after tryptophan depletion (the precursor to serotonin), and clinical manifestations of both BN/BSD and BPD (Steiger et al., 2005). Two studies have examined 5-HTTLPR polymorphism in women with BN/BSD-BPD. Traditionally, 5-HTTLPR polymorphism was categorized using a biallelic model which included an S (short) allele

and an L (long) allele, which coded for low or high serotonin transporter activity, respectively (Lesch et al., 1996). However, more recent research argues for a triallelic model of the 5-HTTLPR polymorphism as evidence suggests there is a “low-frequency” L allele variant, $L_G$ which functions like the low-function S allele. Simply, the S and $L_G$ alleles can be classified as “low-function” variants and the $L_A$ allele can be classified as a “high-function” variant (Steiger et al., 2007; Steiger et al., 2005). One of the studies conducted analyses using both the biallelic and triallelic models, and the other study used only the biallelic model. Both studies analysed relationship between BPD and allele frequency and both found that those who met the criteria of BPD had higher frequencies of the S allele than their non-BPD counterparts (Steiger et al., 2007; Steiger et al., 2005). When the biallelic model was used in analyses, the S allele was associated with significantly higher instability ($p < 0.02$), insecure attachment ($p < 0.02$ and $p < 0.03$), stimulus seeking ($p < 0.03$), disinhibition ($p < 0.03$), and a significantly lower density of [$^3$H-] paroxetine binding sites (Steiger et al., 2005). When relationships were analysed using the triallelic model no significant effects were obtained in relation to stimulus seeking and insecure attachment but the results pointed in the same direction as the biallelic model (Steiger et al., 2007).

Monoamine oxidase (MAO) is an enzyme involved in removing the neurotransmitters serotonin, dopamine, norepinephrine, and epinephrine from the brain (Young, 2014). Lower MAO activity is consistently observed in individuals with BN/BSD compared to healthy controls (H et al., 2013)(Díaz-Marsá et al., 2011) and Low MAO activity has also been correlated to BPD symptoms including impulsiveness, affect dysregulation, sensation seeking, substance abuse, and suicide ideation and attempts (Buchsbaum et al., 1976; Donohew et al., 2015). Two studies have examined monoamine oxidize (MAO) in relation to groups of women with BN/BSD-BPD, BN/BSD, and HC.

Significantly lower MAO activity is observed in BN/BSD groups compared to HC ($p < 0.05$) (Díaz-Marsá et al., 2011). As well, MAO activity is markedly lower in BN/BSD-BPD than BN/BSD counterparts without BPD ($p < 0.05$) (Díaz-Marsá et al., 2011). Furthermore, this study observed

that platelet MAO activity is inversely related to the severity of BN/BSD symptoms ($p < 0.05$) as well as the severity of BPD ($p < 0.01$) (Díaz-Marsá et al., 2011). Clinical variables that reflect MAO activity (serotonin, dopamine, norepinephrine, and their metabolites) are significantly lower in BN/BSD patients than HC (24-hour excretion of serotonin, $p < 0.01$; 24-hour excretion of dopamine, $p < 0.04$) (Vaz-Leal et al., 2011). Furthermore, MAO activity of BN/BSD-BPD patients is significantly lower than BN/BSD patients (borderline personality traits x dopamine excretion, $p < 0.017$) (Vaz-Leal et al., 2011).

Epigenetic changes occur when a hereditary susceptibility is activated because of environmental pressures (Perroud et al., 2013). One common epigenetic mechanism is DNA methylation. DNA methylation occurs when methyl groups are added to the cytosine of CpG islands (frequently found in the regulatory region of most genes) and leads to reduced DNA accessibility, decreased transcriptional activity, and inhibition of gene expression (Thaler et al., 2014; Toyokawa et al., 2012). Childhood abuse is frequently cited as the "environmental pressure" that causes epigenetic effects correlated with BN/BSD and BPD symptomology and behaviour (Steiger et al., 2013; Thaler et al., 2014) Epigenetic changes that appear to be significant in those with BN/BSD-BPD include methylation of the glucocorticoid receptor promoter gene (NR3C1), brain derived neurotrophic factor (BDNF), and the dopamine receptor gene promoter (D2R2).

The glucocorticoid receptor is central to modulating individuals stress reactivity, and anomalies in this system have been associated with BN/BSD and BPD. ANOVA analyses indicate a significant group x promoter-region site interaction in the 1C region of the NR3C1 gene when comparing BN/BSD-BPD vs. BN/BSD vs. NED groups ($F = 1.75$, $p < 0.02$) (Steiger et al., 2013). When considering methylation levels at individual CpG sites in the 1C region BN/BSD-BPD groups have elevated methylation on positions 10 and 21 compared to methylation levels of HC ($p < 0.03$ in both cases). When comparing methylation levels between BN/BSD and HC groups no differences were observed. As well, group exhibit significantly lower methylation at CpG sites

on the 1H region than the NED group ($p = 0.005$). Once again, methylation levels in the BN/BSD did not differ from controls (Steiger et al., 2013).

BDNF is implicated in regulation of food intake and energy homeostasis in the general population, and is observed to be reduced in BN/BSD populations (Thaler et al., 2014). As well, increased methylation seen in the BPD population (Perroud et al., 2013). Early developmental stress, commonly observed in those with BN/BSD and BPD has been implicated in the hyper-methylation of the BDNF gene (Groleau et al., n.d.). When comparing methylation between individuals with BN/BSD-BPD to HC, the BN/BSD-BPD group demonstrate significantly higher methylation levels at sites 2 ($p < 0.01$), 16 ($p < 0.01$), 19 ($p < 0.05$), and 26 ($p < 0.01$). Additionally, individuals with BN/BSD have higher methylation than HC women at CpG cites 15 ($p < 0.05$), 17 ($p < 0.05$), 19 ($p < 0.05$), 25 ($p <0.01$), and 28 ($p < 0.05$) (Thaler et al., 2014).

Associations are seen between the D2R2 Taq1 polymorphism and symptoms related to both BN/BSD and BPD (e.g. binge eating, emotional eating, food cravings, impulsivity, and novelty seeking) (Groleau et al., 2014). BN/BSD and HC do not differ in mean methylation levels of the D2R2 (mean methylation = 7.35% ±0.67 and mean methylation = 7.11% ± 0.72, respectively). However, women with BN/BSD-BPD show significantly higher levels of D2R2 methylation compared to HC ($p < 0.05$), and slightly higher levels of D2R2 methylation compared to women with BN/BSD ($p < 0.10$) (Groleau et al., 2014).

**Treatment of individuals with BN/BSD-BPD**

Patients with comorbid BN/BSD-BPD present with unique challenges in treatment due to mood intolerance, interpersonal difficulties, and poor global functioning (Thompson-Brenner et al., 2016). Relapse rates of BN/BSD are high; about two thirds of patients relapse one to two years post-treatment (Johnson et al., 1990). Of the individuals that do relapse it is likely that they present with comorbid BPD as many studies have suggested these individuals present with worse treatment outcomes than BN/BSD patients without BPD (Johnson et al., 1990; Lilenfeld et al.,

2006; Stice & Agras, 1999). It is thought that BN/BSD and BPD behaviour interact to hinder treatment, with irregular eating patterns worsening mood, impulsivity, and other BPD symptomology, which, in turn, perpetuates the disordered eating as a maladaptive coping strategy (Thompson-Brenner et al., 2016).

Mentalization-based therapy (MBT) is thought to be beneficial for individuals with BN/BSD-BPD as it has been effective in reducing BPD symptoms - particularly non-suicidal self-injury (NSSI) - in those affected (P. H. Robinson, 2014). NSSI presents in those with BN/BSD as well as those with BPD, and rates of NSSI are higher in individuals with BN/BSD-BPD than those affected with BN/BSD alone (Jacobson & Luik, 2014). The focus of MBT is to enhance mentalizing, which is beneficial for BN/BSD-BPD patients, as these individuals show difficulties with this (Fonagy et al., 2002; Skårderud & Fonagy, 2012). MBT-ED is the form of MBT tailored for those with EDs, and its efficacy has previously been evaluated in the NOURISHED trial (P. Robinson et al., 2016). This randomized-controlled trial compared treatment outcomes in patients with BN/BSD-BPD who received specialist supportive clinical management (SSCM-ED) therapy vs. patients who received MBT-ED. MBT-ED was observed to be superior to SSCM-ED in reducing core body image pathology, specifically shape and weight concerns ($p = 0.029$ and $p = 0.037$, respectively) at 12 and 18 month follow-ups. However, both therapies were equal in reducing all other ED and BPD symptoms (P. Robinson et al., 2016). Thus, MBT-ED may be more beneficial for the treatment of BN/BSD-BPD than other therapies, but there is still a need for improved treatment.

Dialectical behavioural therapy (DBT) has also been proposed to be beneficial for those affected by BN/BSD-BPD as it is considered evidence-based treatment for NSSI, a key feature of BPD, and BN/BSD (Walsh & Eaton, 2014). Originally, DBT was created to treat BPD individuals who presented with affect dysregulation, suicidality/ NSSI, and frequent psychiatric hospitalization (Linehan, 1993), but has been since modified to also treat those with BN/BSD (Safer et al., 2009). DBT may be superior to other traditional types of psychotherapies for individuals with BN/BSD-

BPD as it addresses shared psychopathologies between NSSI and EDs (e.g. childhood trauma, affect dysregulation, and poor interpersonal relationships) (Muehlenkamp et al., 2011). DBT has four targets that are addressed in order of importance; these range from reducing life-threating behaviours, including suicidal urges and self-injuring, to decreasing behaviours that interfere with quality of life, including binge eating and purging, and interpersonal conflicts (Walsh & Eaton, 2014). Although DBT addresses core issues common to both BN/BSD and BPD, and may be superior to other forms of therapy (e.g. cognitive-behavioural therapy) for this population, recovery rates remain less than satisfactory for those with BN/BSD-BPD and more research on effective treatment for this population is needed.

Both MBT and DBT address mentalization difficulties observed in BN/BSD and BPD populations (Roth & Sweatt, 2011). As impairments in mentalization abilities may underscore the complex aetiology of BN/BSD and BPD (Sacchetti et al., 2019), addressing this fundamental aetiological and maintaining factor through treatment may result in more effective outcomes, positively impacting the health and quality of life of those affected with BN/BSD-BPD, decrease caregiver stress and burnout, and decrease burden on the healthcare system due to enhanced recovery rates.

## References


Bateman, A., & Fonagy, P. (2013, February). *Mentalization-based Treatment for Borderline Personality Disorder: A Practical Guide*. http://oxfordmedicine.com/view/10.1093/med/9780198570905.001.0001/med-9780198570905

Bateman, A. W., & Fonagy, P. (2004). Mentalization-Based Treatment of BPD. *Journal of Personality Disorders*, *18*(1), 36–51. https://doi.org/10.1521/pedi.18.1.36.32772

Call, C., Walsh, T., & Attia, E. (2013). From DSM-IV to DSM-5: Changes to eating disorder diagnoses. *Current Opinion in Psychiatry*, *26*(6).

Critchfield, K. L., Levy, K. N., Clarkin, J. F., & Kernberg, O. F. (2008). The relational context of aggression in borderline personality disorder: Using adult attachment style to predict forms of hostility. *Journal of Clinical Psychology*, *64*(1), 67–82. https://doi.org/10.1002/jclp.20434

Fonagy, P., Gergely, G., Jurist, E., & Target, M. (2002). Chapter 9: The Roots of Borderline Personality Disorder in Disorganized Attachment. In *Affect Regulation, Mentalization, and the Development of the Self* (pp. 343–372). Other Press LCC.

Groleau, P., Joober, R., Israel, M., & Zeramdini, N. (n.d.). *Methylation of the dopamine D2 receptor (D2R2) gene promoter in women with bulimia-spectrum disorder: Associations with borderline personailty disorder and exposure to childhood abuse*.

H, S., B, L., P, G., G, T., & M, I. (2013). Methylation of the glucocorticoid receptor gene promoter in bulimic women: Associations with borderline personality disorder, suicidality, and exposure to childhood abuse. *Journal of Eating Disorders*. https://doi.org/10.1002/eat.22113

H, S., J, R., R, J., L, G., M, I., K.r, B., N.m.k.n.y, K., H, H., & S.n, Y. (2007). The 5HTTLPR polymorphism, prior maltreatment and dramatic-erratic personality manifestations in women with bulimic syndromes. *Journal of Psychiatry and Neuroscience*.

Jacobson, C. M., & Luik, C. C. (2014). Chapter 2: Epidemiology and Sociocultural Aspects of Non-suicidial Self-Injury and Eating Disorders. In *Non-Suicidial Self-Injury in Eating Disorders: Advancements in Etiology and Treatment* (First). Springer-Verlag Berlin Heidelberg.

J.l, C., M., D.-M., E, H., J, C., & J, S.-R. (2011). Decreased platelet monoamine oxidase activity in female bulimia nervosa. *European Neuropsychopharmacology*.

Johnson, C., Tobin, D. L., & Dennis, A. (1990). Differences in Treatment Outcomes Between Borderline and Nonborederline Bulimics at One-year Follow-up. *International Journal of Eating Disorders*, *9*(6), 617–627.

Kröger, C., Schweiger, U., Sipos, V., Kliem, S., Arnold, R., Schunert, T., & Reinecker, H. (2010). Dialectical behaviour therapy and an added cognitive behavioural treatment module for eating disorders in women with borderline personality disorder and anorexia nervosa or bulimia nervosa who failed to respond to previous treatments. An open trial with a 15-month follow-up. *Journal of Behavior Therapy and Experimental Psychiatry*, *41*(4), 381–388. https://doi.org/10.1016/j.jbtep.2010.04.001

Lesch, K.-P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., Benjamin, J., Müller, C. R., Hamer, D. H., & Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, *274*(5292), 1527–1531.

Lieb, K., Zanarini, M. C., Schmahl, C., Linehan, M. M., & Bohus, M. (2004). Borderline personality disorder. *The Lancet*, *364*(9432), 453–461. https://doi.org/10.1016/S0140-6736(04)16770-6

Lilenfeld, L. R. R., Wonderlich, S., Riso, L. P., Crosby, R., & Mitchell, J. (2006). Eating disorders and personality: A methodological and empirical review. *Clinical Psychology Review*, *26*(3), 299–320. https://doi.org/10.1016/j.cpr.2005.10.003

Linehan, M. (1993). *Cognitive-behavioral Treatment of Borderline Personality Disorder*. Guilford Press.

Muehlenkamp, J. J., Claes, L., Smits, D., Peat, C. M., & Vandereycken, W. (2011). Non-suicidal self-injury in eating disordered patients: A test of a conceptual model. *Psychiatry Research*, *188*(1), 102–108. https://doi.org/10.1016/j.psychres.2010.12.023

Perroud, N., Salzmann, A., Prada, P., Nicastro, R., Hoeppli, M.-E., Furrer, S., Ardu, S., Krejci, I., Karege, F., & Malafosse, A. (2013). Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. *Translational Psychiatry*, *3*(1), e207. https://doi.org/10.1038/tp.2012.140

Richardson, J. (2012). *Genetic and environmental predictors of comorbid symptoms and treatment response in individuals with bulimia-spectrum disorders*. McGill U., Canada.

Robinson, P. H. (2014). Mentalization-Based Therapy of Non-Suicidial Self-Injury in Eating Disorders: MBT-ED. In *Non-Suicidial Self-Injury in Eating Disorders: Advances in Etiology and Treatment* (first). Springer.

Robinson, P., Hellier, J., Barrett, B., Barzdaitiene, D., Bateman, A., Bogaardt, A., Clare, A., Somers, N., O'Callaghan, A., Goldsmith, K., Kern, N., Schmidt, U., Morando, S., Ouellet-Courtois, C., Roberts, A., Skårderud, F., & Fonagy, P. (2016). The NOURISHED randomised controlled trial comparing mentalisation-based treatment for eating disorders (MBT-ED) with specialist supportive clinical management (SSCM-ED) for patients with eating disorders and symptoms of borderline personality disorder. *Trials*, *17*, 549. https://doi.org/10.1186/s13063-016-1606-8

Roth, T. L., & Sweatt, J. D. (2011). Epigenetic marking of the BDNF gene by early-life adverse experiences. *Hormones and Behavior*, *59*(3), 315–320. https://doi.org/10.1016/j.yhbeh.2010.05.005

Sacchetti, S., Robinson, P., Bogaardt, A., Clare, A., Ouellet-Courtois, C., Luyten, P., Bateman, A., & Fonagy, P. (2019). Reduced mentalizing in patients with bulimia nervosa and

features of borderline personality disorder: A case-control study. *BMC Psychiatry*, *19*(1), 134. https://doi.org/10.1186/s12888-019-2112-9

Safer, D. L., Telch, C. F., & Chen, E. Y. (2009). *Dialectical Behavior Therapy for Binge Eating and Bulimia*. Guilford Press.

Skårderud, F., & Fonagy, P. (2012). Chapter 14: Eating Disorders. In *Handbook of Mentalizing in Mental Health Practice* (First, pp. 347–384). American Psychiatric Association Publishing.

Steiger, H. (2004). Eating disorders and the serotonin connection: State, trait and developmental effects. *Journal of Psychiatry and Neuroscience*, *29*(1), 20–29.

Steiger, H., & Bruce, K. R. (2007). Phenotypes, Endophenotypes, and Genotypes in Bulimia Spectrum Eating Disorders. *The Canadian Journal of Psychiatry*, *52*(4), 220–227.

Steiger, H., Joober, R., Israel, M., Young, S. N., Kin, N. M. K. N. Y., Gauvin, L., Bruce, K. R., Joncas, J., & Torkaman-Zehi, A. (2005). Erratum: “The 5HTTLPR Polymorphism, Psychopathologic Symptoms, and Platelet [3H-] Paroxetine Binding in Bulimic Syndromes.” *Journal of Eating Disorders*, *37*(3), 281. https://doi.org/10.1002/eat.20161

Stice, E., & Agras, W. S. (1999). Subtyping bulimic women along dietary restraint and negaive affect dimensions. *Journal of Consulting and Clinical Psychology*, *67*(460–469).

Tasca, G. A., & Balfour, L. (2014). Attachment and eating disorders: A review of current research. *International Journal of Eating Disorders*, *47*(7), 710–717. https://doi.org/10.1002/eat.22302

Thaler, L., Gauvin, L., Joober, R., Groleau, P., de Guzman, R., Ambalavanan, A., Israel, M., Wilson, S., & Steiger, H. (2014). Methylation of BDNF in women with bulimic eating syndromes: Associations with childhood abuse and borderline personality disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *54*, 43–49. https://doi.org/10.1016/j.pnpbp.2014.04.010

Thompson-Brenner, H., Shingleton, R. M., Thompson, D. R., Satir, D. A., Richards, L. K., Pratt, E. M., & Barlow, D. H. (2016). Focused vs. Broad enhanced cognitive behavioral therapy for bulimia nervosa with comorbid borderline personality: A randomized controlled trial. *International Journal of Eating Disorders*, *49*(1), 36–49. https://doi.org/10.1002/eat.22468

Toyokawa, S., Uddin, M., Koenen, K. C., & Galea, S. (2012). How does the social environment 'get into the mind'? Epigenetics at the intersection of social and psychiatric epidemiology. *Social Science & Medicine*, *74*(1), 67–74. https://doi.org/10.1016/j.socscimed.2011.09.036

Vaz-Leal, F. J., Rodríguez-Santos, L., García-Herráiz, M. A., & Ramos-Fuentes, M. I. (2011). Neurobiological and Psychopathological Variables Related to Emotional Instability: A Study of Their Capability to Discriminate Patients with Bulimia Nervosa from Healthy Controls. *Neuropsychobiology*, *63*(4), 242–251. https://doi.org/10.1159/000323445

Walsh, B. W., & Eaton, J. E. (2014). Dialectical Behavioural Therapy. In *Non-Suicidial Self-Injury in Eating Disorders: Advances in Etiology and Treatment* (1st ed., pp. 127–145). Springer-Verlag Berlin Heidelberg.

Young. (2014). Monoamine oxidase. *Essential Oil Saftey*. http://www.sciencedirect.com/topics/page/Monoamine_oxidase

Zanarini, M. C., Williams, A. A., Lewis, R. E., Reich, R. B., Vera, S. C., Marino, M. F., Levin, A., Yong, L., & Frankenburg, F. R. (1997). Reported pathological childhood experiences associated with the development of borderline personality disorder. *The American Journal of Psychiatry*, *154*(8), 1101–1106. https://doi.org/10.1176/ajp.154.8.1101