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on schizophrenia and bipolar disorders

De novo gene mutations highlight patterns of genetic and neural complexity in schizophrenia

Nature Genetics, 2012 October 3; 44(12):1365–9

Brain volumes in schizophrenia: a meta-analysis in over 18,000 subjects

Schizophrenia Bulletin, 2012 October 5; Epub ahead of print

Genetic schizophrenia risk variants jointly modulate total brain and white matter volume

Biological Psychiatry, 2012 October 3; Epub ahead of print

Thalamocortical dysconnectivity in schizophrenia

American Journal of Psychiatry, 2012 October; 169(10):1092–9

Delayed white matter growth trajectory in young nonpsychotic siblings of patients with childhood-onset schizophrenia

Archives of General Psychiatry, 2012 September; 69(9):875–84

Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia

Molecular Psychiatry, 2013 February; 18(2):206–14

The nature of dopamine dysfunction in schizophrenia and what this means for treatment: meta-analysis of imaging studies

Archives of General Psychiatry, 2012 August; 69(8):776–86

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Framingham's team of medical writers prepares original abstracts of these articles, in a structured format that presents the main points at a glance. Our aim is to convey the essence of each article in a concise but readable style.
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DE NOVO GENE MUTATIONS HIGHLIGHT PATTERNS OF GENETIC AND NEURAL COMPLEXITY IN SCHIZOPHRENIA

Nature Genetics, 2012 October 3; 44(12):1365–9

AUTHORS: Xu B, Ionita-Laza I, Roos JL, Boone B, Woodrick S, Sun Y, Levy S, Gogos JA, Karayiorgou M
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BACKGROUND & AIM: Genetics are known to play an important role in the development of schizophrenia, and the contribution of rare *de novo* copy-number variants to the risk of the disorder has been well established. However, there is less evidence about the role of *de novo* nucleotide-level variants. The aim of this study was to identify *de novo* aetiologies in schizophrenia by performing exome sequencing of proband–parent family trios.

STUDY DESIGN: Genetic study.

ENDPOINTS: *De novo* gene mutations.

METHOD: The study was performed in a group of 146 Afrikaner and 85 American proband–parent family trios, including patients with a diagnosis of schizophrenia or schizoaffective disorder, and 34 unaffected Afrikaner control trios with no history of treatment for psychiatric conditions, or mental illness in the first- or second-degree relatives. Previous scans had determined that no subjects carried any rare *de novo* copy-number variants. A total of 795 exomes were sequenced, with raw sequencing data being mapped to the human reference genome using the Burrows-Wheeler Aligner. Candidate *de novo* variants were tested using standard Sanger sequencing to validate the presence of each mutation in the proband and its absence in the parental genomes.

RESULTS: In the Afrikaner probands, there were 93 confirmed *de novo* exonic point mutations, including 92 single-nucleotide variants and one dinucleotide substitution. The point mutation rate in the captured coding sequence was 1.73×10^{-8} mutations per base per generation, which was not significantly different to the rate of 1.28×10^{-8} in the control group. There were 80 non-synonymous and 13 synonymous changes, giving a ratio of 6.15, which was significantly higher than normally expected (2.23). There was also an increased prevalence in the rate of *de novo* events that would lead to a loss of function (7.5% in cases versus 2.9% in controls). In the US cohort, the point mutation rate was also 1.73×10^{-8} mutations per base per generation. The non-synonymous-to-synonymous ratio of 3.42 was higher than normal, but not significantly so, and the rate of loss-of-function *de novo* events was 9.4%. Four genes were affected by recurrent *de novo* events across the two groups.

CONCLUSION: *De novo* mutations in schizophrenia affect a variety of genes with different functions, but many have a high expression in early foetal life.

BRAIN VOLUMES IN SCHIZOPHRENIA:
A META-ANALYSIS IN OVER 18 000 SUBJECTS

Schizophrenia Bulletin, 2012 October 5; Epub ahead of print

AUTHORS: Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS
CENTRES: Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, Utrecht; Developmental Science, Institute of Psychology, Leiden University; Leiden Institute for Brain and Cognition, Leiden, the Netherlands

BACKGROUND & AIM: Schizophrenia is known to be associated with structural brain abnormalities. Despite improvements in magnetic resonance imaging (MRI) techniques in the last few years, however, no recent meta-analyses of volumetric MRI studies in schizophrenia have been conducted to determine effect sizes. Furthermore, the relationships between brain abnormalities, antipsychotic treatment and intelligence quotient (IQ) have not been evaluated. The aim of this study was therefore to conduct a meta-analysis, including recent MRI data, of volumetric brain alterations in various cerebral regions in patients with schizophrenia.

STUDY DESIGN: Meta-analysis.

ENDPOINTS: Total and regional brain volumes.

METHOD: A literature search identified 317 eligible studies using MRI to compare brain volumes between schizophrenia patients and healthy control subjects. These included a total of 382 study samples, 9098 patients (771 antipsychotic-naive) and 9231 controls, and studied a total of 38 different brain structures. Effect sizes and potential modifying factors were extracted from the studies, and meta-analysis for each brain structure was performed using Cohen's *d* statistic and taking into account the use of antipsychotic medication and IQ scores.

RESULTS: In the group of schizophrenia patients who had received antipsychotic medication, intracranial brain volume was significantly reduced by 2.0% compared with the control subjects (d= –0.17), while total brain volume was significantly decreased by 2.6% (d= –0.30). The effect size varied from –0.22 to –0.58 across different brain regions, with the largest effects seen in grey matter structures. In the group of antipsychotic-naive patients (Table), intracranial brain volume was reduced by 1.7% and total brain volume was reduced by 2.0% compared with controls. Volume reductions in the caudate nucleus (d= –0.38) and thalamus (d= –0.68) were greater in antipsychotic-naïve than in medicated patients, while grey matter loss was greater in medicated patients, and white matter loss was similar between the two groups.

CONCLUSIONS: Schizophrenia was associated with a small but highly significant reduction in intracranial volume and a loss in total brain volume, related to a combination of early neurodevelopmental processes and illness progression.

Comparison of brain volumes between antipsychotic-naive schizophrenia patients and controls

Bilateral brain structure	Numbers of samples (studies)	Mean weighted effect size (Cohen's *d*)	*p-v*alue for *d*	Average weighted difference (%)
Intracranial volume	17 (17)	–0.14	0.041	–1.7
Total brain volume	15 (15)	–0.21	3.0×10^{-3}	–2.0
Total grey matter	10 (10)	–0.36	6.6×10^{-5}	–3.8
Total white matter	10 (10)	–0.18	0.042	–2.4
Total cerebrospinal fluid	7 (7)	0.31	0.011	7.6

GENETIC SCHIZOPHRENIA RISK VARIANTS JOINTLY MODULATE TOTAL BRAIN AND WHITE MATTER VOLUME

Biological Psychiatry, 2012 October 3; Epub ahead of print

AUTHORS: Terwisscha van Scheltinga AF, Bakker SC, van Haren NE, Derks EM, Buizer-Voskamp JE, Boos HB, Cahn W, Hulshoff Pol HE, Ripke S, Ophoff RA, Kahn RS; for the Psychiatric Genome-wide Association Study Consortium

CENTRE FOR CORRESPONDENCE: Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, the Netherlands

BACKGROUND & AIM: Thousands of single nucleotide polymorphisms (SNPs) contribute towards the susceptibility to schizophrenia. Each genetic variant has only a small individual effect, but together they are likely to contribute to a complex and heterogeneous mechanism of inheritance. It is also possible that subsets of these disease-associated SNPs are linked to distinct heritable, disease-associated phenotypes (endophenotypes) of schizophrenia. Brain and white matter volume is a highly heritable phenotype with a strong genetic origin, and may therefore be an excellent candidate endophenotype for schizophrenia-associated SNPs. The aim of this study was to investigate the combined effect of schizophrenia-associated loci on brain volume.

STUDY DESIGN: Genetic study.

ENDPOINTS: Total brain and white matter volume.

METHOD: The study included 152 patients with schizophrenia or schizoaffective disorder and 142 healthy control subjects, for whom magnetic resonance imaging data were available. Volume measures of the intracranium, total brain, and cerebral grey and white matter were determined from the images. Genotyping was performed in all participants, and a total of 117,924 SNPs were selected for analysis. Odds ratios for the association between each variant and schizophrenia were calculated, and a polygenic schizophrenia (risk) score was calculated for each SNP based on the number of risk variants carried by an individual multiplied by the logarithm of the odds ratio for that particular variant. Logistic regression was performed to examine the association between the polygenic schizophrenia score and total brain and white matter volume.

RESULTS: In both schizophrenia patients and control subjects, the polygenic schizophrenia score was significantly associated with total brain volume (R^2=0.048, p=1.6×10^{-4}), and when disease status was included in the analysis, the effect of polygenic schizophrenia score on brain volume remained significant (R^2=0.038, p=0.001). The polygenic schizophrenia score was also specifically associated with reduced white matter volume (R^2=0.051, p=8.6×10^{-5}). A total of 14,751 SNPs were found to modulate disease status, of which only 2020 influenced both disease risk and white matter. A subset of 186 SNPs was shown to affect white matter volume most strongly, and these SNPs appeared to be located in genes with neuronal functions.

CONCLUSIONS: A number of schizophrenia genetic risk variants were associated with the development of white matter, suggesting that abnormalities in white matter growth increase schizophrenia risk.

THALAMOCORTICAL DYSCONNECTIVITY IN SCHIZOPHRENIA

American Journal of Psychiatry, 2012 October; 169(10):1092–9

AUTHORS: Woodward ND, Karbasforoushan H, Heckers S
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BACKGROUND & AIM: Different regions of the brain cortex are connected to specific areas in the thalamus by thalamocortical pathways. There is evidence that dysfunction of these thalamocortical networks is involved in the pathogenesis of schizophrenia, and may account for some of the clinical symptoms seen in the disorder. However, it is not known if there is general disruption of the networks or if individual pathways are affected differently. The aim of this study was to examine the functional connectivity between the cortex and thalamus in patients with schizophrenia, and determine whether specific thalamocortical networks are affected differently.

STUDY DESIGN: Cross-sectional study.

ENDPOINT: Functional connectivity.

METHOD: The study involved 62 patients with schizophrenia and 77 healthy control subjects who all underwent resting-state functional imaging. Mean intrinsic low-frequency blood-oxygen-level-dependent (BOLD) signal fluctuations across various brain regions were determined and entered into a seed-based functional connectivity analysis. The connectivity between six major divisions of the cortex and associated areas of the thalamus was mapped. In addition, clinical symptoms of psychosis were quantified with the Positive and Negative Syndrome Scale (PANSS).

RESULTS: Each distinct cortical region examined was connected with specific, largely non-overlapping, areas of the thalamus in both healthy control subjects and schizophrenia patients. However, there were some differences between patients and controls. Compared with healthy subjects, schizophrenia patients had reduced functional connectivity between the prefrontal cortex and the dorsomedial thalamus, and increased connectivity between the motor and somatosensory cortex and the thalamus. There were no differences between the groups for temporal lobe, posterior parietal cortex, or occipital lobe connectivity to the thalamus. Supplementary analyses indicated that the changes in functional connectivity were not related to differences in grey matter content within the thalamus or to the dosage of antipsychotic medication being received. In exploratory analyses, there were no significant correlations between functional connectivity and PANSS clinical symptoms or illness-relevant demographic characteristics.

CONCLUSIONS: Several of the functional networks connecting the brain cortex to the thalamus were abnormal in patients with schizophrenia, including both hypo- and hyper-connectivity in different regions, implicating atypical late brain maturation in the disease.

DELAYED WHITE MATTER GROWTH TRAJECTORY IN YOUNG NONPSYCHOTIC SIBLINGS OF PATIENTS WITH CHILDHOOD-ONSET SCHIZOPHRENIA

Archives of General Psychiatry, 2012 September; 69(9):875–84

AUTHORS: Gogtay N, Hua X, Stidd R, Boyle CP, Lee S, Weisinger B, Chavez A, Giedd JN, Clasen L, Toga AW, Rapoport JL, Thompson PM
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BACKGROUND & AIM: Cortical grey matter abnormalities seen in patients with childhood-onset schizophrenia are also present at an early age in their non-psychotic siblings. There is evidence, however, that these deficits normalize in siblings by the age of 18 years, suggesting that they may be age-specific and normalized by protective factors, possibly environmental or genetic in origin. White matter abnormalities are also present in patients with childhood-onset schizophrenia, but it remains unclear whether they can also be observed in non-psychotic siblings. The aim of this study was to examine longitudinal brain development in non-psychotic siblings of childhood-onset schizophrenia patients to uncover whether white matter growth differences could be observed in comparison with healthy controls.

STUDY DESIGN: Longitudinal cohort study.

ENDPOINT: White matter growth rates.

METHOD: A total of 49 healthy siblings (mean age 16.1 years, 30 females) of patients with childhood-onset schizophrenia were evaluated prospectively during this 5-year longitudinal study. All images were acquired using a 1.5-T magnetic resonance imaging (MRI) scanner, and participants were scanned prospectively every 2 years. Images were compared with those of 57 healthy controls (mean age 16.9, 28 females). White matter growth rates were computed with tensor-based morphometry and compared in three age ranges; 7 to <14 years (pre-adolescent), 14 to <18 years (post-pubertal/adolescent), and 18 to 28 years (young adult).

RESULTS: As expected, both non-psychotic siblings and healthy controls showed active white matter growth (1–2% per year, bilaterally), and when all age groups were combined, there was no significant difference overall between the two groups across the whole brain spatially. However, compared with age-matched controls, pre-adolescent siblings showed slower white matter growth rates in the parietal lobes (false discovery rate q=0.05, critical p=0.001 in the bilateral parietal white matter), and post hoc analysis, split by hemisphere, detected a growth rate difference only on the left side (critical p=0.004). No difference in growth rate was observed at older ages, however. In three-dimensional maps, siblings sustained a more constant growth rate compared with controls; growth rates in the siblings slowed by 0.2–0.8% per year, whereas rates in healthy controls slowed by 0.5–1% per year.

CONCLUSION: Non-psychotic siblings of patients with childhood-onset schizophrenia showed early white matter growth deficits on MRI, which normalized with age.

INCREASED INFLAMMATORY MARKERS IDENTIFIED IN THE DORSOLATERAL PREFRONTAL CORTEX OF INDIVIDUALS WITH SCHIZOPHRENIA

Molecular Psychiatry, 2013 February; 18(2):206–14

AUTHORS: Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T, Cairns M, Weickert CS
CENTRE FOR CORRESPONDENCE: Schizophrenia Research Laboratory, Neuroscience Research Australia, Randwick, New South Wales, Australia

BACKGROUND & AIM: A number of lines of evidence from human and animal studies suggest that immune system activation and inflammation are involved in the development of schizophrenia. Microarray studies have provided some information on changes in the expression of inflammation-related genes in patients with schizophrenia, but the available techniques have had limited sensitivity. This problem can be overcome with next-generation sequencing, and the aim of this study was to use this technique to examine the transcriptome of the dorsolateral prefrontal cortex of the brain in order to identify gene expression changes associated with schizophrenia.

STUDY DESIGN: Post-mortem study.

ENDPOINTS: Neuroimmune mRNA expression, and microglial density.

METHOD: Post-mortem tissue samples from the dorsolateral prefrontal cortex of 20 patients with schizophrenia and 20 matched controls were examined using next-generation sequencing, specifically RNA-Seq, in order to quantify neuroimmune mRNA expression levels. The results were confirmed in an expanded cohort (37 patients and 37 controls) using quantitative real-time polymerase chain reaction. In addition, microglial density was measured using immunohistochemistry and western blotting.

RESULTS: A total of 798 differentially regulated transcripts were identified in the dorsolateral prefrontal cortex of schizophrenia patients compared with controls. Network analysis indicated that the inflammatory response was commonly affected, and the findings were confirmed in the expanded cohort. Overall, interleukin (IL)-6, IL-8 and SERPINA3 mRNA transcripts were significantly ($p<0.05$) upregulated in schizophrenia patients, and IL-1β was increased by 29%, though this increase was not significant. The density of microglia/antigen-presenting cells expressing major histocompatability complex-II receptors was increased in the white matter in schizophrenia, and regression analysis found a positive relationship between microglia density and IL-1β mRNA expression in these patients. Cluster analysis of the expanded cohort identified a subgroup of 18 individuals who had elevated levels of the inflammatory markers noted above (high IL-1 β, IL-6, IL-8 and SERPINA3 mRNA expression), compared with 56 who had lower levels. This subgroup was primarily composed of individuals with schizophrenia as opposed to controls (n=14 versus 4, respectively; p=0.007).

CONCLUSIONS: This study found increased expression of genes encoding inflammatory cytokines in the cerebral cortex of a subgroup of patients with schizophrenia. The findings support the concept that inflammatory dysregulation is involved in the pathogenesis of schizophrenia.

THE NATURE OF DOPAMINE DYSFUNCTION IN SCHIZOPHRENIA AND WHAT THIS MEANS FOR TREATMENT:

META-ANALYSIS OF IMAGING STUDIES

Archives of General Psychiatry, 2012 August; 69(8):776–86

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BACKGROUND & AIM: Dopamine dysfunction is thought to underlie the pathophysiology of schizophrenia, and current treatments for the disease work by blocking the dopamine D_2 receptor, albeit that this mechanism is not fully understood. Positron emission tomographic (PET) and single-photon emission computed tomographic (SPECT) imaging allow the assessment of in vivo cerebral dopamine neurotransmission, and a number of studies have been conducted in schizophrenia using these techniques. The aim of the current study was to perform a meta-analysis of PET and SPECT imaging findings on dopaminergic function in schizophrenia, and to consider their implications for treatment.

STUDY DESIGN: Meta-analysis.

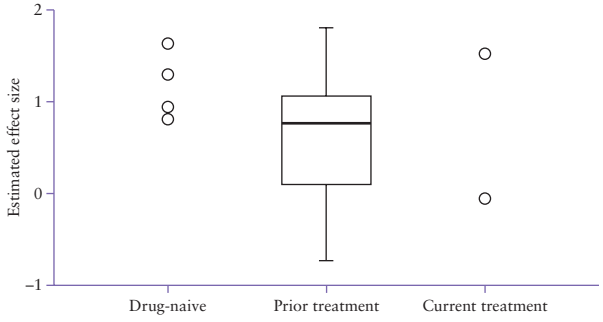
ENDPOINTS: Measures of dopaminergic function.

METHOD: A literature search identified 44 eligible studies that used PET or SPECT imaging to measure in vivo striatal dopaminergic function in a total of 618 patients with schizophrenia and 606 control subjects, and demographic and clinical data were extracted. Random-effects meta-analyses (using Cohen *d* to indicate effect size) were performed on 17 studies that measured presynaptic function, 11 that measured dopamine transporter availability, and 22 that measured dopamine $D_{2/3}$ receptor availability.

RESULTS: Presynaptic dopaminergic function was significantly higher in patients with schizophrenia than in control subjects (d=0.79, 95% confidence interval 0.52–1.07, p<0.001), with a low to moderate heterogeneity in results between studies (I^2=39.92%). The Figure shows the effect sizes for the studies grouped by antipsychotic treatment. Schizophrenia was also associated with a small increase in $D_{2/3}$ receptor availability (d=0.26, 95% CI 0.001–0.52, p=0.049), with moderate to large heterogeneity between studies (I^2=63.93%), but this was not evident in drug-naïve patients, and was affected by the imaging methodology used. There was no significant difference in dopamine transporter availability (d= –0.34, 95% CI –0.75 to 0.07, p=0.10).

CONCLUSION: The largest source of dopaminergic abnormality in schizophrenia is in the presynaptic regions, and these are not targeted by current treatments which act mainly on $D_{2/3}$ receptors.

Effect sizes for studies of presynaptic dopaminergic function, by antipsychotic treatment history. In the box plot, the horizontal line represents the median.



AUDITORY VERBAL HALLUCINATIONS IN PATIENTS WITH BORDERLINE PERSONALITY DISORDER ARE SIMILAR TO THOSE IN SCHIZOPHRENIA

Psychological Medicine, 2012 September; 42(9):1873–8

AUTHORS: Slotema CW, Daalman K, Blom JD, Diederen KM, Hoek HW, Sommer IE
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BACKGROUND & AIM: There is no consensus on the phenomenology and severity of hallucinations in individuals with borderline personality disorder (BPD). As diagnostic criteria fail to account for the occurrence of longer-lasting hallucinations in BPD, clinicians have difficulty categorizing the auditory verbal hallucinations (AVH) experienced by these patients, often describing them as 'pseudohallucinations'. The aim of this study was to evaluate and characterize the phenomenology of AVH in patients with BPD compared with schizophrenia patients and otherwise healthy individuals.

STUDY DESIGN: Cross-sectional study.

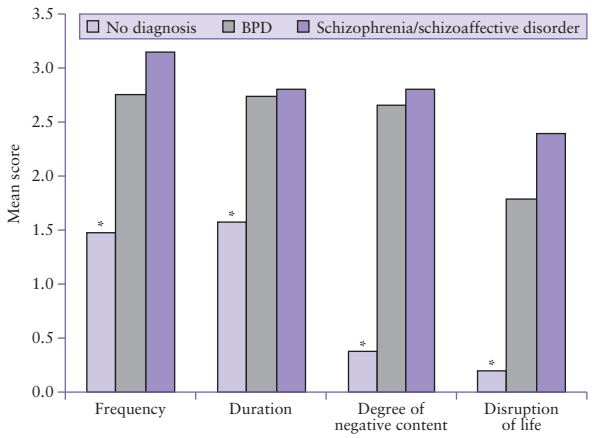
ENDPOINT: Phenomenological characteristics of AVH.

METHOD: The phenomenological characteristics of AVH in 38 female patients with BPD (mean age 34 years) were compared with those of 51 patients who had previously been diagnosed with schizophrenia (n=36) or schizoaffective disorder (n=15) using the Psychotic Symptom Rating Scales, and with 66 healthy women who reported experiencing AVH.

RESULTS: Patients with BPD experienced AVH for a mean duration of 18 years, with a mean frequency of at least one per day. Scores for 'negative content', 'distress', 'disruption of life', and 'controllability' among patients with BPD were high. There were significant differences for all AVH-related items between healthy individuals with AVH and patients in the two other groups (Figure), except for 'perceived location', and 'loudness'. No differences in the phenomenological characteristics of AVH were found among patients diagnosed with BPD and those with schizophrenia/schizoaffective disorder, except for 'disruption of life', which was higher in the latter. Compared with otherwise healthy women experiencing AVH, patients with BPD had higher scores on almost all items of the Psychotic Symptom Rating Scales.

CONCLUSION: Auditory verbal hallucinations in patients with borderline personality disorder were similar to those in patients with schizophrenia, and different from those in healthy individuals.

Mean score on AVH-related items of the Psychotic Symptom Rating Scales



* Significantly different from the other two groups

PRENATAL ANTIPSYCHOTIC EXPOSURE AND NEUROMOTOR PERFORMANCE DURING INFANCY

Archives of General Psychiatry, 2012 August; 69(8):787–94

AUTHORS: Johnson KC, LaPrairie JL, Brennan PA, Stowe ZN, Newport DJ
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BACKGROUND & AIM: Antipsychotics are now being used to treat depressive, bipolar and anxiety disorders as well as psychotic illness. These medications are known to cross the placenta, and data from animal studies have suggested that memory and learning deficits may occur in adult rats prenatally exposed to them. However, human reproductive safety data regarding the long-term neurodevelopmental impact of antipsychotics on the foetal central nervous system are very limited. The aim of this study was to assess the impact of prenatal exposure to antipsychotics, antidepressants, and maternal psychiatric illness on infants aged 6 months.

STUDY DESIGN: Prospective, observational study.

ENDPOINTS: Infant Neurological International Battery (INFANIB) score; number of trials required to achieve a 50% decrease in infant fixation during the visual habituation task; and mean time looking at the stimulus across 10 trials.

METHOD: The study included 309 mother–infant pairs from the Emory Women's Mental Health Program (n=270) and the general community (n=39). All the infants had been exposed during pregnancy to antipsychotics (n=22), antidepressants (n=202) or no psychotropic agents (n=85), and all were assessed at 6 months postpartum. Infant neurodevelopmental status was assessed using a visual habituation paradigm using a neutral female face, and the standardized INFANIB which examines neuromotor functioning by testing posture, muscle tone, reflexes and motor skills.

RESULTS: Significantly lower mean INFANIB scores were observed in infants prenatally exposed to antipsychotics compared with those exposed to antidepressants or no psychotropic agents (63.86 versus 68.58 and 70.12, respectively) after controlling for significant covariates (p<0.01 for each comparison). Only 19% of the antipsychotic-exposed infants fell within the INFANIB normal range compared with 32% of antidepressant-exposed and 50% of non-exposed infants. Prenatal medication exposure had no significant effect on the number of trials to habituate or the average looking time during the habituation task. Maternal psychiatric history, including depression, psychosis and overall severity/chronicity were significantly associated with INFANIB scores (all p<0.05), and the number of months of maternal depression during pregnancy was associated with longer habituation look times (p<0.02).

CONCLUSION: Prenatal exposure to antipsychotics may affect neuromotor performance in infants aged 6 months. However, the relative contribution of antipsychotic medications and maternal mental illness on the neurodevelopment of infants remains to be determined.

ASSOCIATION OF MENTAL DISORDERS IN EARLY ADULTHOOD AND LATER PSYCHIATRIC HOSPITAL ADMISSIONS AND MORTALITY IN A COHORT STUDY OF MORE THAN 1 MILLION MEN

Archives of General Psychiatry, 2012 August; 69(8):823–31

AUTHORS: Gale CR, Batty GD, Osborn DP, Tynelius P, Whitley E, Rasmussen F
CENTRE FOR CORRESPONDENCE: Child and Adolescent Public Health Epidemiology Group, Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden

BACKGROUND & AIMS: Mental disorders are associated with increased mortality. However, much of the evidence for this association is based on individuals whose disorder was severe enough to require hospital admission. The aims of this study were to assess the risk of death associated with mental disorders diagnosed in young men during a medical examination at conscription for military service, and to compare it with the risk associated with hospital admission for these disorders.

STUDY DESIGN: Prospective cohort study.

ENDPOINT: All-cause mortality.

METHOD: The analysis included 1,087,257 men who underwent psychiatric and medical assessment as part of military conscription examinations between 1969 and 1994 in Sweden. The mean age at assessment was 18.3 years (range 16–25), and none of the men had been previously admitted to a psychiatric hospital. Data for psychiatric hospital admission and mortality were obtained from national registers.

RESULTS: On the conscription examination, 61,677 (5.6%) of the men were diagnosed with schizophrenia, other non-affective psychotic disorders, bipolar disorders, depressive disorders, neurotic and adjustment disorders, personality disorders, alcohol-related disorders, or other substance use disorders during the conscription examination. During a mean follow-up of 22.6 years, there were 15,110 deaths. After adjustments, men who had received a diagnosis of any mental disorder had a significantly higher risk of death than those without such diagnosis. Age-adjusted hazard ratios according to diagnoses at conscription ranged from 1.81 (95% confidence interval 1.54–2.10) for depressive disorders through 3.78 (95% CI 1.68–8.31) for schizophrenia to 5.55 (95% CI 1.79–17.2) for bipolar disorders. Equivalent results according to subsequent hospital diagnoses ranged from 5.46 (95% CI 5.06–5.89) for neurotic and adjustment disorders to 11.2 (95% CI 10.4–12.0) for other substance use disorders in men born from 1951 to 1958, and increased in men born later. These associations were not primarily due to deaths from suicide and were partially attenuated for smoking, alcohol intake, intelligence, educational level and late-life socioeconomic status.

CONCLUSIONS: In a large cohort of men undergoing psychiatric assessment as part of military conscription examinations, a diagnosis of mental disorder was associated with increased mortality, demonstrating that the increased risk of premature death is not confined to those with illnesses severe enough for hospitalization.

LITHIUM AND GSK3-β PROMOTER GENE VARIANTS INFLUENCE WHITE MATTER MICROSTRUCTURE IN BIPOLAR DISORDER

Neuropsychopharmacology, 2013 January; 38(2):313–27

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BACKGROUND & AIM: Lithium is an important drug in the treatment of bipolar disorder, and works by inhibiting glycogen synthase kinase 3-β (GSK3-β), either directly by competing with magnesium or indirectly by increasing its phosphorylation state. Some genetic variants of GSK3-β are associated with less severe symptoms of bipolar disorder and a better clinical response to lithium, and have also been shown to protect against grey matter loss in schizophrenia and major depressive disorder. Bipolar disorder is characterized by white matter loss, and preliminary studies have reported a protective effect of lithium. The aim of the current study was to investigate the effects of GSK3-β promoter gene variants and lithium treatment on white matter integrity in bipolar disorder.

STUDY DESIGN: Cross-sectional study.

ENDPOINTS: Measures of white matter microstructure.

METHOD: The study included 70 patients with a diagnosis of bipolar disorder type I who had been affected by a major depressive episode. A total of 50 were drug-free while 20 were being treated with lithium, and none had received electroconvulsive therapy in the previous 6 months. DNA was extracted from whole blood samples, from which the rs334558 single nucleotide polymorphism was genotyped. Diffusion tensor imaging was performed to assess white matter integrity, and tract-based spatial statistics with threshold-free cluster enhancement were carried out to assess fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity. The differences in these parameters between rs334558*C carriers and T/T homozygotes were analysed by running a permutation-based non-parametric inference.

RESULTS: The GSK3-β rs334558*C variant was associated with increases in axial diffusivity in several white matter fibre tracts, including the corpus callosum, forceps major, anterior and posterior cingulum bundle, left superior and inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left posterior thalamic radiation, bilateral superior and posterior corona radiata, and bilateral corticospinal tract. Increases in mean diffusivity were also seen in many of the same regions. Lithium treatment was also associated with similar increases in axial and mean diffusivity. Duration of lithium treatment positively correlated with axial and mean diffusivity in several white matter tracts, mainly in the left hemisphere.

CONCLUSION: Lithium treatment and the less active GSK3-β promoter gene variants have a marked positive effect on white matter microstructure in bipolar disorder.

NEUROPSYCHOLOGICAL PERFORMANCE AND FAMILY HISTORY IN CHILDREN AT AGE 7 WHO DEVELOP ADULT SCHIZOPHRENIA OR BIPOLAR PSYCHOSIS IN THE NEW ENGLAND FAMILY STUDIES

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BACKGROUND & AIMS: While pre-morbid neurocognitive impairments have been found in patients with schizophrenia, much less is known about such pre-morbid impairments bipolar disorder. Furthermore, no studies to date have reported an association of family history of psychosis with neuropsychological impairment in younger children who later develop either schizophrenia or bipolar disorder. The aims of this study were to assess the neuropsychological functioning of young children who later developed psychosis, and to evaluate the impact of family history of psychosis on pre-morbid neuropsychological functioning.

STUDY DESIGN: Nested case–control study.

ENDPOINTS: Neuropsychological status at age 7, diagnosis of schizophrenia, and family history of psychosis.

METHOD: A total of 99 patients with psychosis and 101 controls were selected from the New England cohort of the Collaborative Perinatal Project, in which neuropsychological data were systematically collected at age 7 years for adults diagnosed with psychotic disorders. Cognitive functioning was assessed with a full-scale intelligence quotient (IQ) based on seven subtests, four normalized factor scores, and 10 individual scores from the intelligence and achievement tests used in the profile analysis.

RESULTS: IQ scores at age 7 were significantly lower (by 9.8 points) in children who went on to develop psychoses compared with healthy controls, as were scores for neuropsychological factors (Table); however, none of the comparisons between psychosis subgroups were significant. Exploratory analyses of individual IQ subtests showed that patients with schizophrenia disorders had non-significantly lower scores on all 10 individual measures than those with bipolar illness. Neuropsychological impairment at age 7 was identified in 42.2% of patients with schizophrenia, 22.9% of those with bipolar disorder and 7% of controls. Psychosis in first-degree relatives significantly increased the severity of childhood impairment for schizophrenia, but not for bipolar disorder.

CONCLUSION: Neuropsychological deficits were found in a substantial proportion of children who went on to develop schizophrenia as adults, particularly in children with a family history of schizophrenia in a first-degree relative. The findings were less pronounced in those who subsequently developed bipolar disorder.

Prospective age 7 childhood data from adult cases and controls: full-scale IQ and 4 neuropsychological factor scores (*p<0.01, **p<0.001)

	Controls (n=101)		All psychoses (n=99)	
	Mean	Standard deviation	Mean	Standard deviation
Full-scale IQ	106.8	12.6	97.0**	14.9
Factor 1 (academic achievement)	0.23	0.8	−0.31*	1.2
Factor 2 (verbal ability)	0.34	0.9	−0.36*	1.1
Factor 3 (perceptual motor)	0.15	1.0	−0.31	1.1
Factor 4 (attention and working memory)	0.34	0.8	−0.31**	1.1

Minimiinformation Sverige

Zyprexa® 2,5 mg, 5 mg, 7,5 mg, 10 mg dragerade tabletter (olanzapin)
Zyprexa® Velotab, 5 mg, 10 mg, 15 mg, 20 mg frystorkade tabletter (olanzapin)
Zyprexa® 10 mg pulver till injektionsvätska, lösning (olanzapin)
Olanzapin Lilly 2,5 mg, 5 mg, 7,5 mg, 10 mg, 15mg, 20mg, dragerade tabletter (olanzapin)

ATC-kod: N05AH03
Indikation: *Tabletter och Velotab*: Vuxna: behandling av schizofreni. Underhållsbehandling till patienter som visat initial klinisk respons. Behandling av måttlig till svår manisk episod. Profylaktisk behandling av återfall i bipolär sjukdom hos patienter som svarat på olanzapinbehandling vid manisk episod.
Injektionsvätska, lösning: Vuxna: Snabb kontroll av agitation och stört beteende hos patienter med schizofreni eller manisk episod när oral behandling inte är lämplig. Behandling med ZYPREXA pulver till injektionsvätska, lösning ska avslutas och oralt olanzapin sättas in så snart det är kliniskt lämpligt.
Kontraindikationer: Känd risk för glaukom med trång kammarvinkel.
Datum för översyn av produktresumén: 2012-06-27 (Zyprexa), 2012-04-10 (Olanzapin Lilly)
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