TECHNICAL COMMENTARY

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Motor dysfunction

Introduction

Subtle deviations in various developmental trajectories during childhood and adolescence may foreshadow the later development of schizophrenia. Studies exploring these deviations (antecedents) are ideally based on representative, population-based samples that follow the cohort from birth through childhood and adolescence to adulthood. These studies can provide unique insights into the changes in developmental trajectories that may be associated with later development of schizophrenia[1].

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 given priority 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[2]. Reviews with 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)[3]. 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 three systematic reviews that met our inclusion criteria[1, 4, 5].

- High quality evidence suggests schizophrenia is associated with a medium-sized effect of delays in walking unsupported in infancy, and small effects of delays in standing and sitting unsupported in infancy.
- High quality evidence suggests youth (≤ 16 years) who developed schizophrenia in adulthood were more likely to display deficits in motor function than youth who did not develop the disorder (medium-sized effect).

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Motor dysfunction

Dickson H, Laurens KR, Cullen AE, Hodgins S

Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia

Psychological Medicine 2012; 42(4): 743-755

View review abstract online

Comparison	**Prospective or record linkage assessment of motor function in childhood and adolescence and the later development of schizophrenia.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests youth (≤ 16 years) who later develop schizophrenia in adulthood may display significant deficits in motor function than youth who do not develop the disorder.**

Motor functioning

Youth aged ≤ 16 years who subsequently developed a schizophrenia spectrum disorder displayed significant deficits in motor function compared to youth who did not develop the disorder (medium-sized effect);

4 studies, N = 7,358, d = 0.56, 95%CI = 0.38 to 0.74, $p < 0.001$, Q = 1.87, $p < 0.60$, I^2 = 0%

Consistency in results‡	Consistent
Precision in results§	Precise
Directness of results‖	Direct

Filatova S, Koivumaa-Honkanen H, Hirvonen N, Freeman A, Ivandic I, Hurtig T, Khandaker GM, Jones PB, Moilanen K, Miettunen J

Early motor developmental milestones and schizophrenia: A systematic review and meta-analysis

Schizophrenia Research 2017; 188: 13-20

View review abstract online

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Comparison	**Motor milestones in childhood and the later development of schizophrenia.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests schizophrenia is associated with a medium-sized effect of delays in walking unsupported, and small effects of delays in standing and sitting unsupported in infancy. There were no effects of holding head up or grabbing objects.**
Motor functioning	
Significant, medium-sized effect of increased risk of schizophrenia in adulthood with delayed walking unsupported in infancy; Walking unsupported: 5 cohort studies, N = 17,882, g = 0.46, 95%CI 0.27 to 0.64, $p < 0.001$, I^2 = 53.4%, p = 0.072 *Significant, small effects of increased risk of schizophrenia in adulthood with delayed standing and sitting unsupported in infancy;* Standing unsupported: 4 cohort studies, N = 17,658, g = 0.28, 95%CI 0.16 to 0.40, $p < 0.001$, I^2 = 0%, p = 0.548 Sitting unsupported: 4 cohort studies, N = 19,810, g = 0.18, 95%CI 0.05 to 0.31, p = 0.007, I^2 = 0%, p = 0.254 *There were no significant relationships between schizophrenia and holding head up and grabbing objects in infancy;* Holding head up: 3 cohort studies, N = 14,279, g = 0.10, 95%CI -0.08 to 0.15, p = 0.09, I^2 = 0%, p = 0.495 Grabbing object: 3 cohort studies, N = 14,233, g = 0.04, 95%CI -0.08 to 0.15, p = 0.55, I^2 = 0%, p = 0.422 Authors report no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Welham J, Isohanni M, Jones P, McGrath J

The Antecedents of Schizophrenia: A Review of Birth Cohort Studies

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Motor dysfunction

Schizophrenia Bulletin 2009; 35(3): 603-623 View review abstract online	
Comparison	**Prospective assessment of motor dysfunction in childhood and adolescence and the later development of schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, appears consistent, unable to assess precision, direct) suggests schizophrenia is associated with a range of motor dysfunction in childhood.**
Motor functioning	
5 birth cohorts (N = 36,837) 1 British cohort (N = 4746) reported delayed motor development at age 2 compared to controls (sitting, standing walking, teething and talking – particularly walking – measured by physician records). No differences in attainment of bladder and bowel control; Walking; difference in means = 1.2 months, $p = 0.005$. 1 British cohort (N = 12,537) reported slow to develop continence and poor coordination and vision at age 7 ($p < 0.01$ measured by parental assessment). At age 11, more likely than controls to be recorded as incontinent – no difference in vision and motor coordination (physician measured). At age 16, more likely to be rated as clumsy ($p < 0.01$ - physician measured). 1 Finish cohort (N = 10,569) reported delayed learning to stand, walk, speak and attaining continence at age 1 (health worker measured). At age 16, for those who later developed schizophrenia, late learning to stand was associated with poor school performance. 1 US cohort (N = 8013) reported unusual movements at age 4 and 7 (tremors, tics, spasms or athetoid movements – measured by standardised psychological and neurological examinations) and poor gross and fine motor co-ordination at age 7. Absence of expected developmental decline in unusual movements. 1 New Zealand cohort (N = 972) reported delay in walking at age 3 (measured by maternal retrospective recall, Bayley Motor Scales and pediatric neurologist) adjusted for sex and socio-economic status. At age 3, females only had poorer motor skill (Basic Motor Ability Test) and more neurologic signs (OR = 4.6, McCarthy Motor Scales). At age 3, no differences for other infant milestones; smiling, sitting up, continence, fed self, talking words and sentences. At age 5 and 9, but not at age 7, females had poorer motor skill (Basic Motor Ability Test).	
Consistency in results	Appears consistent
Precision in results	Unable to assess; CIs are not reported.
Directness of results	Direct

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Explanation of acronyms

CI = Confidence Interval, *g* = Hedges g standardised mean difference, I^2 = degree of heterogeneity between study results, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant)

Motor dysfunction

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[6].

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† 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 randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized 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[6].

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[7]. 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.

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.

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).

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.

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‡ 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[6];

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

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§ 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[8].

‖ 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 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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