Title

The relationship between white matter and cognitive function in bipolar disorder: A systematic review protocol

Authors

Georgia F. Caruana^a, Sean P. Carruthers^b, Michael Berk^{d-f}, Susan Rossell^{b,c}, Tamsyn E. Van Rheenen^{a,b}

^a Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Victoria, 3053, Australia

^b Centre for Mental Health, Faculty of Health, Arts & Design, Swinburne University of Technology, Victoria, 3122, Australia

^c School of Medicine, IMPACT SRC, Deakin University, Victoria, 3216, Australia

^d Centre for Youth Mental Health and Orygen, The National Centre of Excellence in Youth Mental Health, University of Melbourne, Victoria, 3052, Australia

^e Barwon Health, University Hospital Geelong, Victoria, 3220, Australia

^f Florey Institute for Neuroscience and Mental Health, University of Melbourne, Victoria, 3052, Australia

^g St Vincent's Mental Health, St Vincent's Hospital, VIC, Australia

Contact:

GFC: gcaruana@student.unimelb.edu.au

SPC: scarruthers@swin.edu.au

Abstract

Cognitive dysfunction is becoming increasingly established as a core feature of bipolar disorder (BD), however the neural substrates underpinning these deficits remain unclear. Converging neuroimaging evidence has proposed alterations in white matter as being related to cognitive outcomes BD, yet to date, no body of work has aggregated these findings. In this systematic review protocol, we outline an approach to examine, summarise and appraise available literature investigating the relationship between cognition and white matter in BD.

N.B. The following protocol for a systematic review has been developed in accordance with the most recent PRISMA-P recommendations. The PRISMA-P checklist has been designed to assist in the preparation of a systematic reviews; particularly those focused on clinical intervention trials. The following protocol has been written as a guide for a systematic review of empirical research studies, and thus not all of the PRISMA-P recommendations are relevant. As such, various items have been omitted or exchanged for those which the authors deem more appropriate and contextual for a review of this type.

1. Introduction

Cognitive impairments, particularly in the key domains of processing speed, learning and memory, attention, and executive functioning are becoming increasingly recognised as core features of bipolar disorder (BD) (Vieta et al., 2018). Observed during the active mood states of depression and mania, and persisting through euthymia, these deficits may be considered trait-like in nature (Cardoso et al., 2015; Cullen et al., 2016). However, despite these symptoms being repeatedly observed in BD, the neurological mechanisms subserving them are yet to be fully elucidated.

Investigations into the relationship between brain and behaviour has linked cognition to white matter (WM) volume and integrity (Filley & Fields, 2016). Organised into inter and intra hemispheric tracts, WM connects cortical and subcortical grey matter regions to provide for the transfer of information within neural networks (Lebel & Deoni, 2018). Thus, WM is involved in the coordination of neural activity and subsequent behavioural functioning (Madden et al., 2009). This role of facilitating connectivity within the brain is thought to be optimal when WM tracts maintain their microstructural integrity. WM microstructure is unique in its highly organised myelinated axons that limit the diffusion of intra and extracellular water in directions other than along the main axis of the fibre (Assaf & Pasternak, 2008). The tendency of water to diffuse in one direction, termed anisotropy, reflects the integrity of the axons, myelin sheath and overall bundle coherence of WM tracts (Soares et al., 2013). WM integrity can be quantified using the specialised magnetic resonance imaging (MRI) modality diffusion weighted imaging (DWI), with four key measures contributing to its estimation; i) fractional anisotropy (FA), describing the overall magnitude of the anisotropy within the WM tracts; ii) axial diffusivity (AD), describing the tendency for diffusion along the principal direction of the axon fibre; iii) radial diffusivity (RD), describing the tendency for diffusion perpendicular to axonal walls; and iv) mean diffusivity (MD), describing the average of the principal water diffusivity in the three diffusion directions (Assaf & Pasternak, 2008). Of these measures, a decrease in FA is primarily used to suggest compromised WM tract integrity (Mori et al., 2009).

Understanding the role of WM in the context of cognition has been aided by these DWI measures, whereby variation in the FA values of various WM tracts has been associated with variation in cognitive processes (Fjell et al., 2011). In healthy individuals, FA in the frontal, parietal and temporal lobes has been correlated with processing speed, executive function and memory deficits (Roberts et al., 2013). FA in the corpus callosum has also been shown to affect the global efficiency of cognitive function (Fryer et al., 2008; Kerchner et al., 2012). In BD,

alterations in this neural circuitry have been shown, and suggest that WM may be relevant to the cognitive deficits reported in people with the disorder (Favre et al., 2019; Nortje et al., 2013).

At a macrostructural level, additional WM abnormalities include WM hyperintensities and changes to WM volume. Hyperintense WM signals can be identified via T2 MRI; these lesions representing pathologies such as demyelination, reduced glial density, cortical thinning, cerebral atrophy or hypoxia (Tomimoto, 2015). WM hyperintensities are considered to underlie cognitive and emotional dysfunction, and are associated with the BD patient population (Mahon et al., 2010). The total volume of WM in the brain, particularly hemispheric WM volume, has been regarded as a predictor of cognitive performance (Kloppenborg et al., 2014), and is also a relationship of interest in BD.

In recent years, there have been an increasing number of studies focused on the relationship between WM and cognition in BD. To date, no single body of work has yet aggregated and synthesised the findings. Therefore, a systematic review of the literature in this area is required and would make a valuable contribution to the field. The aim of this systematic review is therefore to appraise and summarise literature regarding the relationship between cognition and WM in people with BD. With this overarching objective, the proposed review will aggregate available findings to provide a description of the specific domains of cognition impacted by WM in BD, and determine the extent to which the relationships between cognition and WM differ from healthy controls. This work will look to provide insight into the possible mechanisms and directionality (e.g. by examining WM lesions, component measures of FA or measures of free water imaging) underlying the relationship between WM and cognition in people with BD. Furthermore, we aim to understand the particulars of the relationship between WM and cognition, within euthymic, depressive or manic episodes of BD, and/or across the BD diagnoses spectrum (including BD I, BDII and BD not otherwise specified (NOS)), if sufficient evidence is available.

2. Methods

2.1 Eligibility criteria

Record eligibility for inclusion in this review will be established through two screening stages.

At stage one, a record will be eligible if it is:

1. Written in English and is empirical in its format
 - a. Case reports and reviews/meta-analyses will be excluded

- b. Includes patients with formal diagnoses of BD, at any age and in any mood state, including those with:
 - i. a diagnosis of BD I, BD II or BD NOS
 - ii. in/around their first episode
 - iii. those with multiple episodes or 'established' BD
- 2. Has utilised neuroimaging methodologies to examine WM microstructure, WM hyperintensities and/or WM volume, in the context of cognition, using whole brain or region of interest approaches
- 3. Explores WM-cognition relationships
 - a. Includes general cognition, defined as non-emotional cognition, or one or more of the key domains relevant to BD, including executive functioning, processing speed, attention, verbal, visual and working memory, fluency, as tested by validated experimental measures of cognition
 - b. Includes social cognition, defined as the perception and processing of social and emotional information (e.g. emotional intelligence, facial emotion recognition and theory of mind tasks)

At stage two a full-text record will be deemed eligible for inclusion in the review if, in addition to meeting all of the stage one criteria:

- 1. The article is a peer reviewed original article, for which the full-text is available
 - a. Abstract only texts will be excluded
 - b. Case studies will be excluded
- 2. Any domain of cognition is behaviourally and objectively measured using a validated task
 - a. Cognitive tasks employed in the context of functional MRI, EEG, MEG or other psychophysiological techniques will be excluded, due to limits of neuroimaging.
- 3. WM has been measured, either microstructurally (utilising DWI, with measures reported including FA, MD, RD and AD, or utilising alternate microstructural techniques such as free water analysis) or macrostructurally (utilising MRI paradigms such as T1/T2 weighted imaging, fluid attenuation inversion recovery (FLAIR) sequence, etc, to measure WM hyperintensities and volume).
- 4. Presents the results of a BD-only analysis

- a. Cross diagnostic investigations (e.g. first episode psychosis/schizophrenia-spectrum + BD, major depressive disorder + BD etc) that report BD only analysis will be included.
 - b. Records that only report the results of a cross-diagnostic analysis will be excluded.
- 5. An independent sample is investigated
 - a. Data presented must be from an independent sample and not a re-analysis of a previously published sample. In the instance that the same sample has been analysed more than once, the first article alone will be included in the systematic review, if otherwise eligible.

2.2 Information Sources

All relevant literature published after January 1 1980 as of the date of 19 March 2021 will be accessed through the online databases PubMed, Scopus and Web of Science. The reference lists of relevant review articles will be reviewed for relevant content.

2.3 Search Strategy

The search strategy employed will be optimized for the respective database, ensuring all database specific technicalities and variations are accounted for. The record type included in this review will be restricted to published empirical articles available online. Conference abstracts will be considered under the premise of full-length companion texts being available, however abstract online conference records will be excluded.

To ensure exhaustive and rigorous methods are applied to this review, once all relevant empirical articles are accounted for, a secondary phase of this search strategy will be applied to review articles that fall within the search terms. Any review article itself will be utilised for the sole purpose of an additional search through its reference list to ensure and confirm that all pertinent articles have been viewed.

Once data collection of all eligible records is complete, the search strategy will be repeated, with a specific date restriction to those published one month before the original search commenced. This step will once again corroborate that any new records published online during the time in which the search and data collection is being undertaken have been captured prior to commencement of the final data synthesis. The specifics of the final search strategy utilised for each database will be made available in the appendix of this review's manuscript.

The search terms defined for this review were captured from the predominant keywords relevant to this field, as identified from the authors' personal files. There were selected based on the three focal concepts of this review: bipolar disorder, cognition and white matter. Combinations of the following search terms will be used in each database, with each search term truncation/wildcard searching performed as required.

Bipolar disorder

bipolar disorder, bipolar, bipolar I disorder, bipolar II disorder, mood disorders, affective disorders, mania, manic, unipolar mania, bipolar depression, depression, depressive, psychiatric disorder, psychiatry, first episode, manic episode, episode, acute manic episode, rapid cycling

Cognition

cognition, cognitive, neurocognition, neurocognitive, neuropsychology, neuropsychological, cognitive function, cognitive decline, cognitive profile, cognitive variability, cognitive ability, cognitive performance, cognitive dysfunction, cognitive impairment, cognitive deficit, cognitive switching, cognitive control, cognitive subgroups, neuropsychological subgroups, intelligence, IQ, memory, learning, attention, vigilance, inhibition, processing speed, executive functioning, flexibility, reasoning, problem solving, decision making; cognitive control

White matter

white matter, brain imaging, neuroimaging, imaging, magnetic resonance imaging, MRI, structural MRI, diffusion tensor imaging, DTI, diffusion imaging, diffusion, diffusion weighted imaging, white matter tracts, tractography, structural neuroimaging, fractional anisotropy, tract-based spatial statistics, TBSS, biomarkers, white matter lesion, white matter hyperintensities, white matter microstructure, micro-structural integrity, brain, glia, microglia, myelin, myelination, structural brain network, functional connectivity, connectivity, connectomics, connectome, white matter pathway, neuroanatomy, aging, mean diffusion, axial diffusion, radial diffusion, freewater imaging, freewater of the tensor, intracortical myelin, extracellular freewater, cellular white matter, extracellular white matter, white matter hyperintensities, white matter lesions, white matter volume

3. Study Records

3.1 Data Management

The results of this search, including all records' title, author list, abstract, keywords and provided digital article identifier (e.g. DOI, URL) will be saved and stored to EndNote citation management software. A separate directory folder will be created to save any and all review articles deemed relevant. Empirical records that are extracted from review article reference lists that are deemed relevant to this review will be cross-referenced with those saved from the primary search results. All duplicates will be removed, whilst approved records will have their identifying details entered into a digital spreadsheet, from which the checklists for proceeding screening stages can be created.

Any records that meet stage one eligibility criteria will have their full text article sourced and saved to EndNote and additional stage two records will be exported into a separate digital spreadsheet for data extraction.

3.2 Selection Process

A two-stage collaborative selection process will be conducted to establish record eligibility. Separate stage one and stage two checklists will be administered to document a record's full adherence to the aforementioned eligibility criteria. Completed checklists will be fully disclosed in the appendices of the final manuscript.

Stage one of the selection process will see to titles, abstracts and keywords undergoing an initial screen by two reviewers (GFC & SC). If a record does not have an available online abstract, the full text article will be sourced. The stage one checklist will be completed independently by each reviewer, with a consensus agreement obligatory to confirm a record's eligibility for inclusion. Any discrepancies at stage one will be discussed between the reviewers until a consensus is reached. If a consensus is unable to be accomplished TVR will serve as an adjudicator. Records that pass stage one's screening criteria will have their full text acquired.

If both reviewers deem a record to be considered but not yet confirmed due to lack of complete information, the record will proceed to stage two. At stage two, one reviewer (GFC) will screen the full text article of each record that has passed stage one's criteria. This screening will be required to meet the stage two inclusion criteria. If records do not pass this additional stage, details and reasons of their exclusion will be documented. In the instance that a record's eligibility remains to be uncertain, TVR will serve as the adjudicator once more.

A copy of the completed stage two checklist will be distributed to all authors to ensure that checklist adherence is reliable and accurate. Any final discrepancies will be discussed by all authors to meet the required full consensus agreement.

3.3 Data Collection Process

Data extraction will be conducted by primary reviewer (GFC) using a checklist, pre-approved by all authors partaking. This checklist will include all data items, as to be described in section 3.4 of this protocol. This checklist will too be included in the appendix of the final manuscript of this review. All available data items of the above noted checklist will be completed for each eligible record included in this review. Adherence to this checklist will be audited and verified by one of the remaining authors.

3.4 Data Items

Data items will be extracted and centred around the three themes: sample characteristics, methodology and cognition-white matter relationships. Within each of the above themes we will detail:

a. Sample Characteristics

Patient: sample size, age, sex, handedness, education years, diagnosis, diagnostic measure, age of illness onset, illness duration, symptom severity (symptom rating measure), number of episodes, psychosis history, current medications, hospitalisations.

Healthy controls: sample size, mean age, sex, handedness, mean education years.

b. Methodology

bi. WM analysis: it will be pertinent to record the specifics of this analysis, beginning with whether WM macrostructures or microstructures have been measured; ie/ if the study is reporting on WM integrity or WM hyperintensities/volume. Additional details relevant to the type of WM investigated will be extracted as follows:

bii. WM microstructure: approach (whole brain, ROI), processing pipeline and data acquisition (including image registration, scan length, normalisation methods, distortion and artefact correction), program and modelling (e.g. Tractography, TBSS, MRtrix, free water, graph theory), region definition

(manual or automated), measure analysed (e.g. FA, MD), use of coordinates and/or brain atlas, confounding factors, statistical analysis applied.

biii. WM macrostructure: approach (whole brain, ROI), MRI paradigm and sequences utilised (e.g. T1, T2, FLAIR imaging), processing pipeline and data acquisition (including image registration, scan length, acquisition orientation, normalisation methods, distortion and artefact correction), volumes acquired, level of contrast applied, segmentation method, white matter masks utilised, intensity thresholds, modelling programs used, confounding factors, statistical analysis applied.

biv. Cognitive function results: this review will extract and analyse the manner by which cognitive function was measured within each study; accounting for neuropsychological measures, whether a global cognitive score was utilised or if studies specified cognitive domains, notation of premorbid IQ and the relationship between cognitive performance and BD state. The overarching statistical effect size and correlation significance across all studies included will be reported upon.

bv. Other: This review will additionally outline how any WM structure-cognition relationship was analysed, significance/non-significance of relationship, appropriate statistical correction, effect sizes (cognition-structure relationship), if a HC sample is used.

c. **White Matter-cognition relationships**

Any proposed relationship between WM and cognition will be extracted, noting the type and directionality of said association, in addition to consideration of any group differences observed between BD patients who are in different phases of the illness. Furthermore, any factors driving this relationship, for example, medication effects, will too be reported on within the scope of this review.

3.5 Quality Assessment

A quality assessment will be performed on each record deemed eligible for review, during data collection. Records included in this systematic review will be evaluated in terms of their respective methodology and result transparency, using a generalised quality assessment tool was developed based upon the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. This statement will encompass the expected variability

in eligible study design (e.g. interventional, cross-sectional, case-control). For each of the eligible studies, an overall quality assessment score will be calculated by rating all applicable items of the adapted-STROBE as either: 0 (does not meet criteria), 1 (does meet criteria), or not applicable. The final score for each study will be calculated as a percentage of the total number of applicable items. A copy of the quality assessment tool is provided at the end of this protocol document.

4. Data Synthesis

4.1 Criteria for quantitative synthesis

The suitability to undertake a meta-analysis will be decided after an initial scan of the number of appropriate studies. Any sub-group analysis will be decided post-hoc, based on the suitability of the extracted data.

4.2 Qualitative Synthesis

A systematic narrative synthesis will be provided in the discussion section of this review, to address the objective outlined herein. Through text and tables, the narrative synthesis will summarise the results of the search/data collection to address the relationship between WM integrity and cognition in people with bipolar disorder (and in comparison to healthy controls), both within and between the included records. Tables will be used to summarise sample demographic characteristics, cognitive measures/domains utilised, and the statistical designs employed to understand cognition-WM relationships, and the results of these analyses for each record included in this review.

5. References

- Assaf, Y., & Pasternak, O. (2008). Diffusion Tensor Imaging (DTI)-based White Matter Mapping in Brain Research: A Review. *Journal of Molecular Neuroscience*, 34(1), 51-61. <https://doi.org/10.1007/s12031-007-0029-0>
- Cardoso, T., Bauer, I. E., Meyer, T. D., Kapczinski, F., & Soares, J. C. (2015). Neuroprogression and Cognitive Functioning in Bipolar Disorder: A Systematic Review. *Current Psychiatry Reports*, 17(9), 75. <https://doi.org/10.1007/s11920-015-0605-x>
- Cullen, B., Ward, J., Graham, N. A., Deary, I. J., Pell, J. P., Smith, D. J., & Evans, J. J. (2016). Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: A systematic review. *J Affect Disord*, 205, 165-181. <https://doi.org/10.1016/j.jad.2016.06.063>
- Favre, P., Pauling, M., Stout, J., Hozer, F., Sarrazin, S., Abé, C., Alda, M., Alloza, C., Alonso-Lana, S., Andreassen, O. A., Baune, B. T., Benedetti, F., Busatto, G. F., Canales-Rodríguez, E. J., Caseras, X., Chaim-Avancini, T. M., Ching, C. R. K., Dannlowski, U., Deppe, M., Eyler, L. T., Fatjo-Vilas, M., Foley, S. F., Grotegerd, D., Hajek, T., Haukvik, U. K., Howells, F. M., Jahanshad, N., Kugel, H., Lagerberg, T. V., Lawrie, S. M., Linke, J. O., McIntosh, A., Melloni, E. M. T., Mitchell, P. B., Polosan, M., Pomarol-Clotet, E., Repple, J., Roberts, G., Roos, A., Rosa, P. G. P., Salvador, R., Sarró, S., Schofield, P. R., Serpa, M. H., Sim, K., Stein, D. J., Sussmann, J. E., Temmingh, H. S., Thompson, P. M., Verdolini, N., Vieta, E., Wessa, M., Whalley, H. C., Zanetti, M. V., Leboyer, M., Mangin, J. F., Henry, C., Duchesnay, E., Houenou, J., & for the, E. B. D. W. G. (2019). Widespread white matter microstructural abnormalities in bipolar disorder: evidence from mega- and meta-analyses across 3033 individuals [Article]. *Neuropsychopharmacology*, 44(13), 2285-2293. <https://doi.org/10.1038/s41386-019-0485-6>
- Filley, C. M., & Fields, R. D. (2016). White matter and cognition: making the connection. *J Neurophysiol*, 116(5), 2093-2104. <https://doi.org/10.1152/jn.00221.2016>
- Fjell, A. M., Westlye, L. T., Amlien, I. K., & Walhovd, K. B. (2011). Reduced white matter integrity is related to cognitive instability. *J Neurosci*, 31(49), 18060-18072. <https://doi.org/10.1523/jneurosci.4735-11.2011>
- Fryer, S. L., Frank, L. R., Spadoni, A. D., Theilmann, R. J., Nagel, B. J., Schweinsburg, A. D., & Tapert, S. F. (2008). Microstructural integrity of the corpus callosum linked

- with neuropsychological performance in adolescents. *Brain and Cognition*, 67(2), 225-233. <https://doi.org/https://doi.org/10.1016/j.bandc.2008.01.009>
- Kerchner, G. A., Racine, C. A., Hale, S., Wilhelm, R., Laluz, V., Miller, B. L., & Kramer, J. H. (2012). Cognitive Processing Speed in Older Adults: Relationship with White Matter Integrity. *PLoS One*, 7(11), e50425. <https://doi.org/10.1371/journal.pone.0050425>
- Kloppenburg, R. P., Nederkoorn, P. J., Geerlings, M. I., & van den Berg, E. (2014). Presence and progression of white matter hyperintensities and cognition. *Neurology*, 82(23), 2127. <https://doi.org/10.1212/WNL.0000000000000505>
- Lebel, C., & Deoni, S. (2018). The development of brain white matter microstructure. *Neuroimage*, 182, 207-218. <https://doi.org/https://doi.org/10.1016/j.neuroimage.2017.12.097>
- Madden, D. J., Bennett, I. J., & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. *Neuropsychol Rev*, 19(4), 415-435. <https://doi.org/10.1007/s11065-009-9113-2>
- Mahon, K., Burdick, K. E., & Szeszko, P. R. (2010). A role for white matter abnormalities in the pathophysiology of bipolar disorder. *Neuroscience & Biobehavioral Reviews*, 34(4), 533-554. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2009.10.012>
- Mori, S., Oishi, K., & Faria, A. V. (2009). White matter atlases based on diffusion tensor imaging. *Current opinion in neurology*, 22(4), 362-369. <https://doi.org/10.1097/WCO.0b013e32832d954b>
- Nortje, G., Stein, D. J., Radua, J., Mataix-Cols, D., & Horn, N. (2013). Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder. *J Affect Disord*, 150(2), 192-200. <https://doi.org/https://doi.org/10.1016/j.jad.2013.05.034>
- Roberts, R. E., Anderson, E. J., & Husain, M. (2013). White matter microstructure and cognitive function. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, 19(1), 8-15. <https://doi.org/10.1177/1073858411421218>
- Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Frontiers in neuroscience*, 7, 31-31. <https://doi.org/10.3389/fnins.2013.00031>
- Tomimoto, H. (2015). White matter integrity and cognitive dysfunction: Radiological and neuropsychological correlations [<https://doi.org/10.1111/ggi.12661>]. *Geriatrics &*

Gerontology International, 15(S1), 3-9.

<https://doi.org/https://doi.org/10.1111/ggi.12661>

Vieta, E., Berk, M., Schulze, T. G., Carvalho, A. F., Suppes, T., Calabrese, J. R., Gao, K., Miskowiak, K. W., & Grande, I. (2018). Bipolar disorders. *Nat Rev Dis Primers*, 4, 18008. <https://doi.org/10.1038/nrdp.2018.8>

6. Appendix

Quality Assessment Checklist

		Criterion Score
Title & Abstract	Clear Study Design	Indicated the study's design with a commonly used term in the title or abstract
	Abstract Content	Provided in the abstract an informative and balanced summary of what was done/found
Introduction	Background/Rationale	Explained the scientific background and rationale for the investigation being reported
	Objectives	Stated specific objectives
	Hypotheses	Stated prespecified hypotheses in line with background rationale
Method	Design	Presented key elements of study design early in the paper
	Setting	Described the setting, location, relevant dates.
	Presented key elements of study design early in the paper	Provided eligibility criteria
	Participants - Source	Provided details of the source, setting, location from which the participants came from
	Participants - Date	Provided details of the date when data was recoded
	Participants - Matched	For matched studies - gave details on the matching criteria
	Measurement	Described all measures in sufficient detail (including best practice criteria for MRI)
	Study Size	Explained how the study size was arrived at
	Statistical Method	Described all statistical methods
Results	Missing Data	Explained how missing data were addressed
	Participants	Reported characteristics of study participants
	Missing Data	Indicated the number of participants with missing data for each variable
	Measure summary	Presented summary of all measures administered
Limitations		Summary of results in line with hypotheses
		Discusses limitations of the study.
		Total Score