TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Optical coherence tomography

Introduction

Optical coherence tomography (OCT) is an imaging technology that assesses the thickness of the peripapillary retinal nerve fibre layer, macular thickness, and volume. It has been used to assess neurologic diseases such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease, and more recently, schizophrenia.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and comprehensive reviews were included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found two systematic reviews that met our inclusion criteria[3, 4].

- Moderate quality evidence finds a medium-sized effect of thinner overall peripapillary retinal nerve fibre layer thickness in people with schizophrenia compared to controls. There were small effects of thinner nasal and temporal peripapillary retinal nerve fibre layers as well as thinner ganglion cell + inner plexiform layers in patients. There were no significant differences in superior or inferior retinal nerve fibre layers or in choroidal or macula thickness and volume.

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Lizano P, Bannai D, Lutz O, Kim LA, Miller J, Keshavan M

A Meta-analysis of Retinal Cytoarchitectural Abnormalities in Schizophrenia and Bipolar Disorder

Schizophrenia Bulletin 2020; 46: 43-53

View review abstract online

Comparison	**Retinal cytoarchitectural abnormalities in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, inconsistent, precise, direct) finds a medium-sized effect of thinner overall peripapillary retinal nerve fibre layer thickness in people with schizophrenia compared to controls. There were small effects of thinner nasal and temporal peripapillary retinal nerve fibre layers as well as thinner ganglion cell + inner plexiform layers in patients. There were no significant differences in superior or inferior retinal nerve fibre layers or in choroidal or macula thickness and volume.**
Retinal cytoarchitectural abnormalities	
A medium-sized effect of thinner overall peripapillary retinal nerve fibre layer in patients; 7 studies, N = 558, SMD = -0.51, 95%CI -0.85 to -0.17, $p < 0.05$, $I^2 = 73\%$, $p < 0.01$ There were no moderating effects of age, sex, disease duration, OCT device, and study quality. Subgroup analyses found small reductions in nasal and temporal peripapillary retinal nerve fibre layers as well as in ganglion cell + inner plexiform layers, in patients compared to controls. There were no significant differences in superior or inferior retinal nerve fibre layers or in choroidal or macula thickness and volume (volume was reduced only after adjustment for publication bias).	
Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

Pan J, Zhou Y, Xiang Y, Yu J

Retinal nerve fiber layer thickness changes in Schizophrenia: A meta-analysis of case-control studies

Optical coherence tomography

Psychiatry Research 2018; 270: 786-91 View review abstract online	
Comparison	**Assessment of retinal nerve fibre thickness changes in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, inconsistent, unable to assess precision, direct) suggests thinner retinal nerve fibre layer in people with schizophrenia.**
Retinal nerve fibre layer thickness	
Significantly thinner retinal nerve fibre layer in people with schizophrenia; 7 studies, N = 465, MD = -5.12, 95%CI -7.96 to -2.29, p = 0.0004, I^2 = 61%, p = 0.02 Subgroup analysis found reduced retinal nerve fibre layer thickness in the inferior quadrant, the nasal quadrant, and the temporal quadrant, but not in the superior quadrant. Authors report no evidence of publication bias.	
Consistency in results‡	Inconsistent
Precision in results§	Unable to assess; MDs are not standardised.
Directness of results‖	Direct

Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardised mean difference, vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[5].

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally within-group difference from pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[5].

Correlation coefficients (eg r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[6]. lnOR stands for logarithmic OR where a lnOR of 0 shows no

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difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[7].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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