TECHNICAL COMMENTARY

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Eye movement dysfunction

Introduction

Smooth pursuit eye movement is a visual tracking reflex evoked by a smoothly moving target, usually elicited by stimuli presented on a computer monitor. The aim of the smooth pursuit reflex is to maintain the image of the moving target on the fovea, the region of the retina with the highest density of photoreceptors. The neural pathways involved in generating smooth pursuit are a complex network from the cortical visual pathways through to the brainstem ocular motor nuclei (III, IV and VI), and consequently an alteration in smooth pursuit performance may not in itself shed light on the actual nature of the dysfunction.

Components of smooth pursuit which are quantified include gain in the open and closed loops, as well as rates and amplitudes for both intrusive and anticipatory saccades (fast eye movements). Closed loop gain is an index of temporal synchrony of the eye and the target during pursuit and is estimated as the ratio of the respective velocities. Open loop gain is the average acceleration during the initiation of pursuit, in the first 100ms. During this period there is no visual feedback and so the movement is solely a result of visual motion signal input. Spontaneous saccades can occur during smooth pursuit: these can either be anticipatory saccades which facilitate movement towards the target, such as reflexive visually guided saccades; or intrusive saccades, which interrupt the smooth tracking of the target, such as catch-up saccades, back-up saccades, and memory-guided saccades.

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 2010 that report results separately for people with a diagnosis of bipolar 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 version was 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 that describes a preferred way to present a meta-analysis. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. Reviews rated as having less than 50% of items checked have now 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)[1]. The resulting table represents an objective summary of the

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available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found one systematic review that met our inclusion criteria[2].

- Moderate to low quality evidence suggests reaction time and error rates in antisaccade tasks are increased, and accuracy is decreased in people with bipolar disorder compared to controls. People with major depression also show increased reaction time and error rates, with no differences in accuracy. On predictive tasks, people with bipolar disorder perform similarly to controls, while people with major depression show reduced accuracy and increased correction rates. On smooth pursuit tasks, both people with bipolar disorder and depression show less pursuit gain and more initial eye accelerations and catch-up saccades. On fixation tasks, people with bipolar disorder showed more inhibition error than controls.

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Carvalho N, Laurent E, Noiret N, Chopard G, Haffen E, Bennabi D, Vandel P

Eye movement in unipolar and bipolar depression: A systematic review of the literature

Frontiers in Psychology 2015; 6

View online review abstract

Comparison	**Eye movement dysfunction in people with bipolar disorder or major depression vs. controls.**
Summary of evidence	**Moderate to low quality evidence (large sample, unable to assess consistency or precision, direct) suggests reaction time and error rates in antisaccade tasks are increased, and accuracy is decreased in people with bipolar disorder compared to controls. People with major depression also show increased reaction time and error rates, with no differences in accuracy. On predictive tasks, people with bipolar disorder perform similarly to controls, while people with major depression show reduced accuracy and increased correction rates. On smooth pursuit tasks, both people with bipolar disorder and depression show less pursuit gain and more initial eye accelerations and catch-up saccades. On fixation tasks, people with bipolar disorder showed more inhibition error than controls.**
Saccadic eye movements	
43 studies, N > 1,000 (exact N for each outcome is unclear) Antisaccade tasks Reaction time and error rates were increased, and accuracy was decreased, in people with bipolar disorder. People with major depression showed increased reaction time and error rates, with no differences in accuracy when compared to controls. Predictive tasks No differences in reaction time, accuracy and final eye position between bipolar disorder and controls. People with major depression showed reduced accuracy and increased correction rates. Smooth pursuit tasks Both people with bipolar disorder and depression showed less pursuit gain and more initial eye accelerations and catch-up saccades. Fixation task People with bipolar disorder showed more inhibition error than controls.	
Consistency in results‡	Unable to assess; no measure of consistency is reported.

Eye movement dysfunction

Precision in results§	Unable to assess; no measure of precision is reported (CIs).
Directness of results‖	Direct

Explanation of acronyms

CI = confidence interval, N = number of participants, vs. = versus

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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[3].

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† Different effect measures are reported by different reviews.

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.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally 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) that 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[3].

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[4]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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.

‡ Inconsistency refers to differing estimates of 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, these criteria should be relaxed[5].

‖ 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 that 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 and is therefore 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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