TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Familial physical features

Introduction

First-degree relatives of people with schizophrenia may show attenuated signs of the illness, such as physical features commonly identified with the disorder. These may include structural and/or functional anomalies as well as movement disorders. This topic also considers the incidence of other physical conditions (including cancer) in relatives of people with 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, 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[1]. 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)[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 18 systematic reviews that met our inclusion criteria[3-20].

- High quality evidence suggests a decreased incidence of any cancer in parents and siblings of people with schizophrenia compared to the general population.

Structural anomalies

- Moderate to high quality evidence suggests relatives of people with schizophrenia may have greater pituitary volume, reduced hippocampal and total grey matter volume and third ventricle volume. Moderate quality evidence also suggests reductions in bilateral anterior cingulate gyrus, right insula,

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

left amygdala, left subcallosal gyrus and left inferior frontal gyrus.

Functional anomalies

- High quality evidence shows relatives have impairment in closed loop gain during smooth pursuit eye movement tasks. Moderate to high quality evidence also suggests increased intrusive anticipatory saccades, impairment in fixational stability, and increased error rate in visual and memory guided saccades.
- Moderate to high quality evidence finds large effects of increased P50 ratio and reduced P50 suppression, a medium-sized effect of reduced P300 amplitude, a small to medium-sized effect of longer latency, and a small trend effect of reduced MMN amplitude in relatives of people with schizophrenia.
- Moderate quality evidence suggests increased activation during cognitive tasks in the right inferior frontal gyrus. There was altered activation during cognitive control tasks in the left middle frontal gyrus, dorsolateral prefrontal cortex, parietal cortex, and the thalamus. During working memory tasks, relatives show altered activation in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, parietal cortex, and the cerebellum. During language processing, relatives show altered activation in the right ventrolateral prefrontal cortex, and the parietal cortex. During executive functioning tasks, there is increased activation in the right superior and middle frontal gyri, right thalamus, left inferior parietal cortex, and left precuneus. Decreased activation is found in the right middle, inferior, and left superior frontal gyri, the right precentral gyrus, right lingual gyrus, left thalamus, right parietal cortex, left medial frontal and cingulate gyri, left superior temporal gyrus, and the left cerebellum.
- Moderate to high quality evidence shows a large effect of increased neurological soft signs (NSS), and a small increase in the risk of dyskinesia and parkinsonism in relatives.
- Moderate to high quality finds a medium-sized increase in glutamate+glutamine in the frontal lobes of relatives. Moderate to low quality evidence suggests reduced glutamate/glutamine ratio in the dorsolateral prefrontal cortex of relatives, and reduced N-Acetylaspartate/creatine ratio in the anterior cingulate cortex and hippocampus of relatives.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Aiello G, Horowitz M, Hepgul N, Pariante CM, Mondelli V

Stress abnormalities in individuals at risk for psychosis: A review of studies in subjects with familial risk or with ‘‘at risk’’ mental state

Psychoneuroendocrinology 2012; 37: 1600-1613

View review abstract online

Comparison	**Hypothalamic-pituitary-adrenal (HPA) axis abnormalities in relatives of people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (medium to large samples, unable to assess precision, appears consistent, direct) suggests relatives of people with schizophrenia may display abnormalities in HPA axis function and reduced hippocampal brain volume.**

Stress response/reactivity

2 studies reported increased emotional reactivity to stress in relatives;

1 study, N = 87 reported a significant association between levels of emotional sensitivity to stress in patients and in their siblings and a significant association between positive symptoms in patients and stress reactivity in siblings.

1 study, N = 138 reported that higher levels of familial risk for psychosis correlates with higher levels of emotional sensitivity to daily stress.

1 of 3 studies reported increased cortisol levels in relatives compared to controls;

1 study, N = 123 reported higher cortisol stress response and higher cortisol during the day in siblings compared to controls.

1 study, N = 151 reported increased cortisol and HVA response in patients compared to controls, but no difference in relatives compared to controls.

1 study, N = 44 reported no difference in cortisol levels in response to adrenocorticotropic hormone (ACTH) or homovallinic acid (HVA) between relatives and controls.

Pituitary

1 of 2 studies reported larger pituitary in relatives;

1 study, N = 183 reported larger pituitary (measured with MRI) in relatives of schizophrenia than in controls, with largest pituitary in patients on antipsychotics.

1 study, N = 130 reported significantly larger pituitary (measured with MRI) in people with schizophrenia, but no difference between relatives and controls.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Hippocampus	
11 studies reported reduced hippocampus volume in relatives compared to controls; 1 study (N = 80) reported no difference in hippocampal volume between affected and unaffected monozygotic twins, but smaller hippocampus compared to controls. Affected dizygotic twins had smaller hippocampus than their unaffected twin. Another study (N = 41) reported that in monozygotic twins discordant for schizophrenia, the affected twin had a smaller hippocampus than the unaffected twin. 4 studies (N = 465) reported hippocampus volume reduction in both relatives and patients compared to controls. One of these studies (N = 109) reported no difference between schizophrenic probands and their unaffected monozygotic and dizygotic twins. 1 study (N = 138) reported smaller hippocampus (correlating with obstetric complications) and shape abnormalities in the anterior hippocampus in relatives and patients compared to controls. 2 studies (N = 273) reported bilateral hippocampus/amygdala/ thalamus volume reduction in relatives and patients compared to controls. 1 study, (6 families, total N unclear) reported smaller hippocampus amygdala complex in obligate carriers (unaffected, who have affected parent and child), and in affected patients compared to unaffected relatives. 2 studies (N = 209) reported reduced hippocampus volume in relatives, which showed positive correlation with cognitive and memory ability. 4 studies (N = 1,576) reported no differences in hippocampal volume in relatives compared to controls.	
Consistency in results‡	Unable to assess; appears consistent for hippocampus volume.
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct

Boos HB, Aleman A, Cahn W, Hulshoff Pol H, Kahn RS

Brain volumes in relatives of patients with schizophrenia: a meta-analysis

Archives of General Psychiatry 2007; 64(3): 297-304

View review abstract online

Comparison 1	**Whole brain investigation in first degree relatives of people with schizophrenia vs. healthy controls.**

Familial physical features

Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent, precise, direct) suggests first degree relatives of people with schizophrenia have reduced hippocampal and total grey matter volume and third ventricle volume compared to controls.**
Total brain volume	
No significant effect on total brain volume in first degree relatives; 13 studies, N = 1238, *d* = 0.28, 95%CI -0.02 to 0.57, Q = 63.99, *p* < 0.001	
Lateral ventricles	
No significant effect on volume of lateral ventricles in first degree relatives; 7 studies, N = 779, *d* = 0.11, 95%CI -0.05 to 0.27, Q = 5.85, *p* = 0.44	
Third ventricle volume	
Small effect size for decreased third ventricle volume in first degree relatives; 7 studies, N = 832, *d* = 0.21, 95%CI 0.03 to 0.40, *p* < 0.05, Q = 8.31, *p* = 0.22	
Cerebral spinal fluid volume	
No significant effect on cerebral spinal fluid volume for first degree relatives; 4 studies, N = 217, *d* = 0.61 95%CI 0.08 to 1.14, Q = 9.81, *p* = 0.02	
Grey matter volume	
Small effect size of decreased grey matter volume in first degree relatives; 7 studies, N = 534, *d* = 0.18, 95%CI 0.02 to 0.33, *p* < 0.05, Q = 4.68, *p* = 0.70	
White matter volume	
No significant effect on white matter volume in first degree relatives: 7 studies, N = 529, *d* = 0.40, 95%CI -0.04 to 0.83, Q = 33.25, *p* < 0.001	
Amygdala and hippocampus volume	

Medium combined effect size of decreased amygdala and hippocampus volume in first degree relatives; 12 studies, N = 1,280, *d* = 0.52, 95%CI 0.16 to 0.89, *p* < 0.05, Q = 94.17, *p* < 0.001	
Hippocampal volume	
Small effect size of decreased total hippocampal volume in first degree relatives; 9 studies, N = 1,024, *d* = 0.31, 95%CI 0.13 to 0.49, *p* < 0.05, Q = 13.79, *p* = 0.09	
Medium effect size of decreased left hippocampal volume in first degree relatives; 9 studies, N = 943, *d* = 0.47, 95%CI 0.34 to 0.61, *p* < 0.05, Q = 6.56, *p* = 0.58	
Small effect size of decreased right hippocampal volume in first degree relatives; 9 studies, N = 943, *d* = 0.23, 95%CI 0.01 to 0.96 *p* < 0.05, Q = 19.43, *p* = 0.01	
Consistency in results	Inconsistent for total volume, CSF volume, white matter volume, amygdala and hippocampus volume Consistent for all other outcomes
Precision in results	Precise for all outcomes except CSF volume and right hippocampal volume
Directness of results	Direct comparison of whole brain volume in first degree relatives of people with schizophrenia and healthy controls
Comparison 2	**Volumetric comparison of hippocampus in first degree relatives of people with schizophrenia vs. people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests that people with schizophrenia have reduced hippocampal volume, compared to first degree relatives people with schizophrenia.**
Hippocampal size	
Medium effect size for decreased hippocampal volume in people with schizophrenia: 9 studies, N = 846, *d* = 0.43, 95%CI 0.17 to 0.68, Q = 22.28, *p* = 0.004	
Consistency in results	Inconsistent
Precision in results	Precise

Directness of results	Direct comparison of whole brain volume in people with schizophrenia and first-degree relatives of people with schizophrenia

Bramon E, McDonald C, Croft RJ, Landau S, Filbey F, Gruzelier JH, Sham PC, Frangou S, Murray R.M

Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study

NeuroImage 2005; 27: 960-968

View online review abstract

Comparison 1	**Comparison of P300 ERP amplitude and latency (measured as the mean response of PZ and CZ electrodes) in non-psychotic relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests P300 amplitude is reduced and latency is increased in relatives.**
P300 amplitude	
11 studies, N = 985 *Medium effect sizes suggest reduced P300 amplitude, and increased (delayed) latency in relatives:* Amplitude: d = 0.61, 95%CI 0.30 to 0.91, $p < 0.001$ Latency: d = -0.50, 95%CI -0.88 to -0.13, p = 0.009	
Consistency in results	Significant between-study heterogeneity reported for amplitude, $p < 0.001$, and for latency, $p = 0.02$.
Precision in results	Precise
Directness of results	Direct comparison of P300 amplitude and latency in non-psychotic relatives and controls
Comparison 2	**Comparison of P300 ERP amplitude and latency in people with schizophrenia vs. non-psychotic relatives of people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests P300 amplitude is reduced and latency is increased in people with schizophrenia compared to their non-**

	psychotic relatives.
P300 amplitude	
9 studies, N = 579 *Small effect sizes suggest greater reduction in P300 amplitude, and increased (delayed) latency in patients:* Amplitude: d = 0.39, 95%CI 0.05 to 0.73, p = 0.03 Latency: d = -0.28, 95%CI -0.45 to -0.12, p < 0.01	
Consistency in results	Significant between-study heterogeneity reported for amplitude, p = 0.02, and for latency, p < 0.01
Precision in results	Precise for all outcomes
Directness of results	Direct comparison of P300 amplitude and latency in non-psychotic relatives and controls

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 (medium to large samples, consistent, precise, direct) shows relatives of people with schizophrenia show impairment in closed loop gain during smooth pursuit eye movement. Moderate quality evidence (imprecise, inconsistent) suggests relatives of people with schizophrenia show 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 to high quality evidence (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	
Medium effect size suggests 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 = 2,247, *d* = -0.42, SE = 0.07, *p* < 0.05 *Small to medium effect size shows an increase in intrusive anticipatory saccade rate in relatives of people with schizophrenia;* Anticipatory saccades: 15 studies, N = 1,317, *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	
Medium effect sizes suggest increased 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 = 2,155: *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	

Medium effect sizes suggest 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
Medium effect size suggests 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

Catts VS, Catts SV, O'Toole BI, Frost ADJ

Cancer incidence in people with schizophrenia and their first degree relatives – a meta-analysis

Acta Psychiatrica Scandinavica 2008; 117: 323-336

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Comparison	**Cancer rates in people with schizophrenia and first-degree relatives of people with schizophrenia vs. the general population.**
Summary of evidence	**High quality evidence (large samples, consistent, appears precise, direct) suggests decreased incidence of any cancer in parents and siblings of people with schizophrenia compared to the general population.**
Cancer	
A significant decrease in overall cancer incidence in non-psychotic first-degree relatives of people	

with schizophrenia; Parents of people with schizophrenia: 3 studies, N = 70,484, SIR = 0.90, 95%CI 0.88 to 0.93, $p <$ 0.00001, Q-test $p > 0.05$ Siblings of people with schizophrenia: 2 studies, N = 63,267, SIR = 0.89, 95%CI 0.84 to 0.94, $p <$ 0.0001, Q-test $p > 0.05$	
Consistency	Consistent
Precision	Appears precise
Directness	Direct

Chan CK, Xu T, Heinrichs RW, Yu Y, Gong QY

Neurological soft signs in non-psychotic first-degree relatives of patients with schizophrenia: A systematic review and meta-analysis

Neuroscience and Biobehavioral Reviews 2010; 34: 889-896

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Comparison	**Neurological soft sign (NSS) score in relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistencies, precise, direct) shows a large effect of increased NSS in relatives of people with schizophrenia.**
NSS	
Significant, large effect of increased NSS in relatives of people with schizophrenia; 11 studies, N = 1,443, d = 0.974, 95%CI 0.553 to 1.394, Q = 119.04, $p < 0.001$ *NSS-Motor Coordination – medium effect size;* 7 studies, N = 796, d = 0.364, 95%CI 0.070 to 0.657, Q = 21.051, $p < 0.01$ *NSS-Sensory Integration – medium effect size;* 7 studies, N = 796, d = 0.369, 95%CI 0.207 to 0.530, Q = 6.742, p = NS *NSS-Complex Motor Sequencing – small effect size;* 3 studies, N = 301, d = 0.143, 95%CI -0.214 to 0.499, Q = 4.586, p = NS	
Consistency in results	Consistent, apart from overall score and motor coordination.

Precision in results	Precise
Directness of results	Direct
Comparison 2	**Neurological soft sign (NSS) score in relatives of people with schizophrenia vs. people with schizophrenia**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistencies, precise, direct) shows a large effect of increased NSS in people with schizophrenia.**
Significant, large effect of increased NSS in people with schizophrenia; 11 studies, N = 1,089, *d* = 0.813, 95%CI 0.587 to 1.039, Q = 32.353, *p* < 0.05 *NSS-Motor Coordination – large effect size:* 5 studies, N = 616, *d* = 0.917, 95%CI 0.745 to 1.088, Q = 2.443, *p* > 0.05 *NSS-Sensory Integration – medium effect size:* 5 studies, N = 616, *d* = 0.492, 95%CI 0.189 to 0.796, Q = 11.724, *p* < 0.01 *NSS-Complex Motor Sequencing – large effect size:* 2 studies, N = 296, *d* = 0.607, 95%CI 0.193 to 1.022, Q = 2.922, *p* > 0.05	
Consistency in results	Consistent, apart from overall score and sensory integration.
Precision in results	Precise
Directness of results	Direct

Chan RCK, Di X, McAlonan GM, Gong Q

Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression

Schizophrenia Bulletin 2011; 37(1): 177-188

View review abstract online

Comparison	**Grey matter changes in people at high risk of schizophrenia vs. healthy controls. People at high risk of schizophrenia were defined as first or second-degree relatives of people with schizophrenia, those meeting the Personal Assessment and**

	Crisis Evaluation clinic criteria, or those with a modification of the catechol-O-methyltransferase gene.
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests high risk individuals have grey matter reductions in bilateral anterior cingulate gyrus, right insula, left amygdala, left subcallosal gyrus, and left inferior frontal gyrus.**
Grey matter changes in high risk individuals	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies; FWHM 10mm, FDR corrected at $p < 0.01$ 8 observational studies, N = 1,031 *Right insula* Talairach coordinates (42, -28, 16), cluster 824mm^3, ALE 0.0109 *Left amygdala* Talairach coordinates (-28, -8, -12), cluster 800mm^3, ALE 0.0112 *Left anterior cingulate* Talairach coordinates (-6, 36, 16), cluster 560mm^3, ALE 0.0114 *Right anterior cingulate* Talairach coordinates (4, 30, 20), cluster 560mm^3, ALE 0.0079 *Right anterior cingulate* Talairach coordinates (6, 30,26), cluster 560mm^3, ALE 0.0074 *Left subcallosal gyrus* Talairach coordinates (-22, 6, -14), cluster 536mm^3, ALE 0.0120 *Left inferior frontal gyrus* Talairach coordinates (-48, 26, -2), cluster 432mm^3, ALE 0.0107	
Consistency	Unable to assess; no measure of consistency is reported.
Precision	Unable to assess; no measure of precision is reported.
Directness	Direct comparison of grey matter in people with schizophrenia and healthy controls.

de Wilde OM, Bour LJ, Dingemans PM, Koelman JH, Linszen DH, Koelman JHTM

A meta-analysis of P50 studies in people with schizophrenia and relatives: differences in methodology between research groups

Schizophrenia Research 2007; 97(1-3): 137-151

View online review abstract

Comparison	**Comparison of P50 ERP ratio in relatives of people with**

	schizophrenia vs. healthy controls.
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, unable to assess precision, direct) suggests P50 ratio is increased in relatives of people with schizophrenia.**
P50 activity	
A significant, large effect suggests increased P50 ratio in relatives of patients with schizophrenia; 6 studies, N = 611, d = 0.85, SD = 0.42, $p < 0.05$	
Consistency in results	Consistent
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Earls HA, Curran T, Mittal V

A Meta-analytic Review of Auditory Event-Related Potential Components as Endophenotypes for Schizophrenia: Perspectives from First-Degree Relatives

Schizophrenia Bulletin 2016; 42: 1504-16

View online review abstract

Comparison	**Comparison of ERP components in relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests a large effect of reduced P50 suppression, a medium-sized effect of reduced P300 amplitude, a small to medium-sized effect of longer latency, and a small trend effect of reduced MMN amplitude in relatives of people with schizophrenia.**
P50 suppression	
A significant, large effect of reduced suppression in relatives; 10 studies, N = 833, g = 0.86, 95%CI 0.44 to 1.27, $p < 0.001$, Q-test $p < 0.001$	

P300 amplitude	
A significant, medium-sized effect of reduced P300 amplitude in relatives; 20 studies, N = 1,829, *g* = -0.52, 95%CI -0.82 to -0.23, *p* < 0.001, Q-test *p* < 0.001	
P300 latency	
A significant, small to medium-sized effect of longer latency in relatives; 17 studies, N = 1,466, *g* = 0.44, 95%CI 0.04 to 0.84, *p* < 0.001, Q-test *p* < 0.001	
MMN	
A trend effect of reduced MMN amplitude in relatives; 11 studies, N = 929, *g* = 0.21, 95%CI -0.01 to 0.42, *p* = 0.06, Q-test *p* = 0.05	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, Cortesi M, Veggiotti P, Politi P, Barale F, McGuire P

Neurofunctional correlates of vulnerability to psychosis: A systematic review and meta-analysis

Neuroscience & Biobehavioral Reviews 2007; 31(4): 465-484

View review abstract online

Comparison	**Whole brain comparison of metabolite levels (measured by Magnetic Resonance Spectroscopy [^{1}H-MRS]) in people at high risk for psychosis (both clinical high risk and genetic high risk) vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium sample, unable to assess precision and inconsistency, direct) suggests reduced glutamate/glutamine ratio in the dorsolateral prefrontal**

	cortex (DLPFC), and reduced N-acetylaspartate/creatine ratio (NAA/Cr) in the anterior cingulate cortex and hippocampus of high-risk individuals when compared with controls. The medial temporal lobe shows no reductions in glutamic acid or glutamine.
Metabolite levels	
4 studies, N = 268 *DLPFC:* Reduced Glu/Gln in individuals at high risk of psychosis *Anterior cingulate cortex:* Reduced NAA/Cr in individuals at high risk of psychosis *Medial temporal lobe:* No difference in glutamatergic metabolite levels *Hippocampus:* Reduced NAA/Cr in individuals at high risk of psychosis	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct
Comparison 2	**Whole brain comparison of metabolite levels (measured by ^{31}P-MRS) in individuals at high risk of psychosis vs. controls**
Summary of evidence	**Moderate to low quality evidence (small sample, unable to assess precision or inconsistency, direct) suggests reduced phosphomonoester (PME) levels in the prefrontal cortex of high-risk individuals. Increased phosphodiester (PDE) levels and disrupted membrane metabolism in the frontal lobes may also be apparent.**
Phospholipid levels	
3 studies, N = 116 *Prefrontal cortex:* Reduced PME levels and reduced phospholipid synthesis in high-risk individuals who later developed schizophrenia *Frontal lobe:*	

Increased PDE levels in high-risk individuals; disrupted membrane metabolism; increased phospholipid breakdown	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct measures and comparison of metabolic activity
Comparison 3	**Whole brain comparison of functional activation (measured by positron emission tomography [PET]) in high-risk individuals vs. controls.**
Summary of evidence	**Low quality evidence (1 small sample) is unclear as to anomalies in whole brain activation or dopamine receptor binding.**
Verbal fluency tasks	
1 study (N = 20) found no significant differences in cerebral perfusion during a verbal fluency task in high-risk individuals compared with healthy controls.	
D1/D2 receptor binding ratio	
1 study (N = 24) found no significant difference in the ratio of D1 and D2 dopamine receptor binding in the unaffected twins of people with schizophrenia, compared with healthy controls.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct measures and comparison of functional activity
Comparison 4	**Whole brain comparison of functional activation (measured by single-photon emission computed tomography [SPECT]) in high-risk individuals vs. controls.**
Summary of evidence	**Low quality evidence (1 small sample) is unclear as to degree of cerebral perfusion and whole brain activation during verbal memory tasks in high-risk individuals.**
Verbal memory tasks	
1 study (N = 70) found reduced cerebral perfusion during a verbal memory task in high-risk individuals, particularly in the inferior prefrontal cortex	
Consistency in results	Unable to assess; no measure of consistency is reported.

Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct comparison of functional activity
Comparison 5	**Whole brain comparison of functional activation (measured by functional magnetic resonance imaging [fMRI]) in relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Low quality evidence (1 small sample per outcome) is unclear as to the direction of the changes in functional activity in the DLPFC, VLPFC, medial frontal gyrus, ACC, striatum, amygdala, thalamus, and cerebellum during cognitive tasks in relatives.**
Verbal initiation	
1 study, N = 63 Medium-sized effect suggests reduced activation in the medial frontal gyrus (*d* = 0.5), thalamus (*d* = 0.5), and cerebellum (*d* = 0.5) during visual initiation tasks in non-psychotic relatives of people with schizophrenia	
Working memory	
Effect sizes reported for three studies in relatives of schizophrenia patients 1 study with two independent cohorts *Cohort one: N = 41* Medium-sized effect suggests increased activation in the DLPFC (*d* = 0.60), VLPFC (*d* = 0.54), and inferior parietal lobe (*d* = 0.58) during working memory tasks in siblings of people with schizophrenia *Cohort two: N = 40* Small effect size suggests increased activation in the DLPFC (*d* = 0.42), VLPFC (*d* = 0.43), and inferior parietal lobe (*d* = 0.48) during working memory tasks in siblings of people with schizophrenia 1 study, N = 24 Large effect size suggests increased activation in the DLPFC (*d* = 0.79), and ACC (*d* = 0.96) during working memory tasks in non-psychotic relatives of people with schizophrenia 1 study, N = 45 Large effect size suggests increased activation in the DLPFC (*d* = 1.0) during working memory tasks in non-psychotic relatives of people with schizophrenia	
Memory guided saccades	
1 study, N = 32 Large effect size suggests reduced activation in the striatum (*d* = 1.34) during working memory guided saccades tasks in non-psychotic relatives of people with schizophrenia	

Emotional face processing	
1 study, N = 39 Medium-sized effect suggests reduced activation in the DLPFC (*d* = 0.51), amygdala (*d* = 1.05) and AFC (*d* = 0.47) during emotional face processing tasks in non-psychotic relatives of people with schizophrenia	
Language lateralisation	
1 study, N = 24 Large effect size (*d* = 1.31) suggests reduced language lateralisation in monozygotic twins discordant for schizophrenia	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct measures and comparison of functional activity

Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, McGuire P, Sacchetti E

Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis

Neuroscience and Biobehavioural Reviews 2011; 35: 1175-1185

View review abstract online

Comparison	**Whole brain comparison of grey matter density in people at high risk of psychosis (both clinical high risk and genetic high risk) compared with controls and people with psychosis.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests decreases in the right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, bilateral parahippocampal/hippocampal regions, and bilateral anterior cingulate in people at high risk compared with controls. Compared with people with psychosis, increases were detected in the amygdala bilaterally, medial frontal gyrus, middle temporal gyrus, and in the right precuneus.** **People at high clinical risk showed decreases in the bilateral anterior cingulate compared with people at high genetic risk. People at high genetic risk showed decreases in the left**

	hippocampus, insula and right superior temporal gyrus compared with people at high clinical risk. People at high risk who developed a psychotic episode showed decreases in the right inferior frontal gyrus, right insula and right superior temporal gyrus compared with those who did not develop psychosis.
Reduced grey matter volume	
19 studies, N = 705 controls and N = 896 people at high risk of psychosis *All - clinical and genetic high risk of psychosis vs. controls;* Decreases were reported in the right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, bilateral parahippocampal/hippocampal regions, and bilateral anterior cingulate. *All - clinical and genetic high risk of psychosis vs. people with psychosis;* Increases were reported in the amygdala bilaterally, medial frontal gyrus, middle temporal gyrus, and the right precuneus. *Genetic high risk of psychosis vs. controls;* Decreases were reported in the left parahippocampal gyrus, and anterior cingulate bilaterally. *Clinical high risk of psychosis vs. controls;* Decreases were reported in the left hippocampus, insula, right superior temporal gyrus, right inferior frontal gyrus, and medial frontal gyrus. *Genetic high risk of psychosis vs. clinical high-risk of psychosis;* People at high clinical risk showed decreases in the bilateral anterior cingulate. People at high genetic risk showed decreases in the left hippocampus, insula and right superior temporal gyrus. *People at high risk who developed a psychotic episode vs. people at high risk who did not develop psychosis;* People at high risk who developed a psychotic episode showed decreases in the right inferior frontal gyrus, right insula and right superior temporal gyrus.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Goghari MV

Executive functioning-related brain abnormalities associated with the genetic liability for schizophrenia: an activation likelihood estimate meta-

analysis	
Psychological Medicine 2011; 41: 1239-1252 View review abstract online	
Comparison	**Whole brain comparison of functional activation during an executive functioning task in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests relatives of people with schizophrenia show increased functional activation during an executive functioning task in the right superior and middle frontal gyri, right thalamus, left inferior parietal and left precuneus. Decreased activation in relatives compared with controls was shown in the right middle and inferior and left superior frontal gyri, right precentral gyrus, right lingual gyrus, left thalamus, right parietal cortex, left medial frontal and cingulate gyri, left superior temporal gyrus, and left cerebellum. Exclusion of region-of-interest studies removed much frontal-lobe specificity. During cognitive control tasks, relatives showed specific activation increases in the left middle frontal gyrus compared with controls, while during working memory tasks, relatives showed increased activation of the right thalamus, right inferior parietal cortex, right middle frontal gyrus and left precuneus. Relatives showed decreased activation in the right middle and inferior frontal gyri, right precentral gyrus, left thalamus and left cingulate gyrus.**
Activation during executive functioning task for all studies **Measured by fMRI**	
All VBM studies, including those assessing voxel-based activation in *apriori* regions of interest, were included in this analysis. 17 studies, N = 456 *Increased activity in relatives of people with schizophrenia compared with controls;* Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 376 mm^3 Right superior frontal gyrus: Talairach coordinates (40, 36, 32), cluster volume 400 mm^3 Right middle frontal/precentral gyrus: Talairach coordinates (46/46/34, 16/24/12, 16/24/12), cluster volume 792 mm^3 Right thalamus: Talairach coordinates (4, -10, 10), cluster volume 344 mm^3	

Left inferior parietal gyrus: Talairach coordinates (-40/-40, -64/-60, 46/44), cluster volume 192 mm^3
Left precuneus: Talairach coordinates (-2, -80, 44), cluster volume 368 mm^3
Decreased activity in relatives of people with schizophrenia compared with controls;
Right middle frontal gyrus: Talairach coordinates (32, 52, 10), cluster volume 424 mm^3
Right middle frontal gyrus: Talairach coordinates (38, 36, 34), cluster volume 1008 mm^3
Right inferior frontal gyrus: Talairach coordinates (52/54, 8/8, 18/24), cluster volume 192 mm^3
Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 152 mm^3
Right precentral gyrus: Talairach coordinates (50, -4, 22), cluster volume 144 mm^3
Left thalamus: Talairach coordinates (-14/-10/-6, -6/-12/-8, 10/12/12), cluster volume 304 mm^3
Left cingulate gyrus: Talairach coordinates (-16, -26, 42), cluster volume 360 mm^3
Right lingual gyrus: Talairach coordinates (10, -78, -2), cluster volume 216 mm^3
Activation during executive functioning task for whole brain studies
Only those studies that assessed *whole-brain* voxel-based activation
Increased activity in relatives of people with schizophrenia compared with controls;
Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 480 mm^3
Right middle frontal/ precentral gyrus: Talairach coordinates (48/46, 16/24, 32/36), cluster volume 176 mm^3
Left inferior parietal cortex: Talairach coordinates (-40/-40, -64/-60, 46/44), cluster volume 264 mm^3
Left precuneus: Talairach coordinates (-2, -80, 44), cluster volume 384 mm^3
Decreased activity in relatives of people with schizophrenia compared with controls;
Left medial frontal gyrus: Talairach coordinates (-12, 64, -2), cluster volume 136 mm^3
Right middle frontal gyrus: Talairach coordinates (36, 28, 42), cluster volume 120 mm^3
Right precentral gyrus: Talairach coordinates (50, -4, 22), cluster volume 200 mm^3
Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 200 mm^3
Left superior temporal gyrus: Talairach coordinates (-62/-58, -12/-4, -4/-2), cluster volume 176 mm^3
Left thalamus: Talairach coordinates (-10/-14/-6, -12/-6/-8, 12/10/12), cluster volume 368 mm^3
Right parietal cortex: Talairach coordinates (24, -48, 42), cluster volume 144 mm^3
Left cerebellum: Talairach coordinates (-8/-14, -42/-40, -32/-38), cluster volume 168 mm^3
Activation during a cognitive control task

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Increased activity in relatives of people with schizophrenia compared with controls; Left middle/ superior frontal gyrus: Talairach coordinates (-28/-26, 48/50, 20/12), cluster volume 168 mm^3
Activation during a working memory task
Increased activity in relatives of people with schizophrenia compared with controls; Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 480 mm^3 Right middle frontal/ precentral gyrus: Talairach coordinates (48/46, 16/24, 32/36), cluster volume 176 mm^3 Right thalamus: Talairach coordinates (4, -10, 10), cluster volume 408 mm^3 Left inferior parietal cortex: Talairach coordinates (-40/-40, -64/-60, 46/44), cluster volume 264 mm^3 Left precuneus: Talairach coordinates (-2, -80, 46), cluster volume 368 mm^3 *Decreased activity in relatives of people with schizophrenia compared with controls;* Right middle frontal gyrus: Talairach coordinates (38, 36, 34), cluster volume 1008 mm^3 Right inferior frontal gyrus: Talairach coordinates (52/54, 8/8, 18/24), cluster volume 176 mm^3 Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 168 mm^3 Left thalamus: Talairach coordinates (-14/-6/-10, -6/-8/-12, 10/12/12), cluster volume 312 mm^3 Left cingulate gyrus: Talairach coordinates (-16, -26, 42), cluster volume 200 mm^3

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Koning JPF, Tenback DE, Van Os J, Aleman A, Kahn RS, van Harten PN

Dyskinesia and parkinsonism in antipsychotic-naive patients with schizophrenia, first-degree relatives and healthy controls: a meta-analysis

Schizophrenia Bulletin 2010; 36(4): 723-31

View review abstract online

Comparison	**Rates of movement disorder (dyskinesia and parkinsonism) in antipsychotic naïve people with schizophrenia and first-degree relatives vs. controls.**

Familial physical features

Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests a small increase in the risk of dyskinesia and parkinsonism in first-degree relatives.**
Dyskinesia	
A small, significant effect size suggests first-degree relatives of people with schizophrenia are also at increased risk of dyskinesia compared with controls; 6 studies, N = 774, OR = 1.38, 95%CI 1.06 to 1.81, *p* = 0.02, Q = 0.73, *p* = 0.98 *A large, significant effect size suggests people with schizophrenia are at increased risk of dyskinesia compared with controls;* 5 studies, N = 407, OR = 3.59, 95%CI 1.53 to 8.41, *p* < 0.01, Q = 1.79, *p* = 0.77 Meta-regressions reported a significant relationship between increasing rates of dyskinesia and increasing age in both people with schizophrenia (β = 0.07, p = 0.02) and controls (β = 0.06, p < 0.01) and longer duration of untreated schizophrenia (β = 0.28, *p* < 0.01), with no relationship to age of onset (β = 0.15, *p* = 0.07).	
Parkinsonism	
A small, significant effect size suggests first-degree relatives of people with schizophrenia are at increased risk of parkinsonism compared with controls; 6 studies, N = 774, OR = 1.37, 95%CI 1.05 to 1.79, *p* = 0.03, Q = 2.30, *p* = 0.81 *A large effect size suggests people with schizophrenia are at significantly increased risk of parkinsonism compared with controls;* 3 studies, N = 234, OR = 5.32, 95%CI 1.75 to 16.23, *p* < 0.01, Q = 0.40, *p* = 0.82 Meta-regressions reported no association between prevalence of parkinsonism and patient age (β = 0.01, *p* = 0.44) or control age (β = 0.03, *p* = 0.27); duration of untreated schizophrenia (β = 0.04, *p* = 0.43) or age of onset (β = 0.01, *p* = 0.82).	
Consistency	Consistent
Precision	Imprecise
Directness	Direct

MacDonald AW, Thermenos HW, Barch DM, Seidman LJ

Imaging genetic liability to schizophrenia: systematic review of fMRI

studies of patients' nonpsychotic relatives	
Schizophrenia Bulletin 2009; 35(6): 1142-1162 View review abstract online	
Comparison	**Whole brain comparison of functional activation in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, unable to assess precision or consistency, direct) suggests functional activity during cognitive control tasks shows alterations (increased *or* decreased) in the DLPFC, parietal, and thalamus of relatives. Activity during working memory tasks also shows alterations in the DLPFC, ventrolateral prefrontal cortex (VLPFC), parietal and cerebellum of relatives. During long term memory tasks, only the VLPFC of relatives shows functional alteration. During language processing tasks the right VLPFC and parietal cortex show functional alterations in relatives.**
Cognitive control tasks	
7 studies investigated functional activity during cognitive control tasks, N = 308. 4 studies investigated the anterior cingulate cortex, 3/4 showed no group differences bilaterally. 7 studies investigated DLPFC, 4/7 showed increased bilateral activity compared with controls. Activity (hyper- and hypo-) was abnormal in 82% of reports. 7 studies investigated VLPFC, 2/7 showed no group differences, two showed abnormal activity. 6 studies investigated the parietal cortex, 3/6 showed increased bilateral activity compared with controls. Activity (hyper- and hypo-) was abnormal in 67% of reports. 6 studies investigated the temporal cortex, 2/6 showed increased activity compared with controls. 6 studies investigated the basal ganglia, 2/6 showed reduced activity compared with controls. 6 studies investigated the cerebellum, 2/6 showed altered activity compared with controls. 6 studies investigated the thalamus, 3/6 showed increased activity compared with controls. Activity (hyper- and hypo-) was abnormal in 86% of reports.	
Working memory tasks	
4 studies (5 independent samples) investigated functional activity during working memory tasks, N = 239. 4 studies investigated the anterior cingulate cortex, 2/4 showed no group differences bilaterally. 5 studies investigated DLPFC, 4/5 showed increased activity compared with controls. Activity	

(hyper- and hypo-) was abnormal in 67% of reports. 4 studies investigated VLPFC, 2/4 showed increased activity compared with controls. Activity (hyper- and hypo-) was abnormal in 67% of reports. 5 studies investigated the parietal cortex, 3/5 showed increased activity compared with controls. Activity (hyper- and hypo-) was abnormal in 67% of reports. 4 studies investigated the temporal cortex, 2/4 showed decreased activity compared with controls. 2 studies investigated the basal ganglia, 1/2 showed increased activity compared with controls. 4 studies investigated the thalamus, 2/4 showed no group differences. 4 studies investigated the cerebellum, 3/4 showed reduced activity compared with controls. Activity (hyper- and hypo-) was abnormal in 60% of reports.
Long term memory tasks
3 studies investigated functional activity during episodic long-term memory tasks, N = 195. 3 studies investigated the anterior cingulate cortex, 3/3 showed no group differences. 3 studies investigated DLPFC, 2/3 showed no group differences, one showed increased activity in the right hemisphere. 3 studies investigated VLPFC, 2/3 showed increased activity compared with controls. 3 studies investigated the parietal cortex, 3/3 showed no group differences. 3 studies investigated the temporal cortex, 3/3 showed no group differences. 3 studies investigated the basal ganglia, 3/3 showed no group differences. 3 studies investigated the thalamus, 3/3 showed no group differences 3 studies investigated the cerebellum, 2/3 showed no group differences, one showed increased activity compared with controls.
1 study investigated functional activity during procedural long-term memory tasks, N = 27. No group difference was reported for cingulate, VLPFC, temporal cortex and cerebellum. Reduced activity in relatives was shown in DLPFC, parietal, temporal, basal ganglia, and thalamus.
Language processing studies
4 studies investigated functional activity during language processing tasks, N = 164. 1/4 showed reduced activity in relatives in the anterior cingulate cortex. 1/4 showed no group differences in DLPFC, and 1/4 showed reduced activity in the right hemisphere (2/4 showed no task-related response). 2/4 showed increased VLPFC activity compared with controls in the right hemisphere only. 3/4 showed increased activity in the right parietal cortex, 1/3 also showed increased activity in the

left parietal. 2/4 showed increased activity in the right temporal cortex, 2/4 showed decreased activity in right temporal cortex. 2/4 showed no group differences in left temporal cortex. 4/4 showed no task-related response in the basal ganglia. 3/4 showed no task-related response in the thalamus, 1/4 showed reduced bilateral activity. 3/4 showed no task-related response in the cerebellum, 1/4 showed reduced activity.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Neelam K, Garg D, Marshall M

A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia

BMC Psychiatry 2011; 11: 139

View review abstract online

Comparison	**NSS score in people with schizophrenia compared with healthy controls and first-degree relatives.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a large effect of increased levels of NSS in first-degree relatives compared to controls.** **Moderate to high quality evidence (precise) suggests a large effect size of increased levels of NSS in people with schizophrenia compared to their first-degree relatives.**
NSS severity scores	
A significant, large effect of increased levels of NSS in first-degree relatives of people with schizophrenia compared with healthy controls; 7 studies, N = 1,082, d = 1.83, 95%CI 1.28 to 2.38, I^2 = 93.1, p < 0.001 *A significant, large effect of increased levels of NSS in people with schizophrenia compared with their first-degree relatives;*	

7 studies, N = 1,040, *d* = 0.92, 95%CI 0.64 to 1.12, I^2 = 74.6, *p* < 0.001	
Consistency in results	Inconsistent
Precision in results	Imprecise for control comparison, precise for comparison between schizophrenia and first-degree relatives
Directness	Direct

Saarinen AIL, Huhtaniska S, Pudas J, Bjornholm L, Jukuri T, Tohka J, Grano N, Barnett JH, Kiviniemi V, Veijola J, Hintsanen M, Lieslehto J

Structural and functional alterations in the brain gray matter among first-degree relatives of schizophrenia patients: A multimodal meta-analysis of fMRI and VBM studies

Schizophrenia Research 2020; Jan: doi.org/10.1016/j.schres.2019.12.023

View review abstract online

Comparison	**Functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggests increased activation in the right inferior frontal gyrus during cognitive tasks.**
Cognitive tasks	
Relatives showed increased activation in the right inferior frontal gyrus; MNI co-ordinates 46, 12, 32, *p* = 0.000001967, 616 voxels, I^2 = 0%	
Consistency in results	Consistent
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Saunders TS, Mondelli V, Cullen AE

Pituitary volume in individuals at elevated risk for psychosis: A systematic

review and meta-analysis	
Schizophrenia Research 2019; 213: 23-31 View review abstract online	
Comparison	**Pituitary volume in people at genetic high risk for psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized sample, consistent, precise, direct) suggests people at genetic high risk for psychosis may show greater pituitary volume than controls.**
Pituitary volume	
A small trend effect of larger pituitary volume in people at high risk for psychosis; 4 studies, N = 291, g = 0.20, 95%CI -0.03 to 0.43, p = 0.094, I^2 = 0%	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Wenneberg C, Glenthoj BY, Hjorthoj C, Buchardt Zingenberg FJ, Glenthoj LB, Rostrup E, Broberg BV, Nordentoft M

Cerebral glutamate and GABA levels in high-risk of psychosis states: A focused review and meta-analysis of ^{1}H-MRS studies

Schizophrenia Research Jan: doi: 10.1016/j.schres.2019.10.050

View review abstract online

Comparison	**Cerebral glutamate measured by ^{1}H-MRS in people at high risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) finds a medium-sized increase in glutamate+glutamine in the frontal lobe of people at genetic high risk of psychosis.**

Familial physical features

Glutamate + glutamine	
A medium-sized, significant effect showed higher glutamate + glutamine levels in the frontal lobe of people at genetic high risk; 4 studies, N = 140, SMD = -0.55, 95%CI -0.89 to -0.21, *p* = 0.001, I^2 = 0% There were no significant differences in the analysis that combined clinical and genetic high-risk individuals.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

β = beta, CI = confidence interval, Cr = creatine, *d* or *g* = Cohen's d or Hedges g standardised mean differences, DLPFC = dorsolateral prefrontal cortex, fMRI = functional magnetic resonance imaging, *g* = Hedge's standardised mean difference, Glu = glutamic acid, Gln = glutamine, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MMN = mismatch negativity, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, N = number of participants, NAA = N-acetylaspartate, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PDE = phosphodiester, PME = phosphomonoester, Q = Q statistic for the test of heterogeneity, SE = standard error, SIR = Standardised Incidence Ratio, SMD = standardised mean difference, VLPFC = ventrolateral prefrontal cortex, vs. = versus

Familial physical features

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[21].

† 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.

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).

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[21].

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[22]. 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Familial physical features

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect 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.

‡ 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 considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[21];

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

§ 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[23].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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