

White matter pathology in patients with borderline personality disorder: A review of controlled DTI studies

Raza Sagarwala, MD
Vanderbilt University Medical Center
Nashville, Tennessee, USA

Henry A. Nasrallah, MD
University of Cincinnati
Cincinnati, Ohio, USA

BACKGROUND: Neuroimaging, especially diffusion tensor imaging (DTI), has emerged as a helpful tool in assessing and characterizing white matter (WM) integrity. The resultant early treatment from early diagnosis is crucial because treatment is often more efficacious. Borderline personality disorder (BPD) is a challenging disorder to diagnose and treat, and has been reported to have various neurobiologic abnormalities. We conducted a search of the literature to review WM pathology findings in BPD.

METHODS: A search was conducted to identify systematic reviews and meta-analyses published from January 2000 to September 2019 that assessed WM integrity in BPD.

RESULTS: Four studies were included. One study demonstrated no difference in WM between BPD and healthy controls. Another study found decreased fractional anisotropy (FA) within the corpus callosum (CC) and orbitofrontal regions. A subsequent randomized controlled trial reported a decrease in FA within the fornix, CC, and right superior/anterior corona radiata with associated increase in radial diffusivity in the left anterior thalamic radiation. The fourth study found a decrease in the axial diffusivity within the cingulum, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus.

CONCLUSIONS: Our review concludes that BPD is associated with measurable WM pathology. Methods such as DTI might emerge as useful tools in the management of BPD. More controlled studies are needed to validate our conclusions.

CORRESPONDENCE

Raza Sagarwala, MD
Department of Psychiatry and
Behavioral Sciences
Vanderbilt University Medical Center
1211 Medical Center Drive
Nashville, TN 37232 USA

E-MAIL

raza.sagarwala@vumc.org



INTRODUCTION

Borderline personality disorder (BPD) is a cluster B personality disorder characterized by multiple symptoms, including fleeting mood shifts that occur secondary to conflict within interpersonal relationships as well as suicidal urges, anger outbursts, self-cutting, and micro-psychotic episodes.¹ Patients with BPD have been found to have poor impulse control, with a lifetime risk of completed suicide of 8%, which makes it crucially important to diagnose and treat these patients early.² Comorbid mood disorders and substance use disorders are also common, leading to high risk-taking behavior that puts these patients at harm.³ Neuroimaging conducted on patients with BPD has suggested underlying pathology within the prefrontal cortex, amygdala, and hippocampus, which is not unexpected given these structures' involvement in emotional processing.⁴ It is also highly genetic.⁵

Neuroimaging has emerged as a helpful tool in assessing and characterizing morphological abnormalities as well as white matter (WM) pathology in a variety of neuropsychiatric disorders. Specifically, diffusion tensor imaging (DTI) has become useful in exploring the underlying microstructural deficits within WM of patients with neuropsychiatric disorders. Diffusion tensor imaging is an MRI technique based on the principle of Brownian motion (random movement) of water molecules. In healthy tissue, water molecules move unhindered and naturally parallel to the axons of neurons.⁶

Through DTI, 4 measurements are computed: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (D_a), and radial diffusivity (D_r). Fractional anisotropy is a measurement of net movement of water molecules that ranges from 0 (equal dispersion of protons in any direction) to 1 (diffusion of protons in a single direction). A decreased FA in relation to healthy controls (HC) might be an indication of underlying neurologic disease within the WM structure.⁷ Axial diffusivity represents movement of water molecules parallel to axons, whereas D_r represents movement of water molecules perpendicular to axons. Both values thus give insight into how effectively neurons are communicating with one another.⁸ Finally, MD is often used as a supplementary value to FA, indicating average molecular movement of protons regardless of direction. **TABLE 1** contains a summary of these terms.

TABLE 1
High-yield diffusion tensor imaging terms

Measurement	Definition
Fractional anisotropy (FA)	Values range between 0 (water motion random) and 1 (directional selectivity of water movement)
Mean diffusivity (MD)	Average molecule motion, regardless of direction
Axial diffusivity (D_a)	Molecule movement parallel to axons
Radial diffusivity (D_r)	Molecule movement perpendicular to axons

Establishing biologic findings in neuropsychiatric disorders is essential for early diagnosis and early intervention. This has been well documented in many neuropsychiatric disorders, including schizophrenia⁹ and bipolar disorder (BD).¹⁰ Because therapy is a staple of treatment of BPD, effective neuroimaging for early diagnosis can play a large role in proper treatment. Diffusion tensor imaging studies have suggested that patients with disorders that include (but are not limited to) schizophrenia,¹¹ BD,¹² major depressive disorder (MDD),¹³ obsessive-compulsive disorder,¹⁴ attention-deficit/hyperactivity disorder (ADHD),¹⁵ posttraumatic stress disorder (PTSD),¹⁶ and Alzheimer's disease (AD)¹⁷ demonstrate a statistically significant decrease in FA within a variety of WM tracts, most commonly the corpus callosum (CC), the largest bundle of approximately 200 million myelinated fibers in the brain.

The purpose of this review is to analyze and synthesize published research on BPD to assess the WM pathology seen within this disorder, and to evaluate if DTI could be used as a reliable diagnostic tool, leading to earlier diagnosis and therapeutic intervention.

METHODS

We conducted a search of PubMed for literature published from January 2000 to September 2019 to identify studies assessing WM pathology in patients with BPD as measured by DTI.

Inclusion criteria. Studies were included in our review if they:

1. were randomized controlled trials (RCTs)

TABLE 2
Randomized controlled trials included in this review

Author	N	White matter pathology
Carrasco et al ¹⁹ (2011)	28 BPD, 26 HC	Decreased FA: knee and anterior (CC) ($P < .005$); orbitofrontal region ($P < .005$)
New et al ²⁰ (2013)	38 BPD, 32 HC	No difference
Gan et al ²¹ (2016)	30 BPD, 31 HC	Decreased FA: fornix ($P < .03$); genu and body of CC ($P < .05$); and right superior and anterior CR ($P < .05$) Increased D_r ; left ATR ($P < .05$)
Ninomiya et al ²² (2018)	35 BPD, 50 HC	Decreased D_a : cingulum ($P < .01$); IFOF ($P < .01$); ILF ($P < .01$)

ATR: anterior thalamic radiation; BPD: borderline personality disorder; CC: corpus callosum; CR: corona radiata; D_a : axial diffusivity; D_r : radial diffusivity; FA: fractional anisotropy; HC: healthy controls; IFOF: inferior front-occipital fasciculus; ILF: inferior longitudinal fasciculus.

2. used participants who fulfilled DSM diagnostic criteria for BPD

3. included WM findings as measured by DTI.

Exclusion criteria. Studies were excluded in our review if they:

1. used participants who were receiving psychotropic medications

2. used participants with a comorbid lifetime diagnosis of schizophrenia, bipolar disorder, or neurologic disorder

3. used participants with personality disorders other than BPD.

RESULTS

Four studies met the inclusion criteria. The results of our search process using the PRISMA method¹⁸ are shown in the **FIGURE**. A summary of the data is included in **TABLE 2**.¹⁹⁻²²

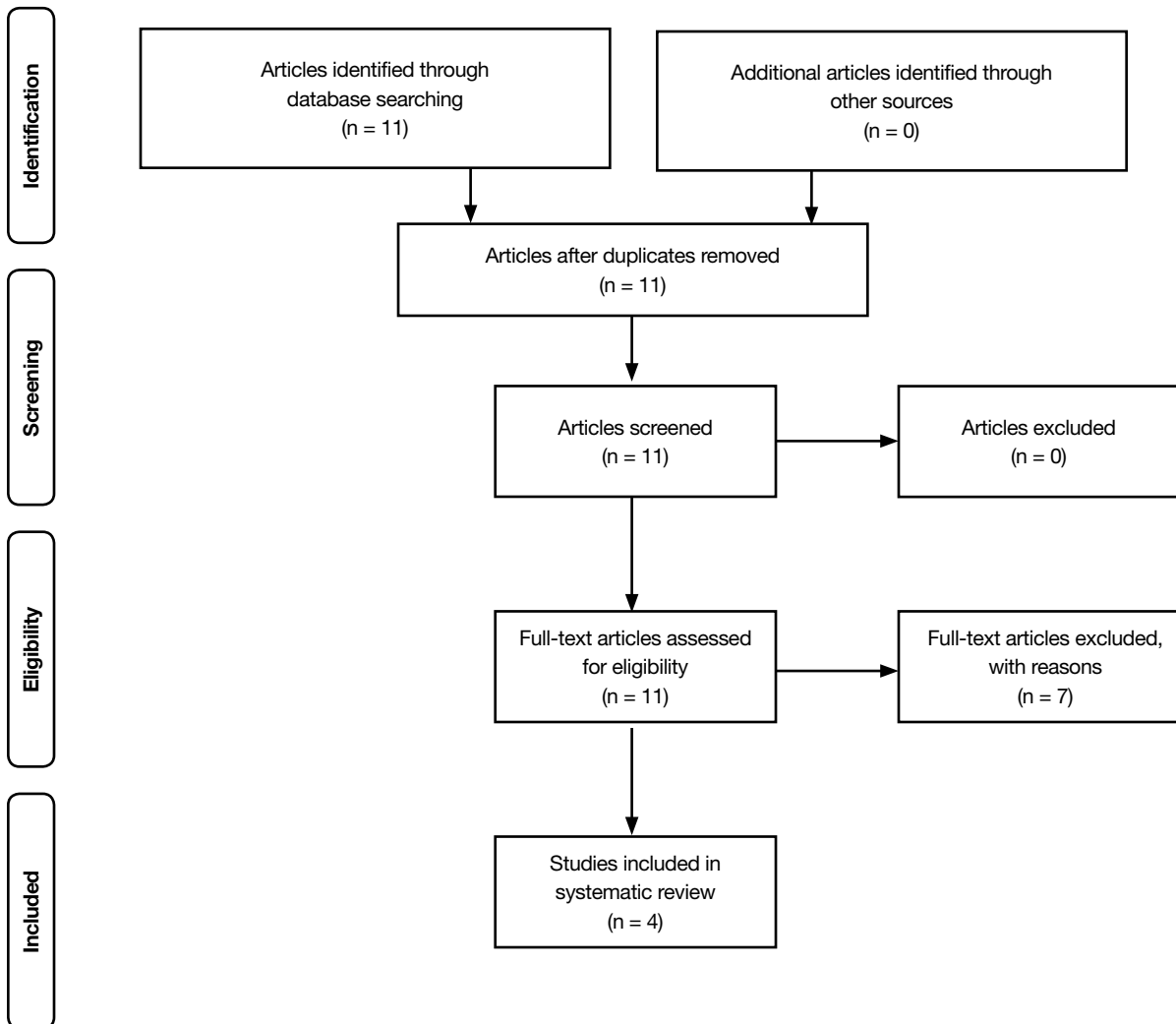
Carasco et al¹⁹ (2011). In this RCT, 28 patients with BPD and 30 HC were recruited to undergo DTI to assess WM pathology within BPD. Tract-based spatial statistics were computed for all patients to identify regions of abnormal FA. When compared to HC, patients with BPD were found to have a decrease in FA within the genu and anterior portion of the CC ($P < .005$) and within the orbitofrontal region ($P < .005$). There were no regions that demonstrated an increase in FA in patients with BPD compared with HC. No significant correlations were found between duration of BPD and FA abnormalities.

New et al²⁰ (2013). In this study, DTI tractography was conducted on 38 adults with BPD and 32 HC.

No statistically significant difference in FA was observed between groups. However, New et al²⁰ also investigated WM pathology in 14 adolescents with BPD receiving pharmacologic therapy and 13 HC. The adolescents with BPD were found to have a significant decrease in FA within the left inferior longitudinal fasciculus (ILF) ($P < .005$) and right ILF ($P < .008$). Because the adolescents with BPD had higher aggression scores on the Buss Perry Aggression Questionnaire²³ and trait anger as measured on the State-Trait Anger Expression Inventory,²⁴ the analysis was repeated with these measures added as covariates. The findings were unchanged. Tract-based spatial statistics analysis within these regions was conducted to better localize the precise regions of FA reduction in adolescents with BPD. Fractional anisotropy reductions were found predominately in the WM tracts of the temporal lobe.

Gan et al²¹ (2016). In this RCT, 30 patients with BPD and 31 HC were recruited to undergo WM analysis on DTI. Results demonstrated significantly lower FA in patients with BPD compared with HC within the fornix ($P < .03$), genu and body of the CC ($P < .05$), and right superior and anterior corona radiata (CR) ($P < .05$). Further, FA values for the fornix were correlated negatively with negative affect ($r = .258$, $P = .047$), whereas FA values for the genu ($r = .290$, $P = .025$) and body ($r = .292$, $P = .024$) of the CC correlated negatively with impulsivity. Fractional anisotropy values for the fornix were correlated negatively to both positive intensity ($r = .281$, $P = .030$) and motor impulsivity ($r = .340$, $P = .008$). The BPD participants were also found to have significantly higher D_r within the left anterior thalamic radiation (ATR)

FIGURE
PRISMA flow diagram



PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

compared with HC ($P < .05$). This D_r value for the left ATR was correlated positively with attention impulsivity ($r = .263, P = .042$).

Ninomiya et al²² (2018). In this study, 35 participants with BPD and 50 HC were enrolled in this RCT. Participants with BPD were found to have a significant decrease in D_a within the cingulum ($P < .01$), inferior front-occipital fasciculus (IFOF) ($P < .01$), and ILF ($P < .01$). The D_a values within the cingulum were negatively correlated with depression scores on the Profile of Mood Score²⁵ ($P < .05$). Additionally, the decrease

in D_a within the IFOF was positively correlated with scores on future denial, or pessimism about the future, on the Depression and Anxiety Cognition Scale.²⁶ No differences were found within the FA, MD, or D_r between the 2 groups.

DISCUSSION

This review provides several lines of evidence that patients with BPD have underlying WM microstructural

dysfunction as measured by DTI. Of the 4 studies presented in this review, 3 demonstrate a statistically significant difference in the WM of non-medicated adult patients with BPD compared with HC. New et al²⁰ found significant changes in FA in adolescents but not adults with BPD, highlighting the pathological changes that occur during adolescence. Although these patients were receiving pharmacotherapy, the decrease in FA values within WM tracts compared with HC is unusual, especially because research suggests that adolescents undergo a period of increased myelination of axons, thereby allowing for maturation of WM tracts.²⁷

On the other hand, Carasco et al¹⁹ proposes that patients with BPD have decreased FA, reflecting impaired integrity of WM within the commissural fibers of the CC and orbitofrontal regions. The orbitofrontal cortex is not only involved in taste and olfaction processing, but is fundamental in reward- and punishment-related behavior. It is through dysfunction of this region that emotional instability may manifest itself in BPD.²⁸ Similarly, WM changes within the CC have been found to be associated with suicidal ideation through the disruption of interhemispheric communication.²⁹ The CC has been shown to be a shared region of pathology among many neuropsychiatric disorders.¹¹⁻¹⁷

Gan et al²¹ adds to these findings, localizing decreased FA within the fornix, CC, and right superior and inferior CR. Subsequent linear correlation models conducted indicate that as the FA value within the fornix decreases, patients tend to present with worsening and intensification of negative affect and an increase in motor impulsivity. Although the fornix has classically been known as an output tract from the hippocampus to the rest of the Papez circuit, the hippocampus is intimately connected to the amygdala, whose key role is in emotional processing.³⁰ Disruption of the neurons within the fornix could thus explain the poor affect and impulsivity that results with microstructure pathology in patients with BPD. Participants with BPD were also found to have significantly higher D_r within the left ATR without associated changes in the FA. As the D_r was increased within the left ATR, participants were found to have worsening of attention. Similar changes within the WM tracts of ATR have also been implicated in ADHD.³¹

Ninomiya et al²² found no change in FA but an associated decrease of D_a within the cingulum, IFOF, and ILF. As the value for D_a decreased within the

cingulum, depression and future denial were found to worsen. The cingulum is a large WM tract integrating the parietal, frontal, and temporal lobes. Through this connectivity, the cingulum acts as a major site for executive control and emotional regulation, and has been associated with pathological findings in several neuropsychiatric disorders, including MDD, schizophrenia, PTSD, and AD.³²

Limitations

Our study has limitations, some of which may explain the mixed findings. First, the literature is sparse on DTI studies conducted on patients with BPD who are not receiving pharmacotherapy, and as a result, only 4 studies were included in this review. Second, because most patients in these studies had received pharmacotherapy in the past, it is difficult to ascertain how much impact this confounding variable had on DTI parameters. Studies of treatment-naïve patients would be ideal because they could better target the effects of BPD on WM. Further, because many patients with cluster B personality disorders have comorbid depression and substance use disorders,³³ it is difficult to isolate these confounding variables to get an accurate understanding of BPD's role in WM pathology. Finally, each of the studies included in this review had a relatively small sample size. Accordingly, our findings must be replicated in large samples to make them generalizable to the BPD population, and more RCTs are needed to expand on this review.

CONCLUSIONS

Our review of this limited literature suggests that patients with BPD might have underlying WM dysfunction in cortical regions associated with emotional processing and executive functioning. Because BPD is a challenging disorder to diagnose early and treat adequately, DTI may eventually play a helpful role in assisting clinicians to address this disorder. However, more RCTs are required to explore WM pathology in BPD and to identify its clinical correlates. ■

DISCLOSURES: The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

REFERENCES

- Paris J, Black DW. Borderline personality disorder and bipolar disorder: what is the difference and why does it matter? *J Nerv Ment Dis.* 2015;203:3-7.
- Pompili M, Girardi P, Ruberto A, et al. Suicide in borderline personality disorder: a meta-analysis. *Nord J Psychiatry.* 2005;59:319-324.
- Kaess M, Brunner R, Chanan A. Borderline personality disorder in adolescence. *Pediatrics.* 2014;134:782-793.
- Schmahl C, Bremner JD. Neuroimaging in borderline personality disorder. *J Psychiatr Res.* 2006;40:419-427.
- Nasrallah HA. Borderline personality disorder is a heritable brain disease. *Current Psychiatry.* 2014;13:19-20,32.
- Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci.* 2008;34:51-61.
- Alexander AL, Lee JE, Lazar M, et al. Diffusion tensor imaging of the brain. *Neurotherapeutics.* 2007;4:316-329.
- Kronlage M, Schwehr V, Schwarz D, et al. Peripheral nerve diffusion tensor imaging (DTI): normal values and demographic determinants in a cohort of 60 healthy individuals. *Eur Radiol.* 2018;28:1801-1808.
- Cheng SC, Schepp KG. Early intervention in schizophrenia: a literature review. *Arch Psychiatr Nurs.* 2016;30:774-781.
- Chia MF, Cotton S, Filia K, et al. Early intervention for bipolar disorder - do current treatment guidelines provide recommendations for the early stages of the disorder? *J Affect Disord.* 2019;257:669-677.
- Duchatel RJ, Weickert CS, Tooney PA. White matter neuron biology and neuropathology in schizophrenia. *NPJ Schizophr.* 2019;5:10.
- Favre P, Pauling M, Stout J, et al; ENIGMA Bipolar Disorder Working Group. Widespread white matter microstructural abnormalities in bipolar disorder: evidence from mega- and meta-analyses across 3033 individuals. *Neuropsychopharmacology.* 2019;44:2285-2293.
- Jiang J, Zhao YJ, Hu XY, et al. Microstructural brain abnormalities in medication-free patients with major depressive disorder: a systematic review and meta-analysis of diffusion tensor imaging. *J Psychiatry Neurosci.* 2017;42:150-163.
- Koch K, Reess TJ, Rus OG, et al. Diffusion tensor imaging (DTI) studies in patients with obsessive-compulsive disorder (OCD): a review. *J Psychiatr Res.* 2014;54:26-35.
- Aoki Y, Cores S, Castellanos FX. Research review: diffusion tensor imaging studies of attention-deficit/hyperactivity disorder: meta-analyses and reflections on head motion. *J Child Psychol Psychiatry.* 2017;59:193-202.
- Siehl S, King JA, Burgess N, et al. Structural white matter changes in adults and children with posttraumatic stress disorder: a systematic review and meta-analysis. *Neuroimage Clin.* 2018;19:581-598.
- Alves GS, Oertel Knöchel V, Knöchel C, et al. Integrating retrogenesis theory to Alzheimer's disease pathology: insight from DTI-TBSS investigation of the white matter microstructural integrity. *Biomed Res Int.* 2015;2015:291658.
- Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8:336-341.
- Carrasco JL, Tajima-Pozo K, Díaz-Marsá M, et al. Microstructural white matter damage at orbitofrontal areas in borderline personality disorder. *J Affect Disord.* 2012;139:149-153.
- New AS, Carpenter DM, Perez-Rodriguez MM, et al. Developmental differences in diffusion-tensor imaging parameters in borderline personality disorder. *J Psychiatr Res.* 2013;47:1101-1109.
- Gan J, Yi J, Zhong M, et al. Abnormal white matter structural connectivity in treatment-naïve young adults with borderline personality disorder. *Acta Psychiatr Scand.* 2016;134:494-503.
- Ninomiya T, Oshita H, Kawano Y, et al. Reduced white matter integrity in borderline personality disorder: a diffusion tensor imaging study. *J Affect Disord.* 2018;225:723-732.
- Buss AH, Perry M. The aggression questionnaire. *J Pers Soc Psychol.* 1992;63:452-459.
- Spielberger CD, Gorsuch RL, Lushene R, et al. Manual for the State-Trait Anxiety Inventory (Form Y). Palo Alto, CA: Consulting Psychologists Press, Inc; 1983.
- McNair D, Lorr M, Droppleman L. POMS Manual: Profile of Mood States. San Diego, CA: Educational and Industrial Testing Services; 1992.
- Fukui I. Development of depression and anxiety cognition scale: toward the construction of a cognitive-behavioral model of depression and anxiety. *Japanese Journal of Behavior Therapy.* 1998;24:57-70.
- Genc S, Smith RE, Malpas CB, et al. Development of white matter fibre density and morphology over childhood: a longitudinal fixel-based analysis. *Neuroimage.* 2018;183:666-676.
- Rolls ET. The functions of the orbitofrontal cortex. *Brain Cogn.* 2004;55:11-29.
- Zhang R, Jiang X, Chang M, et al. White matter abnormalities of corpus callosum in patients with bipolar disorder and suicidal ideation. *Ann Gen Psychiatry.* 2019;18:20. doi:10.1186/s12991-019-0243-5.
- Bubb EJ, Kinnavane L, Aggleton JP. Hippocampal-diencephalic-cingulate networks for memory and emotion: an anatomical guide. *Brain Neurosci Adv.* 2017;1:2398212817723443. doi:10.1177/2398212817723443.
- Bouziane C, Caan MWA, Tamminga HGH, et al. ADHD and maturation of brain white matter: a DTI study in medication naïve children and adults. *Neuroimage Clin.* 2017;17:53-59.
- Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: anatomy, function, and dysfunction. *Neurosci Biobehav Rev.* 2018;92:104-127.
- French JH, Shrestha S. Histrionic personality disorder. Treasure Island, FL: StatPearls Publishing; 2020.