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ROLE OF GUT MICROBIOTA IN THE INTERACTION BETWEEN IMMUNITY AND PSYCHIATRY: A LITERATURE REVIEW

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SUMMARY

Background: *Psychiatric disorders may be correlated with a low-grade systemic inflammation but the origin of this inflammatory response remains unclear and both genetics and environmental factors seems to be concerned. Recent researches observed that gut microbiota seems to have an impact on the brain and immune processes.*

Method: *We review recent literature to a better understanding of how microbiota interacts with brain, immunity and psychiatric disorders. We search on Pubmed, PsycINFO, PsycARTICLES and Sciencedirect articles with the keywords "gastrointestinal microbiota" and "mental disorders" or "psychological stress".*

Results: *We showed links between gut microbiota and brain-gut axis regulation, immune and endocrine system activity, neurophysiological changes, behavior variations and neuropsychiatric disorders. Communications between brain and gut are bidirectional via neural, endocrine and immune pathway. Microbiota dysbiosis and increase gut permeability with subsequent immune challenges seems to be the source of the chronic mild inflammation associated with neuropsychiatric disorders. Repeated immune or stress events early in life may lead to neurodevelopmental disorders or sickness behavior later in life.*

Conclusions: *psychological stress impact gut microbiota with subsequent immune activation leading to neurodevelopmental disorders or sickness behavior and altering neurophysiology and reactivity to stress or lifestyle.*

Key words: *microbiota - psychological stress - psychiatric disorder - immunity*

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INTRODUCTION

We highlighted in a precedent review (Dubois et al. 2018) that psychiatric disorders may be correlated with a low grade systemic inflammation and mild immunosuppression. The origin of this inflammatory response remains unclear and both genetics and environmental factors seems to be concerned. Recent researches observed that gut microbiota seems to have an impact on the brain and immune processes. In this article we review recent literature to a better understanding of how microbiota interacts with brain, immunity and psychiatric disorders.

METHOD AND LIMITATIONS

We search on Pubmed, PsycINFO, PsycARTICLES and Sciencedirect articles with the keywords «gastrointestinal microbiota» and «mental disorders» or «psychological stress». We have as much as possible promoted recent literature (2012 to early 2019) and human studies but they are limited and sometimes have a lower statiscal significance than animals studies. We have been focused on the literature about immunity and endocrine system. Selection and interpretation bias are probably present for the subsequent conclusions.

RESULTS

Links between intestinal microbiota and brain-gut axis

We found several evidences emphasizing the fact that brain – gut axis is influenced by micro-organisms colonising the gut mucosa (gut microbiota). Enteric nervous system (ENS) and central nervous system (CNS) are connected through the vagus nerve. Evidences showed that gut microbiota directly in contact with the ENS could modulate sensory neurons excitability and so information relayed to the brain (Parashar & Udayabanu 2016). Neurotransmitters such as catecholamines or gamma-aminobutyric acid (GABA) (Asano et al. 2012, Barret et al. 2012) are secreted by intestinal microbiota. Bacteria metabolism influences the serotoninergic system by altering tryptophan availability to 5-HT synthesis (Rackers et al. 2018). There is evidences that host neurophysiology is modulated by changes in gut microbiota. Neufeld et al. (2011) observed changes in hippocampal brain derived neurotrophic factor (BDNF) mRNA in germ-free (GF) mice.

Links between intestinal microbiota and behavior

Significant evidences support correlations between behavior and gut microbiota composition. It was showed that intestinal microbiota influences sensitivity to stress. Huo et al. (2017) showed less anxiety-like behavior in GF mice while others studies showed opposite results (Crumeyrolle-Arias et al. 2014). Desbonnet et al. (2014) found a significant social behavior impairment in GF mice. These behavior shifts were normalized following colonization of the gut of GF mice. Short-chain fatty acids (SCFA) such as butyrate, acetate or proprionate (PPA) are produced by microbial fermentation of dietary fiber and is a common preservative added to refined wheat and dairy products. SCFA are known to have neuroactive properties or induce neuroinflam-

mation and are associated with behavioral alterations. It was showed that PPA activate microglia of the hippocampus, white matter, cingulate, and neocortex (MacFabe et al. 2011) and can also alter the excitatory and inhibitory balance in neural circuitry via increased glutamatergic and decreased GABAergic transmission (MacFabe 2012). PPA seems to be linked with autism spectrum disorder symptomatology in human. Higher autistic symptoms are observed after eating food containing PPA and improvement is observed following the elimination of these product (Cenit et al. 2017).

Links between intestinal microbiota and immune system

Moreover, it seems that endocrine and immune system play an important role in the interaction between microbiota and brain. Microbiota composition may interact with hypothalamic-pituitary-adrenal (HPA) axis activity. Huo et al. showed a greater increase of HPA axis hormones levels with increased corticotrophin releasing factor (CRF) expression, elevated adrenocorticotropic hormone (ACTH) with corticosterone/cortisol levels and a reduce glucocorticoid receptor (GR) expression in GF stressed mice (Huo et al. 2017). Furthermore, stress may affect the composition of the gut microbiota and increase gut permeability (Kelly et al. 2015). Cathecholamines are known to induce growth of gram negative bacteria (Lyte & Ernst 1992). CRF might play a role in the stress-induced gut permeability dysfunction (Rodiño-Janeiro et al. 2015). Vanuystel et al. (2014) showed in humans that the mechanism might be the activation of mast cells receptors for corticotropin-releasing hormone. An increase gut permeability or a «leaky» gut facilitates translocation of bacteria into intestinal wall and contribute to the development of local inflammation but also the inflow of bacterial metabolites or harmful substance. Leading to a chronic systemic low-grade inflammation characterized by an increase level of pro-inflammatory cytokines and an activation of the HPA axis and secretion of cortisol (Brzozowski et al. 2016). Lipopolysaccharide (LPS) is a constituent of the outer membrane of Gram-negative bacteria. Toll-like receptor (TLR) are pattern recognition receptors (PRR) expressed by macrophages. LPS binds to TLR4 leading to nuclear factor-kB (NF-kB) activation and pro-inflammatory cytokines upregulation and so activation of immune system in the periphery and brain as well as stimulate the HPA axis (Mayerhofer et al. 2017). Moreover lipopolysaccharide (LPS) is known to produce systemic and psychiatric changes called sickness behavior such as fatigue, anorexia, depressed mood or apathy (DellaGioia & Hannestad 2010).

Links between intestinal microbiota and early life psychological stress

On Wah et al. (2018) showed in rats that early life immune challenges (induce by repeated LPS administration during adolescence or early adulthood) may induce effects long after initial response has dissipated and are risk factor for neurodevelopmental disorders or sickness behavior later in life (such as anxiety or depressive-like behavior). Moreover, they demonstrated that administration of PPA later in life may potentiate symptoms and sickness behavior due to the priming effect of LPS. Perinatal period, early childhood and adolescence are reported to be vulnerable periods for both brain and gut microbiota development. Animals studies showed that stressful events and subsequent gut-brain axis dysregulation early in life lead to brain development perturbations and have consequences on behavior such as anxious-like or social behavior or cognitive function and even immune or metabolic disorders in adulthood (Stiemsma & Michels 2018, Desbonnet et al. 2015). Dysregulation of gut-brain axis early in life is correlated with dysbiosis, reduce BDNF, HPA axis activation, impaired GR-mediated negative feedback and increase stress reactivity in adulthood (Desbonnet et al. 2015, Malan-Muller et al. 2018, Farzi et al. 2018). Moya-Pérez et al. (2017) showed that Bifidobacterium (B. pseudocatenulatum CECT 7765) intake may modulate the consequences of chronic stress on the HPA axis in adulthood with positive consequences in brain biochemistry and behavior.

Links between intestinal microbiota and neuropsychiatric disorders

Evidences revealed that a disturbance of the intestinal ecosystem (dysbiotic microbiota) might be associated with gastro-intestinal disorders but also with neuropsychiatric disorders (Gulas et al. 2018). Functional gastro-intestinal disorders such as inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) are characterized by a stress-induced brain-gut-microbiota alterations and are often associate with psychological distress including anxiety or depression (O'Mahony et al. 2017). But also it was observed that gastrointestinal (GI) symptoms are common in individuals with autistic spectrum disorder (ASD) and studies suggested a microbiota imbalance and an increase gut permeability (or «leaky gut»). It is demonstrated that ASD is correlated with an increase inflammatory markers (such as IL-6 or TNF), immune cells infiltration in the GI tract and increased levels of IgA in stool sample. A recent study performed fecal transplantation in ASD and observed a significant improvement in both GI and behavioral ASD symptoms (Groen et al. 2018, Fowlie et al. 2018). Depressive disorder is correlated with shifts in the microbiome composition (Zhernakova et al. 2016). Variations in levels of Bacteroidetes, Proteobacteria, Actinobacteria and Firmicutes are observed in depressive patients stools compared to controls. But studies showed contradictory results concerning proportions of species represented in stools samples (Jiang et al. 2015, Zheng et al. Lin et al. 2017). Consumption of Lactobacillus and Bifidobacterium is related with a small but significant improvement of depression score in a double-blind

randomized placebo controlled study (Messaoudi et al. 2011). When transferring microbiota from patients with major depression to microbiota-depleted animals characteristics of depression are also transferred (Cenit et al. 2017). In recent findings it was showed that human gut microbiota is involved in host metabolism and weight regulation. Dysbiosis is also demonstrated in anorexia nervosa (AN). Studies found an increase concentration of Methanobrevibacter Smithii (M. Smithii) in patients with AN compared to individuals with normal weight or obese controls. Moreover, negative correlation are found between body mass index and increased concentration of M. Smithii (Seitz et al. 2019).

DISCUSSIONS

Microbiota dysbiosis is associated to behavior alterations and neuropsychiatric disorders

The human gut microbiota includes more than 1,000 species and over 7,000 subspecies. Bacteroidetes (composed by several bacteroides or prevotella species) and Firmicutes (such as Clostridium, Ruminococcus, Lactobacillus) are the most abundant phyla in the gut. Actinobacteria (such as bifidobacterium), Proteobacteria (Enterobacteriaceae such as Escherichia coli), Verrucomicrobia, Fusobacteria, Cyanobacteria and Spyrochaetes are also found in intestinal flora. In adults, the intestinal microbiota consists of strictly anaerobic bacteria and relatively anaerobic bacteria are found but only in small amounts. Composition of microbiota is not constant during lifetime. The development occurs during early childhood and depends for example on maternal health or mode of delivery. After the age of three years the gut microbiota is relatively stable and tends to lose diversity in the elderly (Gulas et al. 2018). We showed that dysbiotic microbiota is connected with gastrointestinal disorders such as inflammatory bowel disease or irritable bowel disease but also with neuropsychiatric disorders such as depression, anxiety, autism or anorexia. Animals model is the most representative to understand the impact of intestinal dysbiosis on the brain and behavior. A total absence of microorganism is characterized by GF mice model correlated with behavior alterations such as impairment in social behavior, anxiety-like behavior and more reactivity to stress. There is also neuro-endocrine changes such as HPA axis hyperactivity and reduce GR expression but also neurophysiological perturbations such as a decrease of BDNF levels in hippocampal region. Dysbiosis is related to change in bacteria constituent or metabolites. Some species seems to have harmful and other protective effects but it is difficult actually to associate specific pattern of dysbiosis with a behavior or a psychiatric disorder. Admistration of probiotics or improvement in lifestyle and diet in depressive patients or ASD are correlated with improvement of the symptomatology. Recently fecal microbiota transplant showed that the phenotype of the donor is transferred to the recipient.

There is bidirectional communications between gut and brain

Interactions between the gastrointestinal tract and the cerebral nervous system (CNS) are more commonly called «brain-gut axis». Within the digestive tract we found millions of neurons forming the ENS whose the role is to regulate autonomic function of the gut such as motricity or secretions. ENS is connected to the brain via vagus nerves. It is well known that emotions such as stress may be accompanied by transit perturbations. Furthermore, we showed that commensal microorganism living along the gut have also the possibility to interfere with autonomic nervous system. Bacteria may secrete several neurotransmitters implicated in communication within the ENS and also CNS. Besides microbiota dysbiosis it is especially through the disturbance of gut permeability that a gut-brain axis dysregulation may be observed. In fact an increase gut permeability (called «leaky» gut) is associated with more bacterial constituents (LPS) or metabolites passing by the blood inflow to the brain or infiltrating the gut mucosa. The mechanisms by which psychological stress result in a «leaky» gut seems to be multiple and probably involve vagus nerve and ENS but also neuroendocrine and immune system with a direct activation of mast cells receptors with corticotropin-releasing hormone (CRF). The subsequent effect of macrophages activation via LPS/TLR interaction is upregulation of pro-inflammatory cytokines and local and/or chronic systemic low-grade inflammation.

Gut microbiota as the source of inflammation leading to psychiatric disorders

Psychological and gastro-intestinal symptoms are often associated in inflammatory bowel disorders but also in psychiatric disorders. This is particularly demonstrated in ASD given both local inflammation and systemic low-grade inflammatory marked by pro-inflammatory cytokines. In a precedent review (Dubois et al. 2018) we showed that a similar chronic mild inflammatory response seems to be involved in most of psychiatric disorders. Cytokines may cross the brain blood barrier (BBB) and activate microglial cells to express more cytokines in the brain. Cytokines may activate indoleamine 2,3-dioxygenase (IDO) transforming tryptophan into kynurenine instead of serotonine. Some bacteria in the gut are also involved in tryptophan metabolism altering tryptophan availability to 5-HT synthesis. Subsequent kynurenine metabolites may interfere with glutamatergic pathway and induce oxidative damage to limbic structures or cognitive impairement. Oxidative stress leads to a reduction of brain derived neurotrophic factor (BDNF) and an activation of nuclear factor kB (NFkB) leading to an upregulation of pro-inflammatory cytokines. These brain alterations are similar to what is observed in some microbiota studies. Particularly studies concerning short-chain fatty acids (SCFA) such as proprionate (PPA) having the capacity to activite microglia and alter glutamatergic/GABAergic balance in neural circuitry and induce neuroinflamation.

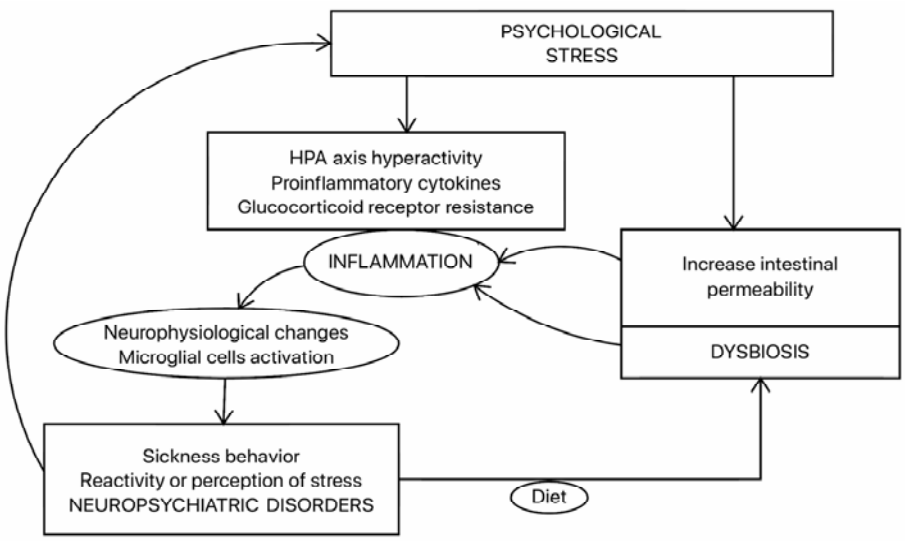

Figure 1. Hypothetical model of interactions between psychological stress, inflammation and gut microbiota

CONCLUSION

We showed that interactions between gut microbiota, psychological stress, psychiatric disorder and immunity are well documented but not fully understood. Acute stress activate HPA axis and pro-inflammatory cytokines and as hypothetized psychological stress have also an impact on gut microbiota and may lead to a deficiency of the intestinal barrier with subsequent immune system activation. Dysbiosis seems to play an important role in this immune chalenge. Psychological distress may impact bacteria composition and ecosytem of gut microbiota. It seems that variations in composition is related to change in bacteria constituent or metabolites. Some species seems to have harmful and other protective effects (Figure 1).

Psychological stress and so repeated immune challenges during more vulnerable period for the brain such as perinatal period, early childhood or adolescence may lead to neurodevelopmental disorders or sickness behavior later in life. Early life inflammation may affect neurophysiology and microglial cells development and activity and psychological stress later in life lead to an exacerbated inflammatory response. Psychiatric disorders are often correlated to a chronic systemic low grade inflammation with concomitant mild immunosuppression. Sickness behavior and eventually psychiatric or neurodevelopmental disorders altering reactivity or perception of stress events and are also associated with poor lifestyle or unhealthy diet directly impacting gut micriobiota.

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Thomas Dubois, Christine Reynaert, Denis Jacques, Brice Lepiece & Nicolas Zdanowicz all made substantial contributions to conception and design and or acquisition of data and/or analysis and/or interpretation of data.

References

1. *American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 5th edition: Washington, DC, 2013*
2. *Andrews G, Issakidis C, Carter G: Short falll in mental health service utilisation. British Journal of Psychiatry 2001; 179:417-425*
3. *Beatson J & Rao S: Depression and borderline personality disorder. Medical Journal of Australia 2013; 199(6 Suppl):S24-S27*
4. *Bender DS, Dolan RT, Skodol AE: Treatment utilization by patients with personality disorders. American Journal of Psychiatry 2001; 158:295–302*
5. *Biskin R, Frankenburg F, Fitzmaurice G, Zanarini M: Pain in Patients with Borderline Personality Disorder. Personal Ment Health 2014; 8:218-227*
6. *Braun V & Clarke C: Using thematic analysis in psychology. Qualitiative Research in Psychology 2006; 3:77-101*
7. *Carlat DJ: The Psychiatric Review of Symptoms: A Screening Tool for Family Physicians. Am Fam Physician 1998; 58:1617-1624*
8. *Chanen A, Thompson KN: Prescribing and borderline personality disorder. Australian Prescriber 2016; 9:49–53*
9. *Choi-Kain L, Zanarini M, Frankenburg F, Fitzmaurice G, Reich D: A Longitudinal Study of the 10-Year Course of Interpersonal Features in Borderline Personality Disorder. J Pers Disord 2010; 24:365-376*
10. *Coid J, Yang M, Tyrer P, Roberts A, Ullrich S: Prevalence and correlates of personality disorder in Great Britain. British Journal of Psychiatry 2006; 188:423-31*
11. *Fischer-Kern M, Kapusta N, Doering S, Horz S, Mikutta C, Aigner M: The Relationship between Personality Organization and Psychiatric Classification in Chronic Pain Patients. Pyschopathology 2011; 44:21-26*
12. *Frankenburg FR, Zanarini MC: The association between borderline personality disorder and chronic medical illnesses, poor health-related lifestyle choices, and costly forms of health care utilization. J Clin Psychiatry 2004; 65:1660-5*
13. *Gross R, Olfson M, Gameroff M, Shea S, Feder A, Fuentes M, Weissman M: Borderline personality disorder in primary care. Archives of Internal Medicine 2002; 162:53–60*

14. Gunderson JG, Morey LC, Stout RL: Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. J Clin Psychiatry 2004; 65:1049-1056
15. Hafting M, Gullbrå F, Anderssen N, Rørtveit G, Smith-Sivertsen T, van Doesum K: Overcoming Clinician and Parent Ambivalence: General Practitioners' Support of Children of Parents With Physical or Mental Illness and/or Substance Abuse. Front. Pyschiatry 2019; 8:724
16. Hesels CJ, Lacuelle OM, van Aken MAG, Resch F, Kaess M: Differentiating BPD in adolescents with NSSI disorder: the role of adverse childhood experiences and current social relationships. Borderline Personal Disord Emot Dysregul 2018; 7:20
17. Holm AL, Begat I & Severinsson E: Emotional pain: Surviving mental health problems related to childhood experiences', Journal of Psychiatric and Mental Health Nursing 2009; 16:636–645
18. Hueston WJ, Mainous AG, Schilling R: Patients with personality disorders: functional status, health care utilization, and satisfaction with care. J Fam Pract 1999; 4254-60
19. Jackson HJ & Burgess PM: Personality disorders in the community: results from the Australian National Survey of Mental Health and Well-being, Part III. Relationships between specific type of personality disorder, Axis I mental disorders and physical conditions with disability and health consultations. Social Psychiatry and Psychiatric Epidemiology 2004; 39:765-767
20. Javaras K, Zanarini M, Hudson J, Greenfield S, Gunderson J: Functional outcomes in community-based adults with borderline personality disorder. Journal of Psychiatric Research 2017; 89:105-114
21. Johnson TM: Vomiting as a manifestation of borderline personality disorder in primary care. J AM Board Fam Pract 1993; 6:385-94
22. Knaak S, Szeto A, Fitch K, Modgill G, Patten S: Stigma towards borderline personality disorder: effectiveness and generalizability of an anti-stigma program for healthcare providers using a pre-post randomized design', Borderline Personal Disord Emot Dysregul 2015; 5:2-9
23. Kulacaoglu F, Kose S: Borderline Personality Disorder (BPD): In the Midst of Vulnerability, Chaos, and Awe. Brain Sci 2018; 18:8, pii:201
24. Nehls N: Borderline personality disorder: Gender stereotypes, stigma, and limited system of care. Issues in Mental Health Nursing 1998; 19:97-112
25. Nehls N: Being a case manager for persons with borderline personality disorder: perspectives of community mental health center clinicians. Arch Psychiatr Nurs 2000; 14:12-18
26. Newton-Howes G, Tyrer P, Johnson T: Personality disorder and the outcome of depression: a meta-analysis of published studies. British Journal of Psychiatry 2006; 188:13-20
27. Markham D: Attitudes towards patients with a diagnosis of borderline personality disorder: Social rejection and dangerousness. Journal of Mental Health 2003; 12:595–612
28. Moran P, Jenkins R, Tylee A, Blizard R, Mann A: The prevalence of personality disorder among UK primary care attenders. Acta Psychiatr Scand 2000; 102:52-7
29. Palihawadana V, Broadbear JH, Rao S: Reviewing the clinical significance of 'fear of abandonment' in borderline personality disorder. Australas Psychiatry 2018; 7:1039856218810154 [Epub ahead of print]
30. Raven C: Borderline personality disorder: Still a diagnosis of exclusion? Mental Health Today 2009; 26–31
31. Rendu A, Moran P, Patel A, Knapp M, Mann A: Economic impact of personality disorders in UK primary care attenders. British Journal of Psychiatry 2002; 181:62-66
32. Rogers B, Dunne E: They told me I had this personality disorder. All of a sudden I was wasting their time: personality disorder and the inpatient experience. Journal of Mental Health 2011; 20:226-233
33. Sansone RA & Sansone LA: Fatal attraction syndrome: Stalking behavior and borderline personality. Psychiatry 2010; 7:42–46
34. Sansone RA, Sinclair JD, Wiederman MW: Disability and borderline personality disorder in chronic pain patients. Pain Res Manag 2010; 15:369–370
35. Sansone RA, Whitecar P, Meler BP, Murry A: The prevalence of borderline personality among primary care patients with chronic pain. Gen Hosp Psychiatry 2001; 23:193-7
36. Seivewright H, Tyrer P, Casey P: A three-year follow-up of psychiatric morbidity in urban and rural primary care. Psychological Medicine 1991; 21:495–503
37. Silk KR: The quality of depression in borderline personality disorder and the diagnostic process. J Pers Disord 2010; 24:25-37
38. Sulzer SH, Muenchow E, Potvin A, Harris J, Gigot G: Improving patient-centered communication of the borderline personality disorder diagnosis. J Mental Health 2016; 25:5-9
39. Sved Williams A, Apter G: Helping mothers with the emotional dysregulation of borderline personality disorder and their infants in primary care settings. Aust Fam Physician 2017; 46:669-672
40. Trull T, Distel M & Carpenter R: DSM-5 borderline personality disorder: At the border between a dimensional and a categorical view. Current Psychiatry Report 2010; 13:43–49
41. Trull TJ, Sher KL, Minks-Brown C, Durbin J, Burr R: Borderline personality disorder and substance use disorders: a review and integration. Clin Psychol Rev 2000; 20:235-253
42. Wehbe-Alamah H, Wolgamott D: Uncovering the mask of borderline personality disorder: Knowledge to empower primary care providers. Journal of the American Association of Nurse Practitioners 2014; 26:292–300
43. Winsper C: The aetiology of borderline personality disorder (BPD): contemporary theories and putative mechanisms. Curr Opin Pyschol 2018; 21:105-110
44. Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G: 10-year course of psychosocial functioning among patients with borderline personality disorder and axis II comparison subjects. Acta Psychiatr Scand 2018; 122:103-109

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