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. Deficits in smooth pursuit and an excess of 'jerky' eye movements were one of the earliest reported phenotypes associated with schizophrenia, and smooth pursuit has since been identified as a candidate endophenotype (phenotype with a clearer genetic connection) for schizophrenia.

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 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent 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, 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

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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 to high quality evidence suggests reduced eye tracking performance in people with schizophrenia compared to controls, particularly in maintenance (closed loop) gain. Moderate quality evidence also suggests increased saccadic intrusion during eye tracking, with the effect largest for leading saccades and catch-up saccades.
- High quality evidence suggests relatives of people with schizophrenia also show impairment in closed loop gain during smooth pursuit eye movement. Moderate quality evidence suggests they show increased error rate of visually and memory guided saccades, impairment in fixational stability, and increased intrusive anticipatory saccades during smooth pursuit eye movement.

Calkins ME, Iacono WG, Ones DS

Eye movement dysfunction in first-degree relatives of patients with schizophrenia: a meta-analytic evaluation of candidate endophenotypes

Brain & Cognition 2008; 68(3): 436-461

View review abstract online

Comparison	**Comparison of measures of eye movement dysfunction in relatives of people with schizophrenia vs. non-psychiatric controls.**
Summary of evidence	**High quality evidence (large samples, precise, consistent, direct) shows relatives of people with schizophrenia have impairment in closed loop gain during smooth pursuit eye movement. Moderate quality evidence (imprecise, inconsistent) suggests relatives of people with schizophrenia also have increased intrusive anticipatory saccades during smooth pursuit eye movement.** **Moderate to high quality evidence (inconsistent) suggests relatives of people with schizophrenia show increased antisaccade error rate of visually guided saccades, longer latencies to all trials and to correct trials, but not to error trials.** **Moderate quality evidence (small to medium-sized samples, imprecise) suggests relatives of people with schizophrenia show impaired amplitude and increased error rate in memory guided saccades and impairment in fixational stability.**

Smooth pursuit eye movement

Significant, medium effect size shows relatives of people with schizophrenia were not as successful as controls at maintaining eye velocity at target velocity during closed loop;

Closed loop gain: 26 studies, N = 2247, d = -0.42, SE = 0.07, $p < 0.05$

Significant, small to medium effect size shows an increase in intrusive anticipatory saccade rate in relatives of people with schizophrenia;

Anticipatory saccades: 15 studies, N = 1317, d = 0.36, SE = 0.07, $p < 0.05$

No differences were found in generic or catch up saccade rates;

Generic saccade rate: 8 studies, N = 617, d = 0.14, SE = 0.10, $p > 0.05$

Catch up saccades: 12 studies, N = 957, d = 0.02, SE = 0.12, $p > 0.05$

Subgroup analyses revealed measures of assessing degree of impairment (global qualitative, “good” or “bad” tracking ratings vs. global quantitative, numerical ratings) showed significantly

different effects on effect size, such that the effect size yielded by qualitative ratings was greater although both methods identified deficits in smooth pursuit function. No other moderators showed significant effect on effect size, including method of assessing closed loop gain; eye movement recording method; task characteristics; or participant characteristics.
Saccadic dysfunction: reflexive visually guided saccades
Significant, medium effect sizes suggest shows antisaccade reflexive error rate, longer latencies to all and to correct trials, but not to error trials, in relatives of people with schizophrenia; Reflexive error rate: 25 studies, N = 2155: d = 0.46, SE = 0.11, $p < 0.05$ Latency to all trials: 10 studies, N = 999, d = 0.34, SE = 0.11, $p < 0.05$ Latency to correct trials: 12 studies, N = 967, d = 0.39, SE = 0.10, $p < 0.05$ Latency to error trials: 6 studies, N = 580, d = -0.16, SE = 0.12, $p > 0.05$ *No significant differences were found in reflexive visually guided saccade function;* Latency: 11 studies, N = 820, d = 0.02, SE = 0.06, $p > 0.05$ Amplitude: 6 studies, N = 286, d = -0.01, SE = 0.13, $p > 0.05$
Saccadic dysfunction: memory guided saccades
Significant, medium effect sizes show increased frequency of errors, and reduced accuracy, but not latency in relatives of people with schizophrenia; Delay errors: 5 studies, N = 171, d = 0.56, SE = 0.29, $p < 0.05$ Accuracy: 5 studies, N = 171, d = -0.66, SE = 0.18, $p < 0.05$ Latency: 4 studies, N = 139, d = 0.06, SE = 0.20, $p > 0.05$
Fixational stability
Significant, medium effect size shows relatives generate more frequent saccades off target than controls during fixation; 7 studies, N = 378, d = 0.51, SE = 0.36, $p < 0.05$

Consistency in results	Consistent for closed loop gain, reflexive error rate, latency to correct trials, and memory guided delay errors and accuracy.
Precision in results	Precise for closed loop gain and anticipatory saccades, reflexive latency, amplitude, error rate and latency to all trials.
Directness of results	Direct

O'Driscoll GA, Callahan BL

Smooth pursuit in schizophrenia: a meta-analytic review of research since 1993

Brain & Cognition 2008; 68(3): 359-370

View online review abstract

Comparison	**Comparison of measures of eye movement dysfunction in people with schizophrenia, schizoaffective or schizophreniform disorders vs. non-psychiatric healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, direct, unable to assess consistency) suggests reduced eye tracking performance in people with schizophrenia, particularly in maintenance (closed loop) gain.** **Moderate quality evidence (imprecise) suggests increased saccadic intrusion during eye tracking in people with schizophrenia, with the effect largest for leading saccades and catch-up saccades.**

Global measures of smooth pursuit

Significant, medium to large effect sizes show impaired eye tracking performance in people with schizophrenia in;

All measures

57 studies, N = 3976, *d* = -0.76, SD = 0.50, 95%CI -0.89 to -0.63, $p \leq 0.001$

Global qualitative ratings

9 studies, N not reported, *d* = 1.55, SD = 0.70, 95%CI 1.01 to 2.02, $p \leq 0.001$

Log signal/noise ratio (investigating similarity between eye trace and target trace)

4 studies, N not reported, *d* = -0.90, SD = 0.28, 95%CI -1.35 to -0.45, $p < 0.01$

Total saccade rate

16 studies, N not reported, *d* = 0.78, SD = 0.66, 95%CI 0.43 to 1.14, $p \leq 0.001$

RMS error (quantifies the cumulative distance between eye and target during pursuit)

10 studies, N not reported, *d* = 0.70, SD = 0.47, 95%CI 0.36 to 1.03, $p \leq 0.001$

Specific measures of the pursuit system

Eye movement dysfunction

Significant, medium to large effect sizes show impaired eye tracking performance in people with schizophrenia in;

Maintenance gain (closed loop)

42 studies, N not reported, *d* = -0.87, SD = 0.40, 95%CI -0.99 to -0.74, *p* ≤ 0.001

Open loop gain

12 studies, N not reported, *d* = -0.45, SD = 0.47, 95%CI -0.75 to -0.15, *p* < 0.01

Catch-up saccade rate

24 studies, N not reported, *d* = 0.47, SD = 0.42, 95%CI 0.29 to 0.64, *p* ≤ 0.001

Catch-up saccade amplitude

10 studies, N not reported, *d* = 0.38, SD = 0.35, 95%CI 0.13 to 0.62, *p* < 0.01

Lag

8 studies, N not reported, *d* = 0.49, SD = 0.43, 95%CI not reported, *p* < 0.05

No significant differences in;

Pursuit latency

8 studies, N not reported, *d* = 0.30, SD = 0.44, 95%CI -0.07 to 0.66, *p* value not significant

Residual predictive gain

5 studies, N not reported, *d* = -0.35, SD = 0.41, 95%CI -0.87 to 0.16, *p* value not significant

Peak predictive gain

5 studies, N not reported, *d* = -0.37, SD = 0.48, 95%CI -1.0 to 0.22, *p* value not significant

Specific measures of intrusive saccades

Significant, small effect sizes show impaired eye tracking performance in people with schizophrenia in;

Anticipatory saccade rate

20 studies, N not reported, *d* = 0.30, SD = 0.26, 95%CI 0.18 to 0.43, *p* ≤ 0.001

Leading saccade rate

10 studies, N not reported, *d* = 1.31, SD = 1.10, 95%CI 0.51 to 2.11, *p* < 0.01

No significant differences in;

Square wave jerk rate

15 studies, N not reported, *d* = -0.10, SD = 0.37, 95%CI -0.31 to 0.10, *p* value not significant

Back-up saccade rate

8 studies, N not reported, *d* = 0.14, SD = 0.38, 95%CI -0.18 to 0.45, *p* value not significant

Eye movement dysfunction

Consistency in results	No measure of heterogeneity is reported.
Precision in results	Imprecise for all outcomes except anticipatory saccades, catch-up saccade, maintenance gain, and qualitative ratings.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect sizes), File-drawer N = number of studies required with a null result to reverse findings, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SD = standard deviation, SE = standard error, SPEMD = smooth pursuit eye movement dysfunction, 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[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 pre to post treatment) and in a randomized 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].

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 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

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independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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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