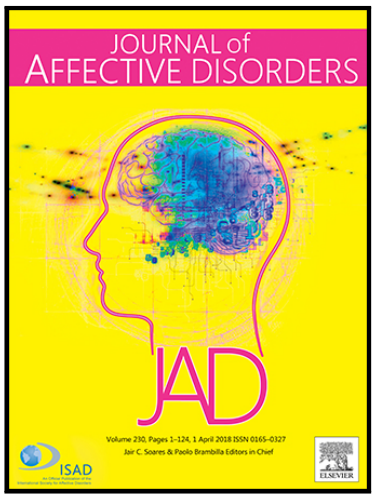

MRI features of clinical outcome in bipolar disorder: a selected review.

N. Dusi , V. De Carlo , G. Delvecchio , M Bellan , J.C. Soares , P. Brambilla

PII: S0165-0327(18)30913-3
DOI: 10.1016/j.jad.2018.05.066
Reference: JAD 9842

To appear in: *Journal of Affective Disorders*

Received date: 27 April 2018
Accepted date: 31 May 2018

Please cite this article as: N. Dusi , V. De Carlo , G. Delvecchio , M Bellan , J.C. Soares , P. Brambilla , MRI features of clinical outcome in bipolar disorder: a selected review., *Journal of Affective Disorders* (2018), doi: 10.1016/j.jad.2018.05.066

Highlights

- This review summarizes sMRI studies exploring the correlation between brain morphology and features of clinical outcome in BD.
- Morphological alterations, mainly in fronto-limbic areas, correlate with worse outcome in BD.
- Heterogeneity across studies and inconsistency on the outcome measures.

MRI features of clinical outcome in bipolar disorder: a selected review.

Dusi N.[1#], De Carlo V.[2#], Delvecchio G.[3], Bellan M[4,5], Soares J.C. [6], Brambilla P.[3,7*]

1. Psychiatry Unit, Department of Mental Health, ASST-Nord Milano, Milan, Italy
2. Department of Psychiatry, University of Milan, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via Francesco Sforza 35, 20122, Milan, Italy
3. Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
4. InterUniversity Centre for Behavioural Neurosciences (ICBN), University of Verona, Verona, Italy
5. UOC Psychiatry, University Hospital Integrated Trust of Verona (AOUI), Italy
6. Department of Psychiatry and Behavioral Sciences, UTHouston Medical School, Houston, Texas, United States of America
7. IRCCS "E. Medea" Scientific Institute, Bosisio Parini (Lc), Italy

* Address for correspondence:

Paolo Brambilla Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy (Email: paolo.brambilla1@unimi.it).

# These authors contributed equally to this article.

Key words: bipolar disorder, cognitive impairment, magnetic resonance, treatment response.

No. of Words (Abstract): 276

No. of Words (Text): 1810

No. of Tables: 2

References: 22

ABSTRACT

BACKGROUND: Bipolar disorder (BD) is a severe and disabling mental illness, which is characterized by selective gray matter (GM) and white matter (WM) brain alterations, as observed by several imaging studies. However, the clinical course of the disease is uncertain and can vary across BD patients, with some having a benign course and others a severe disability. In this perspective, magnetic resonance imaging (MRI) can help identifying biological markers of worse prognosis. **METHODS:** The present selected review aimed at summarizing structural MRI (sMRI) exploring the correlation between brain morphology and features of clinical outcome, which could include treatment response, cognitive impairment and global functioning. **RESULTS:** Overall, the results from the reviewed sMRI studies reported that WM hyperintensities and GM volume reductions, mainly in fronto-limbic areas, correlate with worse outcome in BD. However, the selected studies varied in terms of which outcome measures were selected for each investigation, thus the following observations cannot be conclusive. **LIMITATIONS:** Heterogeneity across studies and inconsistency on the outcome measures adopted limit the conclusion of the present review. Absence of widely shared definitions of outcome should be object of further research on BD in order to indicate more stable features of illness course. **CONCLUSIONS:** Identification of stable markers of illness severity, progression and prognosis may have implications in terms of diagnosis, therapy and rehabilitation strategies, potentially helping clinicians in selecting subgroups of patients who may need specific treatment to preserve cognitive / psychosocial functioning, in the light of personalized approaches. To further characterize outcome in BD, future sMRI studies should longitudinally investigate patients with either poor or good course of the disease, correlating imaging biological measures with clinical, cognitive and genetic markers.

MAIN TEXT

INTRODUCTION

Bipolar disorder (BD) is a severe and disabling mental illness, which is characterized by brain alterations involving gray matter (GM) deficits within prefrontal, parietal, and temporal lobes, along with white matter (WM) impairments, especially in superior longitudinal fasciculus and corpus callosum, as shown by several structural magnetic resonance imaging (sMRI) studies (Houenou et al., 2012). Furthermore, in recent years, sMRI studies have been carried out to investigate the neural correlates associated with functional outcome in BD (Woodward & Heckers, 2015). Indeed, imaging research represents a unique approach in the identification of markers of treatment outcome, global functioning or cognitive performance in patients with bipolar illness (Bellani et al., 2016), which may improve current treatment options. Therefore, in this selected review, we aimed at identifying studies on BD patients that explored the correlation between brain anatomy and clinical outcome, in terms of treatment response, cognitive impairment and global functioning in order to provide a brief overview on this specific topic.

METHODS

A literature search was conducted using PubMed, Psych-Info and Scopus databases. Keywords adopted were "Bipolar disorder/ disease/ illness", "outcome/ poor outcome", "functioning/ poor functioning", "response/ treatment response/ poor response", "cognition/ cognitive impairment/ poor cognition", "imaging/ magnetic resonance/ structural imaging/ structural magnetic resonance". Co-authors independently screened searches to choose potentially pertinent papers among approximately 400 ones. Afterwards, studies with a title or abstract not relevant to topic were excluded. The full text of studies selected was assessed to detect real pertinent papers. We included studies (1) published in English from January 2000 until February 2017; (2) with ≥ 17 and < 70 years old patients; (3) employing case-control and observational trials; (4) investigating the correlation between structural MRI data and outcome in BD patients, regardless of mood phase, as primary or secondary outcomes; (5) where patients had a primary diagnosis of BD, according to DSM III/ IV/ V versions, and underwent a pharmacological treatment, with or without psychotherapy. Studies were excluded if they (i) had samples formed by pediatric or <17/ ≥70 years old patients; (ii) explored brain alterations in BD without, though, linking them to features of clinical outcome, in terms of treatment response, cognitive impairment and global functioning; (iii) used any brain stimulation therapy for BD; (iv) investigated psychotic patients with different diagnoses (unipolar psychotic depression, psychotic mania, substances' induced psychosis).

Finally, as the definition of outcome was not stable across studies, we selected those studies which presented patients' outcome assessments that could include either psychopharmacological treatment resistance, or evaluation scales, which rated hospitalizations, employment, social activity, psychopathology or questionnaires of cognitive performance (cognitive tasks and intelligence evaluation test) or global functioning.

RESULTS

A total of 10 papers have been selected for inclusion. The main findings of the present selected review are shown in Table 1. The studies adopted different definitions of outcome, which included treatment response, cognitive performance and global functioning, thus determining jeopardized observations. In this section we report, first, the associations between WM morphology and features of good and poor outcome, than the association between GM morphology and good and poor outcome. The majority of the reviewed sMRI studies investigated correlations between BD outcome measures and brain WM features. Overall, these sMRI studies reported significant associations between selective WM lesions, mainly in subcortical and periventricular regions, and worse clinical course or treatment resistance (Moore et al., 2001, Regenold at al., 2008), cognitive dysfunction (Rolstadt at al., 2016), and lower global functioning (Forcada et al., 2011). Specifically, deep subcortical WM lesions were associated with poor clinical outcome (a period of at least 2 years of relapsing course of illness, while undergoing adequate treatment) (Moore et al., 2001), or treatment resistance (the average number of relapses requiring hospitalization per year over the previous five years, despite compliance with a standard treatment regimen and without the emergence or exacerbation of a comorbid disorder) (Regenold et al., 2008), while periventricular WM lesions did not correlate with either good or poor outcome (Moore et al., 2001). Interestingly, the association between WM lesions and poor outcome has also been investigated by a recent sMRI study employing a larger sample of BD patients (Rolstad et al., 2016). In this case, it has been reported an association between lower total volume of deep WM lesions and ventricular cerebrospinal fluid (CSF) and better performance in executive functions. Moreover, Forcada et al. (2011) found that greater WM volume, higher general intellectual ability (IQ), lower number of maniac episodes, were predictors of high psychosocial functioning as measured by the General Assessment of Functioning (GAF) scale. In contrast, they reported that cognitive domains, mainly memory, attention and executive functions, did not correlate with alterations in WM volume (Forcada et al., 2011). Finally, and contrary to our expectations, Krabbendam et al. (2000) did not find differences in cognitive outcome between BD patients in remission with or without deep WM lesions. The authors argued that the clinical state might have a significant effect on cognitive performance, which can mitigate the correlation between cognitive impairment and WM lesions.

With regard to GM alterations, the reviewed studies reported that cortical, including frontal and temporal areas, as well as subcortical deficits, mainly anterior cingulate and medial temporal areas, were associated with worse (Nanda et al., 2016) and recurrent (Moorhead et al., 2007, Kozicky et al., 2016) clinical course, poorer cognitive performance (Moorhead et al 2007) and lower functioning (Doris et al., 2004). In particular, Moorhead et al. (2007) found that GM volume reductions in temporal lobe had an inverse association with intellectual function and a direct correlation with the number of mood episodes. Similarly, a recent sMRI study, carried out by Kozicky et al. (2016), showed that BD patients with recurrent course of illness presented reduced GM volumes in middle, inferior, and superior temporal gyri, inferior, medial and orbital frontal gyri, anterior cingulate, parahippocampal gyrus, and inferior parietal lobule, in comparison to BD patients with good outcome. In line with this evidence, Doris et al. (2004) reported that poor outcome BD

patients (defined by means of a specific clinical rating scale, the Mc Glashan scale, which included hospitalizations, employment, social activity, psychopathology and level of functioning), reported a reduction of GM volumes in brain regions within the fronto-temporo-limbic network, mainly in the right hemisphere. Further, Nanda et al. (2016) showed a negative correlation between orbital frontal cortex (OFC) volume and impulsivity, which was considered a mediator of low global functioning and higher suicidal behavior. In contrast, a recent sMRI study by Knochel et al. (2016) did not find correlations between prefronto-temporo-limbic alterations in GM volumes and cognitive impairment, in BD patients (Knochel et al., 2016).

DISCUSSION

In summary, these results suggested that (a) WM hyperintensities correlate with poor outcome, mainly in terms of poorer cognitive performance and (b) GM lesions, particularly in regions within the prefronto-temporo-limbic network, are associated with lower global functioning and worse clinical prognosis (Table 2).

Limbic regions, including medial temporal lobe, anterior cingulate, which are involved in complex dimensions such as learning processes, have been shown to be impaired in BD (Brambilla et al., 2013). Prefrontal cortex regions, in particular OFC in the right hemisphere (Doris at al., 2004), exert a top-down control on limbic regions activity, which include emotional reactions or implicit decision-making (Nanda et al., 2016). Cingulate cortex and subgenual cingulate cortex, which modulate automatic and conscious emotional processing, take part to this network as an integration cortical-subcoritcal node. These prefronto-limbic MRI alterations might determine neuropsychological deficits, which could sustain poor psychosocial functioning and clinical outcome in severe BD patients (Dusi et al., 2017).

This hypothesis have been more widely replicated in schizophrenia spectrum disorders (Chemerinski et al., 2002; Prasad et al., 2005), but should be further investigated in BD. The lack of sufficient literature on the topic gives reason of the absence of a stable and widely accepted definition of outcome measures that take together neuropsychological deficits and clinical “real world” impairments in severe BD patients.

Nonetheless, we ought to highlight that this selection of literature presents some limitations, which influence the generalizability of results. First, the sample sizes were relatively small and the clinical characteristics of BD patients differed across studies, which included psychotic and non-psychotic BD, BD type I and type II, outpatients or inpatients, in different mood states. Second, magnetic fields also varied (0.5 T, n=1; 1.0 T, n=2; 1.5 T, n=4; 2 T, n=1; 3.0 T, n=1). Third, different methodology across studies determined different thresholds of statistical significance, due to the adoption of different correction methods for multiple comparisons. Fourth, the sample of the reviewed studies showed heterogeneous socio-demographic features, which might have played a confounding role. Both, age and gender might influence the development of brain lesions and cognitive impairments, in BD patients. Indeed, different WM alterations have been shown in

bipolar illness, compared to healthy controls, in relation to age, which might suggest an enhanced ageing effect, or a different neurodevelopmental WM trajectory, in these patients (Toteja et al., 2015). Along with age, gender might play a role in the neurobiology of BD as the disease have gender-related clinical differences in terms of clinical onset, presentations, prevalence of mood states and treatment responses (Arnold, 2003). Interestingly, imaging research in BD also reported that gender may play a key role in influencing brain structural and functional deficits within prefrontal and limbic areas (Jogia et al, 2012) as well as in vermis volumes (Serati et al., 2017). However, the majority of the studies took these effects into consideration by adding them as covariates in the statistical analysis of imaging data.

Finally, the definition of functional outcome was not consistent across studies and included several dimensions, such as treatment response, cognitive performance and global functioning. Moreover, this review should be interpreted as a critical selection of major findings on this issue, which cannot be intended as conclusive evidence, but might be considered as a hint for further research on this topic, which have been widely explored for schizophrenia but deserves larger interest in the field of BD.

In conclusion, collectively, the data reviewed above provide interesting evidence of the presence of an association between brain structural measures and functional outcome in BD. Specifically, deep WM lesions and fronto-temporo-limbic GM alterations resulted to be potential index of worse outcome in BD patients. Imaging data could represent a useful tool to design clinical outcome in addition to rating scales, ultimately helping physicians to provide a more personalized approach, including tailored pharmacotherapy and psyco-education as well as more affective and targeted rehabilitative interventions. Indeed, MRI measures might help clinicians identifying subgroups of BD patients who need specific tailored cognitive/ social rehabilitation and personalized psychopharmacological approach (Ferro et al., 2017). Finally, to further characterize BD outcome, future neuroimaging studies should longitudinally investigate chronic poor course of BD disease, correlating imaging markers with clinical ones. Potentially, longitudinal sMRI investigations could define which moderators impact on prognosis and which subgroups of BD patients undergo a progressive cognitive impairment.

Acknowledgments

PB was partially supported by grants from the Ministry of Health (RF-2011-02352308).

REFERENCES

Arnold, L.M. 2003. Gender differences in bipolar disorder. Psychiatric Clinics of North America. 26, 3, 595-620.

Bellani, M., Boschello, F., Delvecchio, G., Dusi, N., Altamura, C. A., Ruggeri, M., Brambilla, P. 2016. DTI and Myelin Plasticity in Bipolar Disorder: Integrating Neuroimaging and Neuropathological Findings. Frontiers in Psychiatry. 7, 21.

Brambilla, P., Perlini, C., Bellani, M., Tomelleri, L., Ferro, A., Cerruti, S., Marinelli, V., Rambaldelli, G., Christodoulou, T., Jogia, J., Dima, D., Tansella, M., Balestrieri, M., Frangou, S. 2013. Increased salience of gains versus decreased associative learning differentiate bipolar disorder from schizophrenia during incentive decision making. Psychol. Med. Mar; 43(3):571-80.

Chemerinski, E., Nopoulos, P.C., Crespo-Facorro, B., Andreasen, N.C., Magnotta, V. 2002. Morphology of the ventral frontal cortex in schizophrenia: relationship with social dysfunction. Biol. Psychiatry 52 (1), 1–8.

Doris, A., Belton, E., Ebmeier, K. P., Glabus, M. F., Marshall, I. 2004. Reduction of cingulate gray matter density in poor outcome bipolar illness. Psychiatry Research: Neuroimaging. 130(2), 153–159.

Dusi, N., Bellani, M., Perlini, C., Squarcina, L., Marinelli, V., Finos, L., Altamura, C.A., Ruggeri, M., Brambilla, P. 2017. . Schizophr. Res. Jan;179:104-111

Ferro, A., Bonivento, C., Delvecchio, G., Bellani, M., Perlini, C., Dusi, N., Marinelli, V., Ruggeri, M., Altamura, A.C.,Crespo-Facorro, B., Brambilla, P. 2017. Longitudinal investigation of the parietal lobe anatomy in bipolar disorder and its association with general functioning. Psychiatry Res. 30;267:22-31.

Forcada, I., Papachristou, E., Mur, M., Christodoulou, T., Jogia, J., Reichenberg, A., Frangou, S. 2011. The impact of general intellectual ability and white matter volume on the functional outcome of patients with Bipolar Disorder and their relatives. Journal of Affective Disorders. 130(3), 413–20.

Houenou, J, d'Albis,. MA., Vederine, F.E., Henry, C., Leboyer, M., Wessa, M. 2012. Neuroimaging biomarkers in bipolar disorder. Front. Biosci. 1;4:593-606.

Jogia, J., Dima, D., Frangou, S. 2012. Sex differences in bipolar disorder: a review of neuroimaging findings and new evidence. Bipolar Disorders. 14: 461-471.

Knöchel, C., Stäblein, M., Prvulovic, D., Ghinea, D., Wenzler, S., Pantel, J., Oertel-Knöchel, V. 2016. Shared and distinct gray matter abnormalities in schizophrenia, schizophrenia relatives and bipolar disorder in association with cognitive impairment. Schizophrenia Research. 171(1–3), 140–8.

Kozicky, J-M., McGirr, A., Bond, D. J., Gonzalez, M., Silveira, L. E., Keramatian, K., Yatham, L. N. 2016. Neuroprogression and episode recurrence in bipolar I disorder: A study of gray matter volume changes in first-episode mania and association with clinical outcome. Bipolar Disorders. 18(6), 511–519.

Krabbendam, L., Honig, A., Wiersma, J., Vuurman, E. F., Hofman, P. A., Derix, M. M., Jolles, J. 2000. Cognitive dysfunctions and white matter lesions in patients with bipolar disorder in remission. Acta Psychiatrica Scandinavica. 101(4), 274–80.

Moore, P. B., Shepherd, D. J., Eccleston, D., Macmillan, I. C., Goswami, U., McAllister, V. L., Ferrier, I. N. 2001. Cerebral white matter lesions in bipolar affective disorder: relationship to outcome. The British Journal of Psychiatry. 178, 172–6.

Moorhead, T. W. J., McKirdy, J., Sussmann, J. E. D., Hall, J., Lawrie, S. M., Johnstone, E. C., McIntosh, A. M. 2007. Progressive gray matter loss in patients with bipolar disorder. Biological Psychiatry. 62(8), 894–900.

Nanda, P., Tandon, N., Mathew, I. T., Padmanabhan, J. L., Clementz, B. A., Pearlson, G. D., Keshavan, M. S. 2016. Impulsivity across the psychosis spectrum: Correlates of cortical volume, suicidal history, and social and global function. Schizophrenia Research. 170(1), 80–86.

Prasad, K.M., Sahni, S.D., Rohm, B.R., Keshavan, M.S. 2005. Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. Psychiatry Res. 140 (2), 147–155

Regenold, W.T., Hisley, K.C., Phatak, P., Marano, M.C., Obuchowski, A., Lefkowitz, D.M., Sassan, A., Ohri, S., Phillips, T.L., Dosanjh, N., Conley, R.R., Rao Gullapalli, R. 2008. Relationship of cerebrospinal fluid glucose metabolites to MRI deep white matter hyperintensities and treatment resistance in bipolar disorder patients. Bipolar Disorders. 10(7): 753–764.

Rolstad, S., Abé, C., Olsson, E., Eckerström, C., Landén, M. 2016. Cognitive reserve lessens the burden of white matter lesions on executive functions in bipolar disorder. Psychological Medicine. 46(15), 3095–3104.

Serati, M., Delvecchio, G., Orsenigo, G., Perlini, C., Barillari, M., Ruggeri, M., Altamura, A.C., Bellani, M., Brambilla, P. 2017. Potential Gender-Related Aging Processes Occur Earlier and Faster in the Vermis of Patients with Bipolar Disorder: An MRI Study. Neuropsychobiology. 75:32-38

Toteja N, Guvenek-Cokol P, Ikuta T, Kafantaris V, Peters BD, Burdick KE, John M, Malhotra AK, Szeszko PR. Age-associated alterations in corpus callosum white matter integrity in bipolar disorder assessed using probabilistic tractographyBipolar Disorders. 2015 Jun;17(4):381-91.

Woodward, N. D., Heckers, S. 2015. Brain Structure in Neuropsychologically Defined Subgroups of Schizophrenia and Psychotic Bipolar Disorder. Schizophrenia Bulletin. 41(6), 1349–1359.

Table 1. Structural MRI studies on imaging fetaures of good/poor outcome among bipolar patients.

AUTHOR	SUBJECTS (Male, Female) Age mean±SD	DIAGNOSIS	OUTCOMES	IMAGING METHODS	MAIN RESULTS
Krabbendam et al., 2000	P: 22 (5, 17) 47.7±8.3y C: 22 (12, 10) 41.4±11.3y	-12 P: BD I -10 P: BD II	HAMD, YMRS, AVLT, SCWT, CST, LDST, GIT	sMRI 1.5 T Deep subcortical WM lesions, Periventricular WM lesions	No cognitive performance difference between P group with and without deep subcortical WM lesions (p< 0,05, not corrected)
Moore et al., 2001	PO: 14 (8, 7) 47.4±10.10y GO: 15 (7, 8) 42.1±13.9y C: 15 (7, 8) 41.9±12.6y	BD I	PO: unwell > 2 y, remission < 8 weeks, poor response to lithium	sMRI 0.5 T Deep subcortical WM lesions Periventricular WM lesions	PO vs GO and C: ↑ Deep subcortical WM lesions (p< 0.05, not corrected) No differences of periventricular WM lesions
Doris et al., 2004	P: 11 (6, 5) 40.5±11.6y C: 16 (7, 9) 39.1±10.5y	BD I	PO =Mc Glashan scale score >14.	sMRI 2.0 T Whole brain	PO vs C: ↓ gray matter density in frontal lobe (left middle/ left precentral/ right middle frontal gyrus), temporal lobe (right superior temporal gyrus), Parietal lobe (left inferior parietal lobule), limbic lobe (right cingulate gyrus) (p< 0.05 corrected for cluster volume)
Moorhead et al., 2007	P: (10,10) 41.5±8.9 y C: (10,11) 38.5±12.6 y	BD I	GAF, NART, RBMT, WASI, YMRS	sMRI 1.0 T Whole brain	P: ↓GM V (hippocampus, fusiform gyrus, cerebellum) correlated with ↓verbal IQ ↑ mood episodes (p< 0.05, not corrected). No correlation GM V/RBMT
Regenold et al., 2008	P: 20 (11, 7) 44.3 ± 11.8y C: 15 (5, 10) 42.5 ± 9.8 y	BD I	Acute symptom severity index (HAMD, YMRS), Treatment resistance index	sMRI 1.5 T Deep, periventricular and total WM hiperintenisities	P: Treatment resistance index correlated with ↑deep WM hyperintensities V (p< 0.05, not corrected)
Forcada et al., 2011	P: 41 (20, 21) 44.3± 11.8 y Relatives: 50 (24,26), 33.7± 12.7 y C: 10 (4, 6) 54.6 ±5.6 y	BD I Axis I: 23 No Axis I: 27	Functional outcome valued on the combined BPRS, YMRS, HAMD, GAF and IQ	sMRI 1.5 T Total intracranial V, total white matter V and total CSF V	P: ↓IQ, ↓total white matter V, predominantly depressive illness course correlated with ↓functional outcome (p< 0.002, Bonferroni correction)
Nanda et al., 2016	P: 125 (37, 88) 36.0±13.0 y C: 305 (146, 159) 37.7±12.2 y	BD I	BIS, SFS, GAF	sMRI 1.0 T OFC ROI analysis	P: ↑BIS score correlated with ↓OFC, ↑impulsivity correlated with ↑suicidal behavior, ↓SFS and GAF (p< 0.05, Benjamini-Hochberg correction)
Kozicky et al., 2016	P: 41(20, 21) 22.9±4.0 y C:25 (11, 14) 22.0±4.0 y	BD I	YMRS, GAF, HAMD	sMRI 3.0 T Whole brain	Precurr vs Pwell: ↓GM V in: -left middle and superior temporal gyri -left precentral, postcentral, inferior frontal gyri and rolandic operculum -right inferior fusiform and inferior temporal gyri -bilateral anterior cingulate and medial frontal gyri -left parahippocampal and

					fusiform gyrus -right postcentral and superior temporal gyri -left inferior parietal lobule -superior temporal pole and orbital inferior frontal gyrus ($p<0.05$ family-wise error corrected)
Rolstad et al., 2016	P: 75 (31,44) 36.5±12.2 y C: 83(42,41) 38.6±14.5 y	BD I or II	D-KEFS, WAIS-III, MADRS	sMRI 1.5 T Whole brain	P: -↑ CR reduced the influence of deep WM hypointensity V on executive performance -↑ total deep WM hypointensity V/ CSF correlated with ↓executive performance ($p<0.05$, Benjamini-Hochberg correction)
Knochel et al., 2016	P: 48 (23, 25) 38.93±9.78 y C: 57 (26, 21) 37.11±9.20 y	BD I	BDI-II, BRMAS, RHS, HVLT-R, BVMT-R, TMT, MWT-B	sMRI 3.0 T Whole brain	P: -No correlation of GM V and clinical/cognitive impairment ($p<0.01$, Bonferroni correction)

"AVLT" Auditory Verbal Learning Task, "BD": bipolar disorder, "BDI-II": Beck Depression Inventory, "BIS": Barratt Impulsiveness scale, "BPRS": brief psychiatric rating scale, "BRMAS": Bech Rafaelsen Mania Scale, "BVMT-R": Brief Visuospatial Memory Test Revised, "C": controls, "CR": cognitive reserve, "CSF": cerebrospinal fluid, "CST": the number-tracking and letter- tracking tasks of the Concept Shifting Test, "D-KEFS": Delis–Kaplan executive function system, "GAF": global assessment of functioning, "GIT": Groningen Intelligence Test, "GM": gray matter, "GO": good outcome, "HAMD": Hamilton scale for Depression, "HVLT-R": Hopkins Verbal Learning Test-Revised , "IQ": intelligence quotient, "LDST": Letter Digit Substitution Test, "MADRS": Montgomery Asberg Depression rating scale, "MWT-B": Mehrfachwahl-Wortschatztest, "NART": National Adult Reading Test, "OFC": orbitofrontal cortex, "P": patients, "PFC": prefrontal cortex, "PO": poor outcome, "RBMT": Rivermead Behavioural Memory Test, "RHS": Revised Hallucination Scale, "SCWT" Stroop Color-Word Test, "SFS": social functioning scale, "sMRI": structural Magnetic Resonance, "T": tesla, "V": volume, "TMT": Trail Making Test, "WASI", Wechsler Abbreviated Scale of Intelligence, "WAIS-III": Wechsler's Adult Intelligence Scale version III, "WM" white matter, "y": years old, "YMRS": young mania rating scale.

Table 2. MRI findings in association with different outcome domains among the reviewed studies

	Treatment response/clinical outcome	**Cognitive performance**	**Global functioning**
White matter	• ↓ Moore et al., 2001 (deep WM lesions) • ↓ Regenold et al., 2008 (deep WM lesions) • ↑ Forcada et al., 2011 (total white matter V)	• ↓ Rolstad et al., 2016 (deep WM lesions) • ↑ Forcada et al., 2011 (total white matter V)	
Gray matter	• ↑ Kozicky et al., 2016 (whole GM V) • ↑ Doris et al., 2004 (GM V in frontal, temporal lobe, parietal lobe, limbic lobes • ↑ Moorhead et al., 2007 (GM V in hippocampus, fusiform gyrus, cerebellum) • ↑ Nanda et al., 2016 (OFC V)	• ↑ Moorhead et al., 2007 (GM V in hippocampus, fusiform gyrus, cerebellum) • ↑ Nanda et al., 2016 (OFC V)	• ↑ Nanda et al., 2016 (OFC V) • ↑ Doris et al., 2004 (GM V in frontal, temporal lobe, parietal lobe, limbic lobes

GM, Gray Matter; OFC, orbitofrontal cortex; V, volume; WM, white matter; ↑, direct correlation; ↓, inverse correlation.