Optical coherence tomography in mild cognitive impairment – systematic review and meta-analysis

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Funding: Dr Noah's PhD is funded by the British Journal of Anaesthesia

Word count: Abstract – 302; Main article 4819

Number of figures: 5

Number of tables: 2

Supplementary appendix: 1

Keywords: Retinal nerve fibre layer thickness, Mild cognitive impairment, optical coherence tomography, older people

Abstract:

Thinning of retinal layers, measured using optical coherence tomography (OCT), is associated with some neurodegenerative disorders such as established Alzheimer's disease and multiple sclerosis. The evidence for retinal layer thinning in both mild cognitive impairment (MCI), a precursor of dementia, and delirium, a potential pre-clinical stage of neurodegenerative disorder, is unclear. We performed a systematic review of the associations, in older people, between retinal layer thickness changes (measured using OCT) and delirium or MCI compared to controls (Protocol registration ID (Prospero) CRD42019122165). We did not identify any relevant studies on delirium. This report is therefore a review of retinal nerve layer changes in mild cognitive impairment. Databases were searched using predetermined keywords such as mild cognitive impairment, retinal nerve fibre layer and delirium. Where there were sufficient data, meta-analyses were performed. Twenty-six relevant studies were identified on retinal layer thickness in people with MCI compared to controls. There was significant heterogeneity in the studies for all retinal layers investigated (retinal nerve fibre layer (RNFL), ganglion cell inner plexiform layer (GCIP), foveal thickness and macular volume). Analysis of 17 studies of mean RNFL thickness in MCI (n = 622) compared to controls (n = 1154), irrespective of the type of OCT device, demonstrated a significant thinning in MCI (SMD: – 0·42 and 95%

confidence interval: - 0·68 to - 0·16). This difference was non-significant when studies using only spectral-domain devices were analysed. Subgroup analysis of studies using spectral-domain devices in amnestic MCI diagnosed using comparable criteria, showed statistically significant thinning of RNFL in amnestic MCI ($p = 0·02$). Meta-analysis of foveal thickness did not show a significant difference between MCI and controls. In conclusion, there is some evidence of an association between retinal nerve fibre layer thinning and MCI. We found no data on the association between RNFL and delirium.

Introduction

In the UK, approximately 12 million people are greater than 65 years old and the size of this age group is increasing faster than those under 65 years.[1] Whilst modern medicine is helping us live longer, the improvement in longevity leaves us with the challenge of preserving quality of life and providing excellent standards of care to an ageing population. Mild cognitive impairment (MCI), i.e. cognitive impairment with minimal impairment of instrumental activities of daily living, provides one such challenge. The prevalence of MCI is estimated as 8.4% for people aged 65 – 69 years, increasing up to 25.2% for those in the 80 – 84 years age group.[2]

The term 'mild cognitive impairment' includes several subtypes of heterogeneous aetiology and consequences.[3,4] The range of diagnostic criteria of MCI used by researchers includes Petersen's criteria, Winblad criteria, NIA-AA clinical criteria, and NIA-AA research criteria amongst others. The amnestic subtype of MCI is more tightly defined and has a more predictable association with subsequent Alzheimer's disease with a conversion rate of around 10 - 12% per year.[5] However, even within this diagnostic category there is some variability in reported outcomes.[6,7] Histopathological findings of increased neurofibrillary tangles in the neocortex and amygdala, suggestive of early Alzheimer's disease, raises

the possibility of pathological commonalities between amnestic MCI and Alzheimer's disease.[8]

Optical coherence tomography (OCT) is a non-invasive method of acquiring cross-sectional images of tissues which has evolved over the years.[9] The newer generation spectral-domain device produces higher resolution images in a shorter time than the older, time-domain OCT devices. However, both types are still currently used in clinically practice.

In Alzheimer's disease an association with thinning of the retinal nerve fibre layer (RNFL), measured using OCT, has been described.[10-12]

In view of this, and the association between thinning of the RNFL and other neurodegenerative conditions such as Parkinson's disease[13] and multiple sclerosis,[14] several investigators have explored the possibility of an association between retinal layer thinning and MCI. The results of these studies have been conflicting, perhaps due to differences in study design, OCT device used, patient selection, variable implementation of a number of diagnostic criteria of MCI, and other factors. In an attempt to achieve clarity from the available studies, some authors have conducted systematic reviews and meta-analyses where sufficient data were available, but again with conflicting results. A recent report, which included a meta-analysis of seven studies (198 MCI eyes and 309 control eyes) on mean RNFL thickness (measured using spectral-domain OCT) and MCI, demonstrated non-significant thinning of mean RNFL in MCI participants.[12] However, the review by Thomson et al, of five studies (214

MCI eyes and 421 control eyes) using either time-domain (three studies) or spectral-domain OCT (two studies) devices, showed a statistically significant thinning of the mean RNFL in MCI compared to controls ($p = 0.005$).[11] On subgroup analysis, based on type of OCT device used, the significant thinning was present only in studies which used time domain OCT devices. In Coppola et al's review, meta-analysis of three studies which used time-domain OCT devices to measure mean RNFL revealed a significant thinning, $p < 0{\cdot}0001$, associated with MCI (68 patients) compared to controls (80 patients).[10] Close scrutiny of the studies included in the reviews showed that while most were on amnestic MCI, at least four different diagnostic criteria of MCI were used.

Currently, clinical diagnosis of MCI is based on interviews and neurocognitive tests. A reliable, quick, consistent and simple screening tool may radically improve timely diagnosis and management.

Objectives

A systematic review to identify and evaluate the literature on the thickness of the different retinal layers, as measured by OCT, in people with MCI compared to controls. We also aimed to review the literature on the thickness of different retinal layers, as measured by OCT, in delirium compared to controls. We were unable to identify any studies on OCT and delirium that fulfilled our a priori criteria. Additional subgroup analysis on studies including only people with amnestic MCI was performed. We analysed each layer e.g. RNFL, ganglion cell inner plexiform layer (GCIP)

etc., independently. Meta-analyses were performed where there were a sufficient amount of homogenous data.

Methods

The protocol was registered on Prospero (Registration ID - CRD42019122165). http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019122165

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines[15] were used in structuring this report.

Eligibility criteria

Original studies published in peer reviewed journals which compared retinal layer thickness in people with delirium or MCI to controls were included. The original protocol included participants aged ≥ 65 years old but because of the variability in the methods used to report age in the studies identified, a mean age of ≥ 65 years was used. Other requirements for inclusion were 1) clear diagnostic criteria for delirium or MCI, 2) stated brand of OCT device used, 3) a control group and 4) availability of full text article. Exclusions included review articles, absence of evidence of retinal screening (history +/- ophthalmologic examination) for confounders such as glaucoma and age related macular degeneration, duplicate reporting and studies on cognitive impairment no dementia (CIND) which was not further characterised.[16]

Information sources

Published reviews

Initially a search of databases of systematic reviews was conducted to assess existing reviews and meta-analysis on OCT and delirium or MCI. Databases searched included the Database of Abstracts of Reviews of Effects (DARE), Cochrane database of systematic reviews, PubMed reviews, Medline reviews, National Institute of Clinical Excellence (NICE) evidence, Joanna Briggs Institute (JBI) database of systematic reviews and implementation report, and Prospero international prospective register of systematic reviews. We found no pre-existing reviews on OCT and delirium. Regarding MCI, reviews identified had a limited number of studies on MCI and OCT[11,12,17] or were largely focussed on retinal layers in Alzheimer's disease with MCI as a secondary subject.[11,18-20]

Current review

A literature search was conducted by two independent researchers (A.N. and D.A.). Databases queried were Medline, EMBASE, PubMed, Scopus, CINAHL, Cochrane, PsycINFO, Web of Science and TRIP. Chosen search dates (1991 for delirium and 1995 for MCI, both until March 2019) were based on the first description of OCT[9] and Petersen's original definition of MCI.[21] The references listed in identified articles and systematic reviews were also searched.

Search

The search strategy used both the search term as a keyword phrase and the relevant database's subject heading where applicable. Examples of

search terms used were mild cognitive impairment, MCI and amnestic MCI (for MCI); delirium, acute confusion, acute brain dysfunction, and toxic psychosis (for delirium); and optical coherence tomography, RNFL, ganglion cell inner plexiform layer and retinal pigmented epithelium (for OCT).

A more detailed description of our search strategy is included in the supplementary appendix.

Study selection

The results of application of the relevant Boolean operators and our article selection process is depicted in the flow charts (supplementary Figures 1 and 2). Studies that fulfilled the inclusion criteria were selected independently by two reviewers (A.N. and D.A.) and any differences resolved by discussion with IK.M.

Data collection process

Data collection was performed independently by two researchers (A.N. and D.A.) using a piloted form. Discrepancies were jointly reviewed and resolved.

Data items

Data items were collected on article information, study design, case and control selection, baseline characteristics, eye and neuropsychology screening, exclusions, diagnostic criteria of MCI or delirium, OCT device used, methodology of acquiring images, signal strength, quality

assessment, use of APOSTEL criteria (articles after 2016),[22] layers measured and findings.

A detailed list of data items collected is included in the supplementary appendix.

Risk of Bias in individual studies

The Quality Assessment for Diagnostic Accuracy Studies (QUADAS)-2 tool was used for this review.[23] Risk of bias was assessed in four domains; patient selection, index test, target condition and reference standard, and flow and timing (flow of patients through the study and timing of index test). Applicability was assessed in three domains; patient selection, index test and target condition, and reference standard. After tailoring by the researchers, the tool was applied independently (A.N. and D.A.) to the studies identified. There were no discrepancies in the individually performed risk of bias.

Summary Measures

Mean +/- SD thickness for each of the retinal layers.

Risk of Bias across studies

Retinal layer thickness is determined via segmentation and measurement by the OCT device or standalone software. Validation of these measurements by human graders is often performed. In order to identify detection bias, data were collected on whether human graders were blinded. In the absence of this information, it was unclear whether the segmentation was accepted as was from the software, in which case the

argument for blinding could be made, or whether human graders were used but not mentioned in the report. For this question in the risk of bias form, we made an assumption that if a human grader was not stated, segmentation check/adjustment was not performed, i.e. the results were from the software and therefore blinded. A further possible source of bias is the different types (time-domain vs. spectral-domain) and models of OCT device used across studies. To accommodate these differences, we analysed studies measuring retinal layers irrespective of device used and performed a subgroup analysis of studies using only spectral domain devices where there were sufficient data. Finally there was a range of diagnostic criteria for MCI used across studies and in some cases, lack of clarity about the subtype of MCI. We therefore performed a subgroup analysis of studies that used similar criteria for amnestic MCI.[4 24]

Synthesis of results and additional analysis

Pre-specified analyses were performed according to pathology (MCI, delirium) and retinal layers examined (RNFL, GCIP, macular volume). Meta-analysis was performed using Review Manager (RevMan 5.3) and R platform (version 3.5.2) for each retinal layer that had a sufficient number of comparable studies. Random effects analysis model was used. The measure of effect size was standardised mean difference (SMD) and the confidence interval (CI) was 95%. Higgins I^2 [25] was used to assess heterogeneity and a funnel plot to assess publication bias.

Results

Study selection

OCT and delirium: Of 18934 documents identified from database search, there were no documents relevant to OCT and delirium (see supplementary Figure 1).

OCT and MCI: The database search yielded 8189 documents of which 6188 were research articles. After screening of search results, 29 potential articles for consideration were identified. Review of full text resulted in exclusion of three articles; one of which was on cognitive impairment no dementia (CIND), another measured retinal thickness using confocal scanning laser ophthalmoscopy and the third article used the clinical dementia rating scale (CDR) as the grouping variable. Twenty-six articles were therefore included in this review (supplementary Figure 2). The number of articles for each retinal layer is depicted in supplementary Table 1.

Study Characteristics

The characteristics of studies included in this review are shown in Table 1.

Risk of bias within Studies

The majority of studies had low or unclear risk of bias. Under-reporting in some aspects, e.g. sampling methods, timing between neurological assessment and retinal imaging, was a common theme.

The result of the risk of bias analysis is depicted in supplementary Figures 3 and 4.

Retinal Nerve Fibre Layer (RNFL) Thickness and Mild Cognitive Impairment (MCI)

General

Twenty-one studies[17,26-45] investigated the RNFL thickness in MCI vs. controls. All studies prospectively collected retinal data. Participant sampling methods were unstated in 15 studies,[17,26-33,35,37,41-43,45] consecutive sampling in three,[34,36,44] and one study each used flyer distribution,[39] frequency matching[40] and cluster sampling.[38] The source of participants was unstated in one study[41] for the MCI group and four studies[32,37,41,43] for the control group.

MCI

Diagnostic criteria for MCI (number of studies) used were Petersen criteria (11),[26,28,32,36-39,41-44] Albert criteria (5),[29-31,40,45] Winblad criteria (2),[34,35] criteria using NIA-ADC UDS battery (1),[17] and MMSE (2).[27,33] Subtypes of MCI based on diagnostic criteria and details given in the articles included amnestic MCI (14),[17,26,28,32,34-39,41-44] MCI due to AD – Core clinical criteria (3),[29,31,45] MCI due to AD – Intermediate likelihood (1),[40] MCI due to AD – Mixed [cerebrovascular disease in 63.6%, CSF Ab amyloid and tau positive in 50% and 25% respectively - positive being within limits of international normative criteria] (1),[30] and amnestic MCI [no reference to activities of daily living] (2).[27,33]

An objective cognitive test common to both MCI group and controls was stated in 18 studies and not stated in three studies.[31,36,41]

The time interval between neurological testing and OCT was on the same day in six studies,[27-29,34,39,42] not stated in 14 studies,[26,30-33,35-38,40,41,43-45] and within a year (unclear) in one study. [17]

OCT

Of the 21 studies, spectral-domain OCT device was used in 15 [17,26,28-32,36-40,42,44,45] and time-domain in six.[27,33-35,41,43] The brands of the devices used included Cirrus (7),[26,28,36,37,39,40,42] Stratus (6),[27,33-35,41,43] Spectralis (5),[17,29-31,38] 3-D Maestro (1),[44] RTVue (1),[32] and custom built UHR-OCT (1).[45] The eyes used in the different studies were mean of both eyes in six,[26-28,39,40,42] both eyes with statistical modelling to account for paired eyes in three studies,[17,29,34] best eye in two studies,[33,35] both eyes with each counted as one in two studies,[37,41] right eye in one study,[44] right eye first choice in another,[45] and finally one random eye in three studies.[30,31,36] The choice of eye(s) was unstated in three studies.[32,38,43] Retinal images were centred on the optic disc in 18 studies, fovea in two,[30,45] and not stated in one (presumed default i.e. optic disc).[42]

Retinal segmentation was performed via the devices' platform software in 20 studies. Non-platform software was used in the remaining study.[45] A manual check for segmentation was stated or alluded to in seven studies.[17,26,29,36,39,40,44]

Findings of studies

After exclusion of the two studies with RNFL measurements centred on the fovea, there were 19 studies which reported on the mean RNFL thickness in MCI and controls, while 15[17,26,28-30,32,34-41,43,44] reported on the mean RNFL thickness for optic nerve quadrants between MCI and controls.

There was statistically significant reduction in the mean RNFL thickness in MCI compared to controls in eight studies[26,27,31,33,34,41-43,45] and no significant reduction in 11 studies.[17,28,29,32,35-40,44]

From the 15 studies that reported on RNFL quadrants, the findings are shown in table 2.

Meta-analysis RNFL

Meta-analysis was performed on studies that measured mean RNFL in the peripapillary region. Two studies[30,45] which measured the RNFL at the fovea were excluded. A further study with retinal measurements well-outside normative values for controls was also excluded.[28] A study that did not provide values for retinal measurements was also excluded.[35] The remaining 17 studies had 622 MCI cases and 1154 controls. There was significantly thinner mean RNFL in MCI compared to controls in this analysis. The standardised mean difference was -0·42 (95% CI: - 0·68 to -0·16) (p = 0·002). Significant heterogeneity was observed (Higgins I^2 – 82%) (Figure 1 and supplementary Figure 5).

RNFL in MCI compared to Controls using spectral-domain devices only

A subgroup analysis was performed which included only studies using a spectral-domain OCT device to measure RNFL, with imaging again centred on the optic disc. There were 12 studies included in this analysis with 479 participants with MCI and 986 controls. Analysis of heterogeneity yielded a Higgins I^2 of 72%. SMD was -0·22 (95% CI of -0·46 to 0·03) (p = 0·08) (Figure 2).

RNFL in amnestic MCI and Controls

A further subgroup analysis was performed including only studies that identified participants as having amnestic MCI using Petersen or Winblad criteria. Thirteen studies, with 540 MCI participants and 1036 controls, were included in this analysis. Analysis of heterogeneity yielded a Higgins I^2 value of 81%. SMD was –0·54 (95% CI of –0·82 to –0·26) (p = 0·0001) (Figure 3)

RNFL in amnestic MCI using spectral-domain OCT only

Further analysis of the amnestic MCI subgroup including studies in which only spectral-domain OCT device was used included 8 studies on 397 MCI participants and 868 controls. Higgins I^2 was 70%, SMD was –0·32 (95% CI –0·58 to –0·06) (p = 0·02) (Figure 4).

Ganglion Cell Inner Plexiform Layer (GCIP) and MCI

General

There were nine studies on GCIP in MCI vs. controls.[17,29-31,36,40,45-47] Data in all studies were prospectively collected. Participant sampling methods included consecutive in one study,[36] frequency matching in another study,[40] and was not stated in seven studies.[17,29-31,45-47] While all studies stated the source of the cases, one study did not state the source of its controls.[46]

MCI

The diagnostic criteria for MCI (number of studies) used in the studies included Albert criteria (7),[29-31,40,45-47] Petersen criteria (1)[36] and criteria using NIA-ADC UDS battery (scores falling 2 SD or more below mean) (1).[17] Based on these criteria, types of MCI (number of studies) included MCI due to AD - Core clinical criteria (5), MCI due to AD - Intermediate likelihood (1), MCI due to AD - Mixed (cerebrovascular disease in 63.6%, CSF Ab amyloid and tau positive in 50% and 25% respectively - positive being within limits of international normative criteria) (1) and amnestic MCI (2).

An objective cognitive test common to both MCI and control groups was stated in seven studies,[17,29,30,40,45-47] not stated in one (used abbreviated mental test in controls)[36] and not clearly stated in one.[31]

The time interval between cognitive assessment and retinal imaging was the same day (1),[29] within a year (1)[17] and not stated (7).[30,31,36,40,45-47]

OCT

All devices used were spectral-domain. Specific devices used included Cirrus (3),[36,40,47] Spectralis (4),[17,29-31] and one study each used Zeiss Angioplex OCTA[46] and custom built UHR OCT device.[45] Selection of eye(s) (number of studies) used included mean of both eyes (1),[40] both eyes with statistical modelling to account for paired eyes (2),[17,29] one randomly selected eye (3),[30,31,36] one eye (right eye first choice) (2)[45,46] and not stated in one.[47] The images were centred on the fovea in eight studies and optic disc in one.[31] Retinal segmentation was performed with platform software in five studies [30,36,40,46,47] and non-platform software in four.[17,29,31,45] Manual segmentation check was performed in four studies [17,29,36,40] and not stated in the remaining studies.[30,31,45-47]

Findings of studies

Of the eight studies that investigated the GCIP thickness (centred on the fovea) in MCI compared to controls, five studies[17,29-31,40,46] found no significant difference and three [36,45,47] showed statistically reduced thickness of GCIP in MCI. Six studies looked at regional GCIP thickness.[29,30,36,45-47] There was no significant reduction in thickness of regional (quadrants or sectors) GCIP in three studies[29,30,46] and the reductions reported in the MCI group in the other three studies were as follows; superior quadrant,[45] superior and inferonasal sectors,[47] and superionasal, inferior and inferotemporal sectors.[36]

Meta-analysis of GCIP in MCI compared to controls

Of the nine studies on GCIP and MCI, eight had images centred on the fovea. On further assessment of these, two were excluded on account of unclear values given for GCIP[17] and values for GCIP reported as a bar chart.[46] In the remaining six studies, GCIP was measured in an area defined by ETDRS circles (28·27mm^2 in three studies[29,30,45] and an elliptical annulus (14·13mm^2) in the remaining studies.[36,40,47] For each area type (ETDRS vs. elliptical annulus) we had complete data (mean and SD/SE) in two studies each. [29,30,36,40] The remaining two papers did not give a numerical value for spread of data.[45,47] As a result of the limited number of studies with data, meta-analysis on GCIP thickness in MCI compared to controls was not performed.

Macular and foveal thickness in MCI compared to controls

General

Five studies reported on macular thickness in people with MCI compared to controls [28,30,34,48,49] four of which included a measurement of mean foveal thickness. OCT data were collected prospectively in four studies and one was stated as retrospective.[48] Sampling methods were not stated in four studies and was consecutively performed in one study.[34] The source of cases and controls was not stated in one study.[49]

MCI

The diagnostic criteria for MCI (number of studies) were Petersen criteria (1),[28] Albert criteria (1),[30] Winblad criteria (1),[34] memory complaints and

MMSE based (1),[49] and DSM-IV criteria (1).[48] Subtypes of MCI (number of studies) were amnestic MCI (3),[28,34,48] amnestic MCI (no comment on activities of daily living) (1) [49] and MCI due to AD - Mixed (cerebrovascular disease in 63.6%, CSF Ab amyloid and tau positive in 50% and 25% respectively - positive being within limits of international normative criteria) (1).[30]

An object cognitive test common to both MCI and control groups was stated or alluded to in four studies. [28,30,34,49] This was not clearly stated in one study.[48]

Time interval between cognitive assessment and OCT (number of studies) was on the same day (2)[28,34] and not stated (3). [30,48,49]

OCT

Spectral-domain devices were used in four studies. Brands of OCT device used were Cirrus (3),[28,48,49] Spectralis[30] and Stratus.[34] Eye(s) used included both eyes (mean used) in one study,[28] both eyes with each counted as one in one study,[49] both eyes with statistical modelling to accommodate paired eyes in one,[34] right eye only in one study[48] and one random eye in one study.[30] All studies used images centred on the fovea. Retinal segmentation was performed using platform software in all studies but manual checking of segmentation was not documented in any of the studies.

Findings

Macular thickness: Three of the studies found no statistically significant difference in macular thickness between MCI participants and controls.[28,30,49] There was a statistically significant reduction in macular thickness in one study[48] and a statistically significant increase in macular inner ring thickness in participants with MCI compared to controls in another.[34]

Foveal thickness: Three of the studies did not find a significant difference in foveal thickness between participants with MCI compared to controls. [28,30,49] Foveal thickness was significantly higher in participants with MCI compared to controls in one study. [34]

Meta-analysis of foveal thickness

Of the five studies, four reported values for mean foveal thickness.[28,30,34,49] A meta-analysis was performed of mean foveal thickness in MCI (101 participants) vs controls (147) in these studies using a random effects analysis model. Analysis of heterogeneity measured by Higgins I^2 was 79%. The SMD for the four studies was 0·05 (95% CI -0·54 to 0·63) (Figure 5).

Macular volume in MCI compared to controls

General

Four studies investigated macular volume in people with MCI compared to controls.[17,26,34,40] All had OCT data collected prospectively. Patient sampling methods were not stated in two studies,[17,26] consecutive

sampling in one[34] and one study used frequency sampling.[40] Sources of cases and controls were stated in all studies.

MCI

The diagnostic criteria for MCI used included Petersen criteria in one study,[26] one study each for Winblad criteria,[34] criteria using NIA-ADC UDS battery (scores falling 2 SD or more below mean)[17] and Albert criteria.[40] Subtypes of MCI included amnestic MCI in three[17,26,34] and MCI due to AD - Intermediate likelihood in one.[40] The time interval between cognitive testing and OCT was the same day in one study,[34] not stated in two studies,[26,40] and within a year in one study.[17] There was at least one common objective cognitive test in the MCI and control groups in all studies.

OCT

Spectral-domain devices were used in three[17,26,40] studies. The OCT brands included Cirrus for two studies,[26,40] and one study each for Spectralis,[17] and Stratus.[34] Mean macular volume from both eyes was used in two studies,[26,40] and both eyes with statistical modelling to account for paired eyes was used in two studies.[17,34] Macular volume measurement was achieved using the devices' platform software in all studies and segmentation or measurement check using graders was stated in three studies and unstated in the fourth study.[34]

Findings

There was no significant difference in macular volume between participants with MCI and controls in two studies.[17,40] One study found the macular volume was statistically reduced in the MCI group[26] and the final study showed macular volume was statistically increased in MCI compared to controls.[34] Unfortunately appropriate data for analysis was only available for three studies[17,26,40] therefore a meta-analysis of macular volume was not performed.

Other retinal layers

Studies on other retinal layers are briefly reviewed here. The three studies identified were on choroid thickness,[49] macular ganglion cell complex (mGCC) (internal limiting membrane to inner nuclear layer),[32] and outer retinal layers.[50] The diagnoses of MCI according to the diagnostic criteria used were amnestic MCI[32] (mGCC study), amnestic MCI (no comments on activities of daily living)[49] (choroid thickness) and MCI due to AD - intermediate likelihood[50] (outer retinal layers). In summary, the findings of these studies were significant reduction of the choroid thickness in the MCI group, significant reduction in the macular ganglion cell complex thickness in the MCI group and no significant difference in outer retinal layers thickness between MCI group and controls.

Discussion

Our findings support the presence of RNFL thinning and MCI, particularly amnestic MCI, similar to, albeit less severe, than associations between RNFL thinning and Alzheimer's disease. We were unable to find any data

regarding delirium and retinal thickness. There was no significant difference between foveal thickness in MCI compared to controls on meta-analysis of four studies. The data are unclear on any association between GC-IPL and MCI. The data are also unclear on the association between macular volume and MCI.

To the authors' knowledge this is the first systematic review that supports the finding of statistically significant thinning of the RNFL when only spectral domain OCT devices were used.[11 12] The negative findings of other reviews may be due to the small number of studies included or perhaps a reflection of the breadth of coverage of the term 'mild cognitive impairment'.

Variability in the diagnosis and use of the term MCI has long been recognised and although efforts have been made to clarify diagnostic criteria and subtypes,[4,24,51,52] consensus diagnostic criteria adopted by all of the research and clinical community, has yet to be achieved.

There are significant concerns about the heterogeneity of studies included in this review most significantly the variations in choice and implementation of diagnostic criteria for MCI. To accommodate these differences, we performed an analysis of RNFL in people with amnestic MCI for all domain OCT devices (figures 3). This analysis included studies using Petersen criteria (10 studies) and Winblad criteria (1 study) and MMSE with no comments on ADLs (2 studies). A repeat analysis that included only studies in which amnestic MCI was diagnosed using

Petersen criteria yielded similar results (SMD -0.41, 95% CI -0.67 to -0.15) albeit with less heterogeneity (I^2 68%). Our analysis of RNFL in amnestic MCI using spectral domain devices only included studies in which Petersen criteria were used to diagnose amnestic MCI (figure 4).

It cannot be overlooked that there are other factors that could impact the thickness of nerve layers in the retina. The studies in this review went some way to address this using their exclusion criteria. Performance of ophthalmic examinations was also stated in all but two studies. Close review of the exclusion criteria revealed that while the presence of diseases associated with macular thinning such as glaucoma and age-related macular degeneration were consistently excluded, more subtle confounders such as axial length or refractive error were more sporadic considerations.

Other differences between studies included variations in retinal image acquisition, e.g. device used, choice of eye and area in retina imaged, and software packages used to measure retinal layers.

There is evidence that retinal measurements are not reproducible between different segmentation and measurement platforms.[53,54] This has been ascribed to differing segmentation algorithms however Folgar[53] showed that even in different models of OCT device made by the same manufacturer, the differences in measurements persisted, albeit to a lesser degree. In addition, normal values for the thickness of retinal layers vary with ethnicity[55,56] bringing into question the appropriateness

of combining the data from different ethnic groups. A further concern of ours is the variability in selection of eye(s). Two studies[37,41] obtained retinal layer measurements from both eyes and counted them as individual units. This may have been an effort to increase the number of data points however the fact that a pair of eyes are correlated cannot be overlooked.[57]

There is also the problem of the older person defined as aged ≥ 65 years old. Normative data for RNFL thickness in this age group covers a broad range. The RNFL thickness has previously been reported to be reduced by approximately 1.5 μm[55] to 2 μm[58] per decade. Age matching between groups, as occurred in the majority of articles in this review, may reduce this effect.

As previously mentioned, axial length and optic disc area may impact on the thickness of the RNFL.[58] These were not factored in in the studies reviewed.

The association between RNFL and MCI may have diagnostic benefits for patients. There is scope for future studies to assess the additional diagnostic power of adding OCT measurement to existing clinical criteria. Similarly, long-term follow-up may elucidate whether RNFL thinning is a biomarker of subsequent dementia following MCI.

In summary, there are no data on the possible association between retinal OCT measurements and the occurrence of delirium. Despite significant study heterogeneity and study design issues, there appears to

be a relationship between MCI, particularly amnestic MCI, and retinal nerve fibre layer thickness. A lack of sufficient studies prevents conclusions about other OCT based retinal measurements.

Conclusion

There may be a role for retinal assessment using OCT in the assessment of mild cognitive impairment, particularly amnestic mild cognitive impairment.

Acknowledgements

The authors express sincere gratitude to Jennie Spendlove for her thorough review of this manuscript.

Funding: Dr Noah's PhD is funded by the British Journal of Anaesthesia.

Conflicts of Interest: None.

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Figures legends

Figure 1: Forest plot of RNFL centred on the optic disc measured using any domain OCT device comparing MCI to controls.

Figure 2: Forest plot of RNFL centred on the optic disc measured with spectral domain OCT comparing MCI to controls.

Figure 3: Forest Plot of RNFL measured using any domain OCT device comparing amnestic MCI to controls

Figure 4: Forest plot of RNFL measured using spectral domain OCT device comparing amnestic MCI to controls

Figure 5: Forest plot of foveal mean thickness as measured using OCT in MCI vs Controls.

Supplementary Appendix legend

One supplementary appendix with the following contents:

- Search strategy with example
- List of data items collected from individual studies

- Supplementary figure 1: PRISMA flow diagram of study selection: optical coherence tomography and delirium
- Supplementary figure 2: PRISMA flow diagram of study: selection for optical coherence tomography and mild cognitive impairment
- Supplementary figure 3: Risk of Bias and applicability concerns summary: review authors' judgements about each domain for each included study
- Supplementary figure 4: Risk of Bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies
- Supplementary figure 5: Funnel plot of studies included in the meta-analysis of RNFL thickness centred on the optic disc in MCI compared to controls
- Supplementary table 1: Number of articles according to retinal layer analysed

Tables

Table 1: Characteristics of articles included in this review.

Author	Year	Country	Type of study	No. of MCI	No. of controls	Mean age of MCI	Diagnostic criteria for MCI	OCT device	OCT type	Retinal layer measured
Gao et al.[26]	2015	China	Prospective	26	21	73.4 +/- 1.5	Petersen Criteria	Cirrus HD-OCT	Spectral domain	RNFL Macula Volume
Paquet et al.[27]	2007	France	Prospective	23	15	78.7 +/- 6.2	MMSE based	Stratus OCT 3	Time domain	RNFL
Jiang et al.[46]	2018	USA	Prospective	19	21	69.6 +/- 9.8	Albert Criteria	Zeiss Angioplex OCTA	Spectral domain	GCIP
Kwon et al.[28]	2017	Korea	Prospective	30	30	72.2 +/- 5	Petersen Criteria	Cirrus HD-OCT	Spectral domain	RNFL Macular volume Macular thickness
Bulut et al.[49]	2016	Turkey	Prospective	38	44	71.7 +/- 7.4	MMSE based	Cirrus HD-OCT	Spectral domain	Choroid thickness Macular thickness
Lad et al.[29]	2018	USA	Prospective	15	18	73.1 +/- 9.1	Albert Criteria	Spectralis OCT	Spectral domain	RNFL GCIP
Querques et al.[30]	2019	Italy	Prospective	12	32	76.3 +/- 6.9	Albert Criteria	Spectralis HRA OCT	Spectral domain	RNFL GCIP (GCL + IPL) GCC Macular Thickness
Jiang et al.[47]	2018	USA	Prospective	20	21	69 +/- 8.2	Albert Criteria	Cirrus OCT	Spectral domain	GCIP
Gimenez Castejon et al.[48]	2016	Spain	Retro.	33	25	68.7 +/- 8	DSM-IV	Cirrus HD-OCT	Spectral domain	Macular Thickness
Ferrari et al.[31]	2017	Italy	Prospective	29	49	70.5 +/- 5.5	Albert Criteria	Spectralis OCT	Spectral domain	RNFL GCIP
Uchida et al.[50]	2018	USA	Prospective	22	36	68.9 +/- 6.8	Albert criteria	Cirrus HD-OCT	Spectral domain	Outer retinal layers
Wu et al.[32]	2018	China	Prospective	24	30	72.3 +/- 9.1	Petersen Criteria	RTVue	Spectral domain	RNFL mGCC
Zhang et al.[33]	2017	China	Prospective	49	49	70.9 +/- 6.1	Petersen Criteria	Stratus 3000 OCT	Time domain	RNFL
Ascaso et al.[34]	2014	Spain	Prospective	21	41	Not separately reported	Winblad Criteria	Stratus OCT 3	Time domain	RNFL Macular Thickness Macular Volume
Feke et al.[35]	2016	USA	Prospective	21	21	74.4 +/- 10.5	Winblad Criteria	Stratus OCT 3000	Time domain	RNFL
Cheung et al.[36]	2014	Singapore	Prospective	41	123	70.4 +/- 10.2	Petersen Criteria	Cirrus HD-OCT	Spectral Domain	RNFL GCIP
Kasl et al.[37]	2016	Czech Republic	Prospective	10	26	72 +/- 8	Petersen Criteria	Cirrus OCT	Spectral domain	RNFL
Knoll et al.[17]	2016	USA	Prospective	17	17	74	2 or more SD below normative NIA-ADC UDS Battery + ADLs	Spectralis HRA+OCT	Spectral domain	RNFL Macular Thickness Macular Volume

Zhu et al.[38]	2014	China	Prospective	47	167	76.1 +/- 8.2	Petersen and DSM-IV Criteria	Spectralis HRA+OCT	Spectral domain	RNFL
Shen et al.[59]	2014	China	Prospective	23	52	74.4 +/- 3.2	Petersen Criteria	Cirrus HD-OCT 4000	Spectral domain	RNFL
Pillai et al.[40]	2016	USA	Prospective	20	34	68.2 +/- 6.7	Albert Criteria	Cirrus HD-OCT 5000	Spectral domain	RNFL GCIP Macular volume
Kesler et al.[41]	2011	Israel	Prospective	24	24	71.0 +/- 10.0	Petersen Criteria	Stratus OCT 3	Time domain	RNFL
Oktem et al.[42]	2015	Turkey	Prospective	35	35	74.1 +/- 6.3	Petersen Criteria	Cirrus HD OCT 5000	Spectral domain	RNFL
Liu et al.[43]	2015	China	Prospective	26	39	70.2 +/- 6.5	Petersen Criteria	Stratus OCT 3	Time domain	RNFL
Sanchez et al.[44]	2018	Spain	Prospective	192	414	76.5 +/- 7.1	Petersen Criteria	3-D OCT Maestro	Spectral domain	RNFL
Shao et al.[45]	2018	USA	Prospective	24	21	69 +/- 8	Albert Criteria	Custom Built UHR OCT device	Spectral domain	RNFL GCIP

Abbreviations: MCI = mild cognitive impairment, OCT = optical coherence tomography, Retro. = retrospective, RNFL = retinal nerve fibre layer, GCIP = ganglion cell inner plexiform layer, mGCC = macular ganglion cell complex, ADL = activities of daily living, NIA-ADC = National Institute on Aging's Alzheimer's Disease Centre, UDS = uniform data set, UHR = ultrahigh resolution.

Table 2: Findings of studies on RNFL quadrant in MCI vs Controls

Quadrant	Significant reduction in thickness	No significant reduction in thickness	Other
Superior RNFL quadrant	4	10	1 – reduction in the superior-temporal region only
Temporal RNFL quadrant	3	11	1 – reduction in the right eye only (both eyes measured)
Inferior RNFL quadrant	2	13	
Nasal RNFL quadrant	1	14	

Abbreviations: RNFL = Retinal Nerve Fibre Layer, MCI = Mild Cognitive Impairment