TECHNICAL COMMENTARY

Minor physical anomalies

Introduction

Minor physical anomalies (MPAs) are subtle anatomical deviations which have little functional or aesthetic impact. MPAs in people with schizophrenia are highly variable, but may include high palate, low-seated ears, cuspidal ear (ears with angled ridges instead of a round curve at the top of the opening into the ear canal), strabismus (cross-eyes), hypertelorism (increased distance between the eyes) and adherent, or attached ear lobes. They may be traced to events occurring prenatally and may represent risk markers for underlying illness susceptibility. MPAs may be important risk indicators when an individual is already at high risk of developing psychosis (for example, having a first-degree relative with psychosis) and when multiple MPAs occur together in one individual[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 were assigned a low, medium or high possibility of reporting bias* depending on how many items

were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. 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 (RCT) 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).

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Results

We found two systematic reviews that met our inclusion criteria[1, 4].

- Moderate to high quality evidence finds a large increase in overall MPA scores in people with schizophrenia compared to controls There were also increased MPA scores in people with schizophrenia compared to relatives, with no differences between relatives and controls.

- Moderate quality evidence suggests MPA frequency is increased in six regions: head, eyes, ears, mouth, hands and feet. Specific MPAs include tongue with irregular smooth-rough spots, single transverse palmar crease (one crease extending across the palm of the hand), syndactyly (wholly or partially united) 2nd and 3rd toes, malformed ears, low set ears, smaller head circumference, and curved fifth finger.

Weinberg SM, Jenkins EA, Marazita ML, Maher BS.

Minor physical anomalies in schizophrenia: a meta-analysis

Schizophrenia Research 2007; 89(1-3): 72-85

View review abstract online

Comparison	MPA scores, measured using the Waldrop scale or a variant, in people with schizophrenia vs. controls.
Summary of evidence	Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests MPA scores are significantly increased in schizophrenia patients.
	Moderate quality evidence (large sample, mostly inconsistent, imprecise, direct) suggests MPA frequency is significantly increased in six regions: head, eyes, ears, mouth, hands and feet. Magnitude of increases was greatest for craniofacial regions including mouth, head and eyes.

MPA scores

Significant, large effect of increased MPA scores in people with schizophrenia;

11 case-control studies, N = 1,903, $^{\dagger}g$ = 1.131, 95%CI 0.762 to 1.501, $p < 0.001$, Q = 128.33, $p < 0.001$

Significant, small to medium-sized increased odds of region-specific MPAs in people with schizophrenia, with no significant differences between regions;

7 case-control studies, N = 873

Head: OR = 2.55, 95%CI 2.02 to 3.21, $p < 0.05$, Q = 3.984, p = NS

Eyes: OR = 2.47, 95%CI 1.45 to 4.21, $p < 0.05$, Q = 16.705, $p \leq 0.01$

Ears: OR = 1.42, 95%CI 1.01 to 2.00, $p < 0.05$, Q = 16.192, $p \leq 0.05$

Mouth: OR = 2.65, 95%CI 1.38 to 5.10, $p < 0.05$, Q = 40.474, $p \leq 0.001$

Hands: OR = 2.14, 95%CI 1.28 to 3.58, $p < 0.05$, Q = 19.555, $p \leq 0.01$

Feet: OR = 2.15, 95%CI 1.38 to 3.35, $p < 0.05$, Q = 12.978, $p \leq 0.05$

Q_b = 8.359, p = 0.14

Consistency in results[‡]	Inconsistent, significant heterogeneity reported for all outcomes except consistent for Q_b and head measurements.
Precision in results[§]	Precise for overall score, imprecise for regional scores

Directness of results‖	Direct comparison and measures

Xu T, Chan RCK, Compton MT **Minor Physical Anomalies in Patients with Schizophrenia, Unaffected First-Degree Relatives, and Healthy Controls: A Meta-Analysis** **PLoS 2011; 6(9): e24129** View review abstract online	
Comparison 1	**MPA scores, measured using the Waldrop scale or a variant, in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a large increase in overall rates of MPAs in people with schizophrenia compared with controls. The following MPAs were observed more often in patients: tongue with smooth-rough spots, single transverse palmar crease, syndactyly of 2nd and 3rd toes, malformed ears, low set ears, smaller head circumference, curved fifth finger.**

MPA scores

A significant, large effect of increased overall MPAs in people with schizophrenia,

14 studies, N = 2,214, d = 0.95, 95%CI 0.63 to 1.27, $p < 0.05$, Q = 150.56, $p < 0.001$

Authors report no difference in results based on the scale used (Waldrop Scale or Modified Waldrop Scale), and sex ratio.

Significant differences were reported for the following MPAs;

10 case-control studies, N = 873

Tongue with smooth-rough spots: 5 studies, N = 594, OR 9.86, 95%CI 2.79 to 34.91, $p < 0.0001$, Q = 0.84, $p > 0.05$

High/steepled palate: 7 studies, N = 1315, OR 5.12, 95%CI 3.00 to 8.75, $p < 0.0001$, Q = 28.26, $p < 0.001$

Single transverse palmar crease: 9 studies, N = 1620, OR 4.77, 95%CI 2.47 to 9.21, $p < 0.0001$, Q = 14.11, $p > 0.05$

Furrowed tongue: 9 studies, N = 1555, OR 4.28, 95%CI 2.43 to 7.55, $p < 0.0001$, Q = 17.85, $p < 0.05$

Syndactyly of 2nd and 3rd toes: 5 studies, N = 730, OR 4.11, 95%CI 1.31 to 12.87, $p = 0.015$, Q =

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4.54, *p* > 0.05

Malformed ears: 6 studies, N = 964, OR 3.87, 95%CI 1.80 to 8.29, *p* = 0.001, Q = 1.89, *p* > 0.05

Epicanthus: 9 studies, N = 1710, OR 3.74, 95%CI 2.16 to 6.50, *p* < 0.0001, Q = 25.51, *p* < 0.01

Low set ears: 8 studies, N = 1179, OR 2.62, 95%CI 1.25 to 5.53, *p* = 0.011, Q = 4.16, *p* > 0.05

Cleft palate: 4 studies, N = 440, OR 2.52, 95%CI 1.13 to 5.59, *p* = 0.024, Q = 11.46 *p* < 0.01

Telecanthus: 7 studies, N = 964, OR 2.34, 95%CI 1.30 to 4.21, *p* = 0.005, Q = 29.85, *p* < 0.001

Smaller head circumference: 5 studies, N = 648, OR 2.17, 95%CI 1.12 to 4.23, *p* = 0.022, Q = 1.74, *p* > 0.05

Curved fifth finger: 7 studies, N = 877, OR 2.04, 95%CI 1.19 to 3.50, *p* = 0.010, Q = 11.33, *p* > 0.05

No significant differences were reported for the following MPAs:

Fine hair: 3 studies, N = 391, OR 2.30, 95%CI 0.89 to 5.97, *p* = 0.086, Q = 5.08, *p* > 0.05

3rd toe longer than 2nd: 3 studies, N = 301, OR 2.25, 95%CI 0.52 to 9.68, *p* = 0.278, Q = 2.04, *p* > 0.05

Hair whorls: 5 studies, N = 832, OR 2.14, 95%CI 0.97 to 4.69, *p* = 0.059, Q = 5.33, *p* > 0.05

Soft and pliable ears: 3 studies, N = 391, OR 2.07, 95%CI 0.66 to 6.53, *p* = 0.212, Q = 2.26, *p* > 0.05

3rd toe equal to 2nd: 4 studies, N = 513, OR 2.01, 95%CI 0.71 to 5.69, *p* = 0.187, Q = 2.70, *p* > 0.05

Asymmetrical ears: 6 studies, N = 1019, OR 1.84, 95%CI 0.80 to 4.26, *p* = 0.152, Q = 1.88, *p* > 0.05

Big gap between 1st and 2nd toes: 6 studies, N = 730, OR 1.43, 95%CI 0.76 to 2.68, *p* = 0.267, Q = 11.38, *p* < 0.05

Adherent ear lobes: 9 studies, N = 1623, OR 1.26, 95%CI 0.78 to 2.03, *p* = 0.343, Q = 7.82, *p* > 0.05

Consistency in results	Inconsistent for: overall score, high/steepled/cleft palate, furrowed tongue, epicanthus, telecanthus, big gap between 1st and 2nd toes
Precision in results	Precise for overall score, imprecise for individual MPAs
Directness of results	Direct
Comparison 2	**MPA scores, measured using the Waldrop scale or a variant, in relatives of people with schizophrenia vs. controls**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests no differences in MPAs between relatives of people with schizophrenia and controls.**
MPA scores	

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No significant differences in overall MPA scores between relatives and controls; 6 studies, N = 569, d = 0.32, 95%CI -0.08 to 0.73, $p > 0.05$, Q = 32.03, $p < 0.01$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**MPA scores, measured using the Waldrop scale or a variant, in people with schizophrenia vs. first-degree relatives of people with schizophrenia.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests MPA scores are significantly increased in people with schizophrenia compared to relatives.**
MPA scores	
Significant, medium size effect of increased overall MPA scores in patients compared to relatives; 6 studies, N = 642, d = 0.45, 95%CI 0.29 to 0.62, $p < 0.05$, Q = 5.04, $p = 0.41$	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, d = Cohen's d and g = Hedges' g = standardized mean differences (see below for interpretation of effect size), MPAs = minor physical anomalies, N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity, Q_b = Q statistic for between group heterogeneity, 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].

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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. 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 effect[5].

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, a 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. A 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.

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).

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

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population sample and its age structure over the duration of observation.

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 independent 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 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. I² 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 be considerable heterogeneity and over this is considerable heterogeneity. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[5];

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

§ 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[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 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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