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REVIEW ARTICLE

How much do we know about schizophrenia and how well do we know it? Evidence from the Schizophrenia Library

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Background. True findings about schizophrenia remain elusive; many findings are not replicated and conflicting results are common. Well-conducted systematic reviews have the ability to make robust, generalizable conclusions, with good meta-analyses potentially providing the closest estimate of the true effect size. In this paper, we undertake a systematic approach to synthesising the available evidence from well-conducted systematic reviews on schizophrenia.

Method. Reviews were identified by searching Medline, EMBASE, CINAHL, Current Contents and PsycINFO. The decision to include or exclude reviews, data extraction and quality assessments were conducted in duplicate. Evidence was graded as high quality if reviews contained large samples and robust results; and as moderate quality if reviews contained imprecision, inconsistency, smaller samples or study designs that may be prone to bias.

Results. High- and moderate-quality evidence shows that numerous psychosocial and biomedical treatments are effective. Patients have relatively poor cognitive functioning, and subtle, but diverse, structural brain alterations, altered electrophysiological functioning and sleep patterns, minor physical anomalies, neurological soft signs, and sensory alterations. There are markers of infection, inflammation or altered immunological parameters; and there is increased mortality from a range of causes. Risk for schizophrenia is increased with cannabis use, pregnancy and birth complications, prenatal exposure to *Toxoplasma gondii*, childhood central nervous system viral infections, childhood adversities, urbanicity and immigration (first and second generation), particularly in certain ethnic groups. Developmental motor delays and lower intelligence quotient in childhood and adolescence are apparent.

Conclusions. We conclude that while our knowledge of schizophrenia is very substantial, our understanding of it remains limited.

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Key words: Biological aetiology, clinical phenomenology, cognition, epidemiology, intervention efficacy, risk factors.

Introduction

In the quest to increase our understanding of schizophrenia spectrum disorders, a vast and ever-expanding body of scientific literature documents the pursuit of this cause. However, robust evidence on schizophrenia remains elusive; many findings are not replicated, and conflicting results are common. In 2008, in an attempt to condense and clarify the state of the available evidence, a series of papers titled 'Just the Facts' assessed a selected sample of evidence from systematic reviews, meta-analyses and primary studies according to three criteria: reproducibility, durability of the findings and whether they were primary to schizophrenia (Keshavan *et al.* 2008; Tandon *et al.* 2008*a*,*b*, 2009, 2010). Similarly, in 2009 an informal consortium (the Minnesota Consensus Group) published a summary of expert opinion outlining the key facets contributing to our understanding of schizophrenia (MacDonald & Schulz, 2009). These papers provided a valuable and comprehensive collation of the literature, but focused on selected areas of research considered most relevant. This approach, while useful for informing priority research directions, does not take a systematic approach to inclusion and objective quality assessment of the available literature, and thus risks overlooking some areas of potential importance that may not have seemed sufficiently salient.

Given the broad state of current knowledge of schizophrenia, encompassing domains of clinical phenomenology, aetiology or pathogenesis, epidemiology and intervention efficacy, it appears imperative

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to undertake a systematic approach to synthesising the literature to avoid any selection biases. While evidence published in the peer-reviewed literature in these research domains is more reliable than information potentially gained by searching the Internet or through personal accounts, it is limited by the quality of the studies and the quality of the data. In this context, the Schizophrenia Library was developed to provide a free, objective and comprehensive ongoing appraisal of the schizophrenia literature, highlighting key areas where evidence is particularly strong, and areas where further attention is needed (www.schizophreniaresearch.org.au/library). To ensure that the most robust evidence is presented, the Library includes only well-conducted systematic reviews, many of which incorporate meta-analyses, and employs a relatively unbiased approach through rigorous systematic methodology, highly sensitive inclusion criteria, and objective quality assessment strategies.

This method does not look at results of individual studies in isolation, but at the body of evidence gained by numbers of studies assessing the same outcomes in the same population. Critics of systematic reviews and meta-analyses suggest that they are prone to publication bias as well as other biases that may be inherent in the primary studies. They have been criticized for ignoring single important or 'landmark' studies that may be highly powered and based on large unbiased samples (however uncommon these may be), with meta-analyses additionally criticized for undue leniency in statistically combining effect sizes of different samples and outcomes (that is, combining 'oranges with apples'). However, a well-conducted systematic review has the ability to make robust, generalizable conclusions exceeding those usually possible from a single primary study, with good meta-analyses potentially providing the closest estimate of the true effect size (Button *et al.* 2013). A well-conducted systematic review will develop research questions and inclusion criteria *a priori* (potentially even publish a review protocol), determine the presence of publication bias statistically, and investigate reasons for heterogeneity via subgroup analyses of differing study quality, samples, measures and outcomes, while also considering potential sources of bias originating from the primary studies. Subgroup analyses can shine light on important reasons for differing effects of treatments, for example, across differing samples and measures. It can also help guide the design of future primary research (Borenstein *et al.* 2009). Our approach uses qualitative assessment of the transparency with which systematic reviews report on the primary literature and, importantly, we determine the reliability of the evidence in question, using a common platform to explore the comparative strength of evidence spanning the broad research domains.

Knowledge gained solely from a compilation and critical appraisal of systematic reviews and meta-analyses is not the only pathway to the truth about schizophrenia. There is also expert consensus, selective reviews and the methods adopted by Keshavan, Tandon and colleagues (Keshavan *et al.* 2008; Tandon *et al.* 2008*a*,*b*, 2009, 2010), which entailed a combination of all three. We were interested in what sort of picture we would get of schizophrenia if we relied solely on a rigorous evaluation of published systematic reviews. While this would avoid many sources of bias, by capturing only what has been subjected to systematic review would ignore potentially true findings in the literature that had not been subjected to such reviews. For this reason, the Schizophrenia Library highlights topics that have not yet been reviewed systematically to encourage further research and reviews in those areas.

We therefore set about summarising the evidence that is currently available in the Schizophrenia Library, in an attempt to clarify what we currently know about schizophrenia and how confident we can be about this knowledge. What we can say that we know with confidence about schizophrenia is drawn from high-quality evidence; that is, evidence from systematic reviews containing large samples and robust results. What we think we know about schizophrenia is drawn from moderate-quality evidence; that is, systematic reviews with limitations in the available data including imprecision, inconsistency, smaller samples or observational study designs that may be prone to bias.

Method

Inclusion criteria and search strategy

Included in the Library are systematic reviews of studies of patients with schizophrenia and related (e.g. schizoaffective) disorders that are published in full text in English from the year 2000. Systematic reviews, by definition, contain an explicit method section with details of inclusion/exclusion criteria and search strategy. We excluded treatment guidelines, overviews, non-systematic reviews, and those systematic reviews with a high likelihood of reporting bias in that they addressed fewer than 33% of items according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al.* 2009). Reviews were identified by searching the databases Medline, EMBASE, CINAHL, Current Contents and PsycINFO using the search strategy: exp Schizophrenia/ OR schizophreni$.tw OR exp

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Psychotic Disorders/ OR schizo$.tw AND review.pt and medline.tw OR meta analysis.pt OR systematic$.tw and (review$ or overview$).tw OR meta?analy$.tw OR meta analy$.tw AND Limit to yr=2000-current. Hand searching reference lists and advance alerts was also undertaken. The decision to include or exclude reviews was conducted in duplicate, with any disagreements settled by discussion. The information contained in this paper is drawn solely from the Schizophrenia Library, but due to the large volume of reviews contained in it, we have cited in the tables only the most current reviews reporting the highest-quality evidence available for each topic. The latest Schizophrenia Library search update was conducted in February 2013, with current contents approaching 1500 reviews categorized into 450 topics. The Schizophrenia Library website (www.schizophrenia research.org.au/library) contains further details of all reviews meeting inclusion criteria. Reviews of genetic studies have not been included in the Library primarily because an existing website (www.szgene.org) has systematically collated the evidence from meta-analyses for genetic associations with schizophrenia (Allen *et al.* 2008).

Quality assessment and data extraction

Quality assessment and data extraction were conducted in duplicate by two of the authors (S.L.M. and A.M.S.) with training in conducting systematic reviews and meta-analyses. Any disagreements were settled by discussion. The reporting transparency of all systematic reviews was assessed using the PRISMA (Moher *et al.* 2009) statement checklist, and the assessments of included reviews are available on the Library website. Systematic reviews with a high risk of reporting bias were excluded. The evidence contained in the reviews was assessed using a strategy adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach (GRADE Working Group, 2004; Guyatt *et al.* 2011*a*). GRADE was developed primarily to appraise treatment or management strategies, using evidence from both randomized controlled trials and observational studies; however, in the absence of robust quality assessment guidelines for other pooled evidence, we have applied GRADE criteria to derive a broad indication of the strength and quality of all the results. In this approach, evidence from randomized controlled trials is considered to be high quality, but may be downgraded to moderate or low quality in the presence of: (1) inconsistency of results (statistically significant heterogeneity of results across studies, assessed using I^2 which represents the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error, and/or using the Q test for within-group heterogeneity) (Guyatt *et al.* 2011*b*); (2) imprecise (wide) confidence intervals (>0.5 in either direction for continuous measures, and >0.25 for risk/odds ratios) (GRADEpro, version 32 for Windows, (http://tech.cochrane.org/gradepro); Guyatt *et al.* 2011*c*); (3) estimated effect sizes from indirect comparisons, populations or interventions (Guyatt *et al.* 2011*d*); and/or (4) a small number of studies reviewed that include only small samples (Cochrane Collaboration, 2008; Guyatt *et al.* 2011*a*). Conversely, evidence from observational studies is intrinsically considered low quality due to the possible effects of confounding factors, but this evidence may be upgraded to moderate or high quality if the data are consistent or precise, if effect sizes or study samples are large, or if there is a dose-dependent response (Guyatt *et al.* 2011*a*). GRADE recommendations of the assessment of potential publication bias, and the extent to which uncontrolled confounders may influence the observed effects were not conducted because these issues are not reported in most reviews. A low-quality rating does not necessarily imply poor-quality research, but is intended to highlight the need for more targeted research in these areas, conducted in accordance with transparent reporting guidelines.

Effect sizes are quantified such that statistically significant ($p<0.05$) correlation coefficients and standardized mean differences of about 0.20 represent a small effect, about 0.50 a medium effect, and about 0.80 or higher a large effect (Cohen, 1988). Statistically significant risk and odds ratios around 1.00 represent a small effect, effects $\geqslant 2.00$ or $\leqslant 0.50$ represent a medium effect, and effects $\geqslant 5.00$ or $\leqslant 0.20$ represent a large effect (Rosenthal, 1996). Significant effect sizes that are unable to be quantified using these standardized guidelines are allocated to an 'unclear effect sizes' category (e.g. incidence rates, prevalence rates, non-standardized mean differences). For this paper, we have included only evidence reporting significant differences between groups for the primary outcome of interest in each review for each comparison in question (details of all results are available on the Library website), and we have grouped this evidence into three domains: treatments, physical or clinical features, and epidemiology. Tables 1–3 describe the significant findings for each domain. Note that all treatments identified here, apart from comparisons of antipsychotics with placebo, are adjunctive to ongoing antipsychotic medication. The evidence with small or unclear effect sizes is too numerous, and some may be insignificant, to warrant presentation here other than by inspection of Tables 1–3.

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Table 1. *Treatments*

- High-quality evidence
  - Large effect sizes[a]
    - Symptoms and relapse
      - Combined pharmaceutical and psychosocial treatment programmes reduce symptoms (Bird *et al.* 2010) and relapse rates (Alvarez-Jimenez *et al.* 2011) in psychotic patients, and prevent transition to psychosis in people at ultra-high risk (Preti & Cella, 2010)
    - Other outcomes
      - Social skills training improves social interactions (Pfammatter *et al.* 2006; Kurtz & Mueser, 2008)
  - Medium effect sizes[a]
    - Symptoms and relapse
      - Antipsychotics improve overall symptoms and reduce relapse rates more than placebo (Mota *et al.* 2002; Duggan *et al.* 2005; Irving *et al.* 2006; Adams *et al.* 2007; Nussbaum & Stroup, 2008; Rattehalli *et al.* 2010; Belgamwar & El-Sayeh, 2011; Leucht *et al.* 2012*a*, *b*)
      - Second-generation antipsychotics (particularly risperidone or olanzapine in various doses) have less extrapyramidal side effects than first-generation antipsychotics (particularly haloperidol in various doses) in patients with first-episode psychosis (Crossley *et al.* 2010)
      - Adjunctive rTMS applied at low frequency (1 Hz) via continuous stimulation to the left temporoparietal cortex reduces auditory hallucinations in the short term (Aleman *et al.* 2007; Demeulemeester *et al.* 2012; Slotema *et al.* 2012), adjusting for inadequate sham conditions and possible publication bias (Demeulemeester *et al.* 2012). Adjunctive rTMS given at high frequency (10 to 20 Hz) applied to the left dorsolateral prefrontal cortex reduces negative symptoms in the short term compared with sham (Dlabac-de Lange *et al.* 2010)
      - Adjunctive oestrogen improves positive and negative symptoms in female patients compared with placebo (Begemann *et al.* 2012)
      - Adjunctive *Ginkgo biloba* reduces positive symptoms, particularly in patients taking first-generation antipsychotics (Singh *et al.* 2010*a*)
      - Cognitive behavioural therapy reduces symptoms, particularly positive symptoms over the long term compared with standard care (Pfammatter *et al.* 2006; Bird *et al.* 2010) and may be more effective over the long term than other psychosocial treatments (Sarin *et al.* 2011; Jones *et al.* 2012)
      - Adjunctive antidepressants improve negative symptoms (Singh *et al.* 2010*b*)
      - Psychoeducation reduces relapse rates (Pfammatter *et al.* 2006)
    - Other outcomes
      - Intensive case management increases treatment adherence and independent living (Dieterich *et al.* 2010)
      - Cognitive remediation improves attention, memory, executive functioning, cognitive flexibility, processing speed, social cognition, social functioning and problem solving (McGurk *et al.* 2007)
      - Integrated psychological therapy improves cognitive and global functioning (Roder *et al.* 2011)
      - Vocational rehabilitation improves competitive employment (Crowther *et al.* 2001)
      - Psychoeducation reduces levels of familial expressed emotion, and improves treatment adherence (Pfammatter *et al.* 2006; Xia *et al.* 2011)
  - Small effect sizes[a]
    - Symptoms and relapse
      - Symptoms are reduced with adjunctive lithium (Leucht *et al.* 2007*a*), NMDA receptor modulators (when not adjunctive to clozapine) (Singh & Singh, 2011) and electroconvulsive therapy (Tharyan & Adams, 2005)
    - Other outcomes
      - Processing speed, verbal fluency, learning, motor skills and global cognition ability are improved in patients taking second-generation antipsychotics compared with patients taking first-generation antipsychotics (Woodward *et al.* 2005)
- Moderate-quality evidence
  - Medium effect sizes[a]
    - Symptoms and relapse
      - Adjunctive non-steroidal anti-inflammatory drugs improve symptoms, particularly positive symptoms (Sommer *et al.* 2012)
      - Clozapine improves symptoms more than typical antipsychotics for treatment-resistant patients, with fewer extrapyramidal effects (Chakos *et al.* 2001; Moncrieff, 2003)
      - Adjunctive *Ginkgo biloba* reduces negative symptoms, particularly in patients taking first-generation antipsychotics (Singh *et al.* 2010*a*)
      - Music therapy improves global state (Gold *et al.* 2009; Mössler *et al.* 2011)

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Family interventions reduce relapse rates (Pharoah *et al.* 2010)
Social skills training improves general psychopathology and reduces relapse rates (Pfammatter *et al.* 2006; Kurtz & Richardson, 2012)

Other outcomes
Crisis interventions reduce family disruption (Murphy *et al.* 2012)
Family interventions improve functioning (Pharoah *et al.* 2010)

rTMS, Repetitive transcranial magnetic stimulation; NMDA, *N*-methyl-D-aspartate; SMD, standardized mean difference; RR, risk ratio; OR, odds ratio.

[a] Interpretation of effect sizes. Large effect sizes=SMD $\geqslant$0.80, RR/OR $\geqslant$5.00 or $\leqslant$0.20. Medium effect sizes=SMD 0.20 to 0.70, RR/OR 2.00 to 4.00 or 0.30 to 0.50. Small effect sizes=SMD <0.20, RR/OR <2.00 (Cohen, 1988; Rosenthal, 1996). Except where otherwise indicated, patients receiving interventions are compared with patients receiving standard care.

Results

High-quality evidence

Large effect sizes

With respect to treatments (Table 1), large effects were found for social skills training in improving social interactions, and combined pharmaceutical and psychosocial treatment programmes for reducing symptoms and relapse rates. Among the physical and clinical features there were large effects for increased striatal presynaptic dopamine function and poor cognitive functioning on several measures (Table 2). There were no large effect sizes in the area of epidemiology (Table 3).

Medium effect sizes

Many treatments for schizophrenia fall into this grouping. Antipsychotic drugs compared with placebo have a medium effect size in reducing symptoms and relapse rates as reported in several different meta-analyses, and second-generation antipsychotics, particularly risperidone and olanzapine, cause fewer extrapyramidal side effects than first-generation drugs, particularly haloperidol, in first-episode psychosis. Low-frequency repetitive transcranial magnetic stimulation (rTMS) reduces auditory hallucinations, and high-frequency rTMS reduces negative symptoms, as do adjunctive antidepressants. Oestrogen therapy in women reduces positive and negative symptom severity, and *Ginkgo biloba* reduces positive symptoms. Among psychosocial treatments, cognitive behavioural therapy reduces symptoms, especially positive symptoms, but does not appear to differ from other psychosocial treatments in this regard, while psychoeducation, intensive case management, cognitive remediation, vocational rehabilitation and integrated psychological therapy all have medium-size effects on several outcome variables as detailed in Table 1.

Physical features of medium effect size include: increased volume of basal ganglia, lateral and third ventricles, and frequency of cavum septum pellucidum; decreased whole brain volume (grey and white matter); decreased grey matter volume in several brain regions as described in Table 2; decreased levels of *N*-acetyl aspartate, and a variety of changes in the N400 wave on recordings of event-related potentials. In relation to clinical features, medium effect sizes are found for a range of cognitive deficits in first-degree relatives (Table 2); theory of mind deficits in clinical high-risk samples; and the relationship of neurocognition and social cognition to functional outcome. Neutral stimuli evoke greater aversive emotion and arousal in patients, co-morbid substance use disorders are associated with fewer negative symptoms, and former cannabis-using patients have better cognitive performance than those without former cannabis use.

In the area of epidemiology, there are medium effect sizes for higher rates of cannabis use during adolescence in patients, and an earlier age of onset in cannabis-using patients. High rates of current and lifetime cannabis use are recorded in patients. From a developmental perspective there are medium effect sizes for delays in walking and poorer motor skills in childhood, and lower intelligence quotient (IQ) scores in childhood and adolescence.

Moderate-quality evidence

Large effect sizes

There are no treatments that fall into this category of evidence. Among physical features there are large effects for increased serum S100B levels in patients, increased markers of infection by several organisms including human endogenous retroviruses, *Chlamydophilia pneumoniae*, *Chlamydophilia psittaci*, *Toxocara* and *Toxoplasma gondii* in patients, and reduced sensory gating (increased P50 ratio) in both patients and their first-degree relatives. Large effect sizes are also found for reduced mismatch negativity (effect size increasing with duration of illness) and minor physical anomalies. In relation to other physical and clinical features,

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Table 2. *Physical or clinical features*

High-quality evidence
- Large effect sizes[a]
  - Patients have increased striatal presynaptic dopamine function (synthesis and release) (Fusar-Poli & Meyer-Lindenberg, 2013*a*), but no difference in presynaptic dopamine transporter density (Howes *et al.* 2012; Fusar-Poli & Meyer-Lindenberg, 2013*a*, *b*)
  - Patients have poor information processing, language skills, verbal learning, prospective memory, working memory and theory of mind (Bokat & Goldberg, 2003; Dickinson *et al.* 2007; Bora *et al.* 2009*a*; Forbes *et al.* 2009; Wang *et al.* 2009; Bora & Pantelis, 2013)
- Medium effect sizes[a]
  - Patients show increases in volume of the basal ganglia, lateral and third ventricles and increased frequency of large cavum septum pellucidum. They show reductions in whole brain volume, grey matter volume in the frontal lobe, superior temporal gyrus, medial temporal lobe, thalamus, insula, anterior cingulate, amygdala, inferior parietal gyrus and cerebellum, and reduced white matter in the mid-sagittal corpus callosum (Wright *et al.* 2000; Baiano *et al.* 2007; Arnone *et al.* 2008; Kempton *et al.* 2010; Adriano *et al.* 2010, 2012; Chan *et al.* 2011; Olabi *et al.* 2011; Trzesniak *et al.* 2011*a*, *b*; Shepherd *et al.* 2012; Fusar-Poli *et al.* 2013; Haijma *et al.* 2013)
  - Patient show increased N400 peak latency and decreased N400 effect during semantic priming tasks, as well as more negative N400 amplitude during congruent stimuli, particularly tasks involving long stimulus onset asynchrony (>500 ms) (Wang *et al.* 2011)
  - Patients have decreased levels of *N*-acetyl aspartate (Brugger *et al.* 2011; Kraguljac *et al.* 2012)
  - First-degree relatives of patients show deficits in general intelligence, executive functioning, attention, language, visual and verbal memory, short- and long-term episodic memory, theory of mind, and smooth pursuit eye movement (Sitskoorn *et al.* 2004; Szoke *et al.* 2005; Whyte *et al.* 2005; Snitz *et al.* 2006; Trandafir *et al.* 2006; Calkins *et al.* 2008; Bora & Pantelis, 2013)
  - People at high clinical risk for psychosis show deficits in theory of mind (Bora & Pantelis, 2013)
  - Neurocognition and social cognition are related to functional outcomes (Fett *et al.* 2011; Schmidt *et al.* 2011; Irani *et al.* 2012)
  - Patients report greater aversive emotion and arousal to neutral stimuli (Cohen & Minor, 2010; Llerena *et al.* 2012)
  - Patients with a current substance use disorder have fewer negative symptoms than patients without a current substance use disorder (Potvin *et al.* 2006)
  - Patients with former cannabis use perform better on cognitive tasks than patients without former cannabis use (Yucel *et al.* 2012)
- Small effect sizes[a]
  - Cognitive deficits are greater in schizophrenia than bipolar disorder (Krabbendam *et al.* 2005; Bora *et al.* 2009*b*; Stefanopoulou *et al.* 2009) and are related to lower levels of insight (Aleman *et al.* 2006)
  - Negative and disorganized symptoms are related to lower IQ, poor reasoning, attention, executive functioning, language skills, learning, speed of processing, visual and verbal memory and social cognition (Nieuwenstein *et al.* 2001; de Gracia Dominguez *et al.* 2009; Dibben *et al.* 2009; Ventura *et al.* 2010, 2013)
  - Patients are more likely to be non-right handed (Sommer *et al.* 2001)
  - There is increased severity of negative symptoms in patients with a family history of psychosis compared with patients without a family history (Esterberg *et al.* 2010), and significant concordance of disorganized and reality distortion symptoms between siblings with schizophrenia (Rietkerk *et al.* 2008)
  - People at high clinical risk for psychosis show deficits in general intelligence, executive functioning, verbal and visual memory, verbal fluency, attention, working memory and social cognition (Fusar-Poli *et al.* 2012*b*)

Moderate-quality evidence
- Large effect sizes[a]
  - Patients have increased S100B protein levels in serum (Schroeter *et al.* 2009)
  - Patients have increased markers for human endogenous retroviruses, *Chlamydophilia pneumoniae, Chlamydophilia psittaci, Toxocara* and *Toxoplasma gondii* (Arias *et al.* 2011; Torrey *et al.* 2012)
  - Patients and their first-degree relatives show increased P50 ratio (not latency), indicating reduced sensory gating (Bramon *et al.* 2004; de Wilde *et al.* 2007), which may not be improved by antipsychotic medication (Su *et al.* 2012)
  - Patients show reduced mismatch negativity, and the effect size increases with increasing duration of illness (Umbricht & Krljes, 2005)
  - Patients have increased occurrence of minor physical anomalies of the head, eyes, mouth, ears, hands and feet (Weinberg *et al.* 2007; Xu *et al.* 2011)

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Patients show increased rigidity of thought, poor IQ, pre-morbid IQ, perceptual problem solving ability, attention, short-term and long-term memory, olfactory identification and acuity, executive functioning, social and emotion processing, slower motor and processing speed, smooth pursuit eye movement and self-recognition (Johnson-Selfridge & Zalewski, 2001; Schultz & Searleman, 2002; Pelletier *et al.* 2005; Dickinson *et al.* 2007; Sprong *et al.* 2007; O'Driscoll & Callahan, 2008; Bora *et al.* 2009*a*; Mesholam-Gately *et al.* 2009; Rajji *et al.* 2009; Chan *et al.* 2010*a*; Knowles *et al.* 2010; Kohler *et al.* 2010; Khandaker *et al.* 2011; Cohen *et al.* 2012; Savla *et al.* 2012; Waters *et al.* 2012)

Antipsychotic-free patients have increased sleep latency and total sleep time, and decreased sleep efficiency and stage 2 sleep (Chouinard *et al.* 2004)

Patients and their first-degree relatives show increased neurological soft signs, including dysfunction in motor coordination and sequencing, sensory integration and disinhibition compared with controls (Chan *et al.* 2010*b*, *c*)

Patients with a cocaine use disorder show increased extrapyramidal symptoms (Potvin *et al.* 2009)

Medium effect sizes[a]

Patients have reduced blood BDNF concentrations, regardless of medication dosage or medication status (Green *et al.* 2011)

Patients have increased markers for Borna disease virus (Arias *et al.* 2011)

Patients show increases in immune system molecules IFN-γ, TGF-β, TNF-α and IL-6; acutely relapsed patients also show increases in IL-10, IL-IRA and IL-8; and first-episode (untreated) patients also show increases in sIL-2R, IL-1β and IL-12. Antipsychotic treatment normalizes levels of IL-1β, TGF-β and IL-6 but not IL-2, IFN-γ and TNF-α (Miller *et al.* 2011)

Patients and first-degree relatives have reduced P300 amplitude and increased P300 latency, particularly when patients are medication-free (Bramon *et al.* 2004, 2005). Patients have increased delta and theta wave activity (Galderisi *et al.* 2009)

Patients with first-episode psychosis have poor processing speed (Mesholam-Gately *et al.* 2009)

Increased severity of positive and negative, but not depressive, symptoms is related to lower levels of insight (Mintz *et al.* 2003)

People at high genetic and clinical risk for psychosis show impaired olfactory identification, but not people who are either at high genetic or clinical risk (Cohen *et al.* 2012)

Patients have reduced pain response; reduced physical response and increased sensory threshold (Potvin & Marchand, 2008)

Small effect sizes[a]

Patients have increased levels of markers for herpes virus-2 (Arias *et al.* 2011)

Patients have decreased levels of essential fatty acids (Fenton *et al.* 2000; van der Kemp *et al.* 2012) and glutamate (Marsman *et al.* 2013), and increased dopamine receptor availability (Howes *et al.* 2012), and glutamine (Marsman *et al.* 2013)

Patients have altered dermatoglyphics, specifically reduced total finger ridge count and reduced total A–B ridge count (Golembo-Smith *et al.* 2012)

Increased severity of positive symptoms is related to poor attention/vigilance (Ventura *et al.* 2010)

Unclear effect sizes[a]

Patients experiencing auditory hallucinations show activation in the bilateral inferior frontal gyri, postcentral gyri, and left inferior parietal lobule, bilateral insula, hippocampus and temporal lobe, compared with when they are not hallucinating (Jardri *et al.* 2011). Compared with patients without hallucinations, hallucinating patients show decreased activation during verbal tasks in the left superior and middle temporal gyri, anterior cingulate cortex and left premotor cortex (Kuhn & Gallinat, 2012). Compared with controls, hallucinating patients show decreased activation during auditory stimuli in the superior temporal gyrus, anterior cingulate, thalamus, superior frontal gyrus and hippocampus (Kompus *et al.* 2011)

During executive functioning and working memory tasks, patients show decreased functional activity in the frontal lobe, parietal cortex, insula/claustrum, fusiform gyrus, cerebellum, right putamen, hippocampus and thalamus, and increased activity in the parietal and anterior cingulate cortex, temporal lobe, lingual gyri, insula and amygdala (Achim & Lepage, 2005; Van Snellenberg *et al.* 2006; Minzenberg *et al.* 2009; Ragland *et al.* 2009). First-degree relatives of patients also show altered brain functional activity compared with healthy controls (MacDonald *et al.* 2009; Goghari, 2011)

During emotion processing, patients show decreased functional activity in the amygdala and hippocampus, superior frontal gyrus, anterior cingulate cortex, medial frontal cortex, temporal lobe and temporo-occipital gyri (Li *et al.* 2010; Anticevic *et al.* 2012; Taylor *et al.* 2012). During emotion perception tasks, patients show decreased activation of the anterior cingulate, medial frontal gyrus, temporal lobe and subcortical structures (Taylor *et al.* 2012)

Patients have reduced white matter integrity in the frontal lobe, corpus callosum, cingulate gyrus, middle and superior temporal gyri, internal and external capsules, parahippocampal gyrus, occipital lobe, posterior cingulate, hippocampus, entorhinal gyrus, fusiform gyrus, amygdala, parietal lobe, arcuate fasciculus and cerebellum (Ellison-Wright & Bullmore, 2009; Bora *et al.* 2011; Patel *et al.* 2011; Kuswanto *et al.* 2012)

The brain of a person with schizophrenia weighs less than the healthy brain (Harrison *et al.* 2003)

First-degree relatives show grey matter volume reductions in the amygdala/parahippocampal gyrus, lentiform nucleus, and medial prefrontal cortex relative to controls. Patients with schizophrenia show reductions of bilateral insula, inferior frontal gyrus and anterior cingulate, relative to unaffected family members (Palaniyappan *et al.* 2012)

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Table 2 (*cont.*)

	Patients have increased basal cortisol, particularly antipsychotic-naïve patients (Bradley & Dinan, 2010), and increased phospholipase A_2 (Berger *et al.* 2002)
	Antipsychotic-naïve patients have reduced baseline temperature, less diurnal variation and changes to circadian peaks, differences in variation between peripheral and core temperature and an altered response (either greater or less) to temperature stress (Chong & Castle, 2004)
	DSM diagnostic criteria assign more males with psychosis to a schizophrenia diagnosis compared with ICD-9, which shows no differences in gender distribution (Beauchamp & Gagnon, 2004)

IQ, Intelligence quotient; BDNF, brain-derived neurotrophic factor; IFN, interferon; TGF, transforming growth factor; TNF, tumour necrosis factor; IL, interleukin; IL-IRA, interleukin receptor; sIL-2R, soluble receptor for interleukin 2; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; SMD, standardized mean difference; RR, risk ratio; OR, odds ratio.

[a] Interpretation of effect sizes. Large effect sizes=SMD $\geqslant$0.80, RR/OR $\geqslant$5.00 or $\leqslant$0.20. Medium effect sizes=SMD 0.20 to 0.70, RR/OR 2.00 to 4.00 or 0.30 to 0.50. Small effect sizes=SMD<0.20, RR/OR <2.00 (Cohen, 1988; Rosenthal, 1996). Unclear effect sizes=unable to be quantified using standardized guidelines. Except where otherwise indicated, schizophrenia patients or their relatives are being compared with healthy controls.

a wide range of cognitive deficits have been confirmed in several studies as shown in Table 2, and antipsychotic-free patients have abnormal sleep patterns on several parameters (Table 2). Patients and first-degree relatives have increased neurological soft signs, and patients with cocaine use disorder have increased extrapyramidal symptoms.

In epidemiological research there are large effects for increased exposure to *Toxoplasma gondii* antibodies and maternal diabetes *in utero*, for low birth weight and for experience of childhood adversities. There are similar effect sizes for rates of schizophrenia in black Caribbean and African migrant groups and their descendants, particularly those living in white communities. Patients have increased mortality due to a variety of causes (Table 3), increased risk of visual impairment and higher rates of tobacco smoking.

Medium effect sizes

In the area of treatment there are medium effect sizes for adjunctive non-steroidal anti-inflammatory drugs (especially for reducing positive symptoms), crisis intervention in reducing family disruption, and clozapine for treatment resistance compared with 'typical' antipsychotics. Similar-level effects are found for social skills therapy for improving general psychopathology and relapse rates, *Ginkgo biloba* for improving negative symptoms, music therapy for improving global state, and family interventions for reducing relapse rates and improving functioning.

Among physical features there are medium effect sizes for reduced brain-derived neurotrophic factor levels in serum, regardless of medication status; increased markers for Borna disease virus; increases in a variety of immune system molecules, some of which are normalized by antipsychotic drugs (Table 2); and reduced P300 amplitude and increased P300 latency in patients and their first-degree relatives. For clinical features, first-episode psychosis patients have poor processing speed; lower levels of insight are associated with increased severity of positive and negative symptoms (but not depressive symptoms), and people at high genetic and clinical risk for psychosis show impaired olfactory identification. Patients show a reduced pain response with increased sensory threshold.

In epidemiological studies there are medium effect sizes for exposure to urbanicity, emergency caesarean section, congenital malformations and uterine atony. There is increased reporting of childhood central nervous system (CNS) viral infections, and increased rates of schizophrenia in first- and second-generation immigrants (especially coming from developing countries). Internalized stigma is related to several adverse subjective and objective phenomena (Table 3). Lifetime risk of suicide is 1.8% (5.6% in the earlier stages of illness), and several clinical factors are significantly associated with suicide (Table 3). Increased symptom severity is associated with decreased objective and subjective quality of life. Longer duration of untreated psychosis is related to poorer clinical and social outcomes and poorer treatment response. Rates of relapse of positive symptoms are 28% at 1 year and up to 54% at 3 years, and are associated with substance use, poor treatment adherence, high levels of critical family comments and poor pre-morbid adjustment. Physicians are the most likely point of first contact, but the most common source of referral to mental health care is the emergency services.

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Table 3. *Epidemiology*

High-quality evidence
- Medium effect sizes[a]
  - Patients have experienced more cannabis use in adolescence (Moore *et al.* 2007), and cannabis-using patients have an earlier age of onset than non-using patients (Large *et al.* 2011*a*)
  - Around 16% of patients are current cannabis users and around 27% have used cannabis sometime over their lifetime (Koskinen *et al.* 2010)
  - Patients have experienced delays in learning to walk in infancy, and had poor motor skills in childhood (Welham *et al.* 2009; Dickson *et al.* 2012). Patients showed lower IQ in childhood and adolescence (Woodberry *et al.* 2008; Dickson *et al.* 2012)
- Unclear effect sizes[a]
  - Worldwide prevalence is around 0.3% for 1-year prevalence, 0.5% for lifetime prevalence and 0.72% for lifetime morbid risk prevalence (Saha *et al.* 2005)
  - Worldwide incidence is between 11 and 15.2 per 100 000 with a 5.6-fold variance across regions (McGrath *et al.* 2004)

Moderate-quality evidence
- Large effect sizes[a]
  - Patients have experienced increased exposure to *Toxoplasma gondii* antibodies *in utero* (Fekadu *et al.* 2010), maternal diabetes, low birth weight (<2000 g) (Cannon *et al.* 2002) and childhood adversities (Matheson *et al.* 2012)
  - There are increased rates of schizophrenia in black Caribbean and black African immigrant groups and in their descendants, particularly those living in white communities (Cantor-Graae & Selten, 2005; Bourque *et al.* 2011; Kirkbride *et al.* 2012)
  - Patients have increased mortality due to natural causes, particularly from cardiovascular, coronary, digestive, endocrine, infectious, genito-urinary, neoplastic, neurological and respiratory diseases (Saha *et al.* 2007)
  - Patients have an increased risk of visual impairment (Oud & Meyboom-De Jong, 2009)
  - Patients show higher rates of smoking (de Leon & Diaz, 2005)
- Medium effect sizes[a]
  - Patients have increased rates of exposure to urbanicity (Vassos *et al.* 2012), emergency caesarean section, congenital malformations and uterine atony (Cannon *et al.* 2002)
  - Patients have increased reporting of childhood central nervous system viral infections (Khandaker *et al.* 2012)
  - There are increased rates of schizophrenia in first- and second-generation immigrants, particularly immigrants from developing countries (McGrath *et al.* 2004; Cantor-Graae & Selten, 2005; Saha *et al.* 2005; Bourque *et al.* 2011)
  - Increased internalized stigma is related to reduced hope, self-esteem, empowerment, self-efficacy, quality of life, social support and treatment adherence (Livingston & Boyd, 2010)
  - Lifetime risk of suicide in patients is around 1.8%, with risk in the earlier stages of the illness being around 5.6% (Palmer *et al.* 2005). Factors significantly associated with suicide include a history of deliberate self-harm, hopelessness, feelings of guilt or inadequacy, depressed mood, suicidal ideas and a family history of suicide (Large *et al.* 2011*b*)
  - Increased positive symptoms, negative symptoms and general psychopathology are related to decreased subjective and objective quality of life and general well-being (Eack & Newhill, 2007)
  - Longer duration of untreated psychosis is related to poorer clinical and social outcomes, and poorer response to treatment (Marshall *et al.* 2005; Large & Nielssen, 2008; Farooq *et al.* 2009; Boonstra *et al.* 2012)
  - Rates of positive symptom relapse are around 28% at 1 year post-treatment and up to 54% at 3 years post-treatment and are associated with substance use, poor treatment adherence, high levels of critical family comments and poor pre-morbid adjustment (Alvarez-Jimenez *et al.* 2012)
  - Physicians are the most likely first point of contact and the most common referral source to mental health care is emergency services (Anderson *et al.* 2010)
- Small effect sizes[a]
  - Patients have increased rates of pre-morbid traumatic brain injury (Molloy *et al.* 2011)
  - There is an increased risk of schizophrenia with winter/spring births, increased latitude and decreased annual mean daily temperature in the northern hemisphere (Kinney *et al.* 2009)
  - Patients have increased childhood and early adolescent social withdrawal, anxiety, depression, social maladjustment, deviant behaviour, aggression, disruptiveness, delusions, hallucinations and general psychopathology. They also have delays in onset and development of talking, poor receptive and expressive language, and poor oral and reading skills in childhood (Tarbox & Pogue-Geile, 2008; Welham *et al.* 2009; Rubio *et al.* 2012)
  - Patients have older fathers at birth (>50 years) (Miller *et al.* 2011)
  - People with a family history of psychosis have an earlier age of onset than people without a family history. Males have an earlier age of onset than females, with no difference between genders after age 45 years (Esterberg *et al.* 2010; Kirkbride *et al.* 2012)

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Table 3 (*cont.*)

Unclear effect sizes[a]
Patients have decreased rates of rheumatoid arthritis, malignant melanoma, prostate cancer and colorectal cancer and increased risk of cardiovascular disease, diabetes, metabolic syndrome, osteoporosis, post-surgery mortality, respiratory failure, deep venous thrombosis, pulmonary embolism and sepsis (Leucht *et al.* 2007*b*; Catts *et al.* 2008; Copeland *et al.* 2008; Osborn *et al.* 2008; Meyer & Stahl, 2009; Oud & Meyboom-De Jong, 2009). Patients also have increased risk of anxiety and personality disorders (Newton-Howes *et al.* 2008; Achim *et al.* 2011)
Patients have increased exposure *in utero* to maternal herpes simplex virus, upper respiratory tract, genital or reproductive infections, and inflammatory cytokines TNF-α and IL-8 (Khandaker *et al.* 2013)
Increased risk of violence in people with schizophrenia may be explained by co-morbid substance use (Fazel *et al.* 2009)
Patients report increased rates of criminal victimization (Maniglio, 2009)
Longer duration of untreated psychosis is associated with the presence of obligatory dangerousness criterion for compulsory treatment (Large *et al.* 2008)
Up to 80% of people following a first episode of psychosis have good or intermediate outcomes up to 3 years from onset (Menezes *et al.* 2006)
Rates of recovery and remission increase over time, from around 13% of patients at 5 years to around 68% of patients by 32 years after first diagnosis (Leucht & Lasser, 2006)
In people at ultra-high risk for psychosis, the transition to psychosis rate is approximately 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years, regardless of the psychometric instruments used to measure transition. Factors increasing transition rates include increasing age, and no exposure to antipsychotic treatment. Studies using the basic symptoms approach to define high risk report higher transition to psychosis rates (48%) than studies using the ultra-high-risk criteria (27%) (Fusar-Poli *et al.* 2012*a*)
The sensitivity of instruments based on ultra-high-risk criteria is 0.81 and specificity is 0.67 (Chuma & Mahadun, 2011)
The public, patients and their relatives predominantly view psychosocial factors as being the cause of schizophrenia, while clinicians predominantly endorse biogenetic causes of schizophrenia. Psychosocial causal views are related to positive attitudes and biogenetic causal views are related to negative attitudes towards schizophrenia (Read *et al.* 2006)
Incidence but not prevalence of schizophrenia is higher in males compared with females (McGrath *et al.* 2004; Saha *et al.* 2005)
Prevalence rates of psychotic disorders in forensic settings are around 3.7%; 3.6% for males and 3.9% for females; 5.5% in low-/middle-income countries and 3.5% in high-income countries (Fazel & Seewald, 2012). Prevalence rates of psychotic disorders in homeless people are around 11% to 13% (Folsom & Jeste, 2002; Fazel *et al.* 2008)
Heritability estimate is 81% (Sullivan *et al.* 2003)

IQ, Intelligence quotient; TNF, tumour necrosis factor; IL, interleukin; SMD, standardized mean difference; RR, risk ratio; OR, odds ratio.

[a] Interpretation of effect sizes. Large effect sizes=SMD $\geqslant$0.80, RR/OR $\geqslant$5.00 or $\leqslant$0.20. Medium effect sizes=SMD 0.20 to 0.70, RR/OR 2.00 to 4.00 or 0.30 to 0.50. Small effect sizes=SMD <0.20, RR/OR<2.00 (Cohen, 1988; Rosenthal, 1996). Unclear effect sizes=unable to be quantified using standardized guidelines. Except where otherwise indicated, schizophrenia patients are being compared with healthy controls.

Discussion

The summary of evidence described above is unique in that it presents a thorough overview of our current knowledge about schizophrenia while providing an objective quality assessment of this knowledge. It was expected that our methodology would yield some results that are 'well known or somewhat trivial' as well as others that are not so well known, unexpected and potentially important.

However, knowledge is not the same as comprehension or understanding, and this knowledge base requires careful reflection if the field is to move closer towards understanding. In doing so it is necessary to consider the sources of this knowledge, to appraise the level of certainty warranted by research findings, and carefully weigh the evidence in the face of a preponderance of medium to small effect sizes and lower-quality evidence. In biomedical research, bias is the primary source of false-positive findings (Ioannidis, 2005). The consequences of bias are high rates of refutation, conflicting or contradictory results, and failure of replication. More highly powered, large studies can help reduce the occurrence of such outcomes, and low-bias meta-analyses may also help in approximating true effects (Ioannidis, 2005; Button *et al.* 2013). The latter is the approach we have taken here, a critical appraisal of well-conducted systematic reviews usually based on well-designed studies.

So, what are the facts? On the whole, the findings are not surprising, although it is very striking that there are solid positive findings, with large and medium

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effect sizes, for numerous adjunctive psychosocial treatments. The magnitude of these treatment effects exceeds the medium effect size obtained for antipsychotics compared with placebo. Adjunctive biomedical treatments, including rTMS, oestrogen, *Ginkgo biloba*, antidepressants and non-steroidal anti-inflammatories, also provide clear benefits in the medium effect size range. This is not to say that these adjunctive treatments are as effective as antipsychotics on their own, but when combined with antipsychotics, on average, they have an additional large- or medium-size effect. These are robust findings, some of which were quite unexpected (e.g. *Ginkgo biloba*), but all have passed the same objective, quality assessment tests as the expected findings such as those on the effectiveness of antipsychotic medications over placebo. Also striking are various markers of infection, inflammation or altered immunological parameters that parallel the findings of increased exposure to infection *in utero* and during childhood that are reported in epidemiological studies. The potential aetiological or pathophysiological role of these processes in schizophrenia can clearly not be ignored. We can be certain that patients have relatively poor cognitive functioning (as do first-degree relatives, but in comparatively attenuated form) and subtle, but diverse and widely replicated structural brain changes, while several electrophysiological measures are certainly altered, namely P50, P300, N400, and mismatch negativity. The presence of minor physical anomalies, neurological soft signs (also in first-degree relatives), and certain sensory changes (reduced olfactory and pain sensitivity), complete the picture of a disorder that irrefutably involves widespread neural dysfunction to a degree apparently not shared by other major psychiatric disorders, with a causal role for altered inflammatory and/or immunological processes that may be infective in origin, at least in some cases, yet is responsive to biomedical and psychosocial therapeutic influences of a wide variety of types.

Second, the epidemiological data furnish evidence for the role of developmental factors in schizophrenia by identifying medium to large effects for pregnancy and birth complications, prenatal *Toxoplasma gondii* exposure, developmental motor delays, lower child and adolescent (pre-morbid) IQ, childhood CNS viral infections, and childhood adversities. In addition, epidemiological research confirms the effects of immigration (first and second generation), membership of racial and ethnic immigrant groups, and urbanicity on risk for schizophrenia. The causal influence of premorbid cannabis use and its role in bringing forward the onset of schizophrenia is also confirmed, yet paradoxically, cannabis use is associated with better cognitive performance in clinical studies. Epidemiological studies also identify incidence and prevalence figures, increased mortality and suicide rates, and confirm that longer duration of untreated psychosis is associated with poorer outcome. Overall, the epidemiological findings suggest a combination of intrinsic (genetic?) and extrinsic (environmental) factors operating during development somewhere between conception and adolescence.

Does this knowledge about schizophrenia increase our understanding of this condition? We would assert that schizophrenia is a disorder of widespread neural dysfunction accompanied by widespread psychological effects that responds moderately well to psychosocial and biomedical therapies. It has an onset and course shaped by a combination of intrinsic and extrinsic factors, that involve anomalies evolving in the early stages of human development and entail, in a proportion of cases, altered inflammatory and/or immunological processes, possibly infective in origin. If these conclusions are true and constitute an advance in our understanding of schizophrenia, it is a very modest advance indeed.

Limitations

We cannot control for bias at the study level, nor at the review level, which may have entailed manipulation in the analyses or in selective or distorted reporting of results. Further, summary effects from meta-analyses may be modestly inflated (Button *et al.* 2013). Some reviews may be prone to sampling bias; for example, 90% of the sample included in the *Ginkgo biloba* review were from China (Singh *et al.* 2010*b*). We have attempted to address potential bias by including only systematic reviews that achieved a satisfactory level of reporting transparency. As we have not included unpublished reviews, reviews published only in abstract form, and reviews published in languages other than English, the results may be subject to publication and language bias. While all attempts were made to be objective during quality assessment, some subjectivity is unavoidable, particularly for reviews not reporting assessment criteria.

In order to facilitate comparison across a range of disciplines, detail has been minimized and represented here solely in terms of effect sizes and standardized quality ratings. This has the benefit of allowing appraisal of research from diverse disciplines in order to highlight findings of substance; however, it has the limitation of losing a vast amount of additional information. Specifics of sample characteristics, secondary comparisons and outcomes, findings that are not statistically significant but may be clinically significant, discipline-specific jargon, and even citations that laid the groundwork for the more recent reviews were

necessarily omitted in order to present only the key outcomes relating to the most up-to-date research in the field. Moreover, the exclusion from the Schizophrenia Library those reviews assessing the associations of genetic risk factors for schizophrenia precludes any consideration of this important literature in this summary of evidence; however, the SZGene database (www.szgene.org) comprehensively collates the extant literature for schizophrenia risk associated with individual polymorphisms. Finally, replicated and robust studies that have not been the subject of a systematic review are not taken into account here, while 'fashionable' topics may be more readily reviewed, potentially biasing our results.

Conclusion

We have presented a succinct summary of the vast available evidence encompassing domains of clinical phenomenology, biology, epidemiology and therapeutics in relation to schizophrenia. We have summarized the more robust evidence and concluded that while our knowledge of schizophrenia is very substantial, our understanding of it remains limited.

Declaration of Interest

None.

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