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Schizophrenia, "Just the Facts": What we know in 2008 Part 1: Overview

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Abstract

For every disorder, there is a set of established findings and accepted constructs upon which further understanding is built. The concept of schizophrenia as a disease entity has been with us for a little more than a century, although descriptions resembling this condition predate this conceptualization. In 1988, for the inaugural issue of *Schizophrenia Research*, at the invitation of the founding editors, a senior researcher, since deceased (RJ Wyatt) [1] published a summary of generally accepted ideas about the disorder, which he termed "the facts" of schizophrenia. Ten years later, in conjunction with two of the authors (MSK, RT), he compiled a more extensive set of "facts" for the purpose of evaluating conceptual models or theoretical constructs developed to understand the nature of schizophrenia. On the 20th anniversary of this journal, we update and substantially expand our effort to periodically summarize the current body of information about schizophrenia. We compile a body of seventy-seven representative major findings and group them in terms of their specific relevance to schizophrenia — etiologies, pathophysiology, clinical manifestations, and treatments. We rate each such "fact" on a 0–3 scale for measures of reproducibility, whether primary to schizophrenia, and durability over time. We also pose one or more critical questions with reference to each "fact", answers to which might help better elucidate the meaning of that finding for our understanding of schizophrenia. We intend to follow this paper with the submission to the journal of a series of topic-specific articles, critically reviewing the evidence.

1. Background

Schizophrenia has been described as the "worst disease affecting mankind" (Editorial, 1988). Because of the pervasiveness of associated deficits and frequently life-long course, it is among the top ten leading causes of disease-related disability in the world (Murray and Lopez, 1996; World Health Organization, 2001). Despite vigorous study over the past century, however, its etiology and pathophysiology remain relatively obscure and available treatments are only modestly effective. Our incomplete understanding of the nature of schizophrenia cannot principally be ascribed to a paucity of findings. In fact, the several hundred thousand publications pertaining to schizophrenia to-date describe thousands of discrete findings. While many such findings have not been replicated, several hundred have been corroborated to varying extents. But which of these findings can be considered established and exactly what do these facts tell us about the nature of schizophrenia?

In 1988, for the inaugural issue of Schizophrenia Research, a senior researcher (Richard J Wyatt, RJW,

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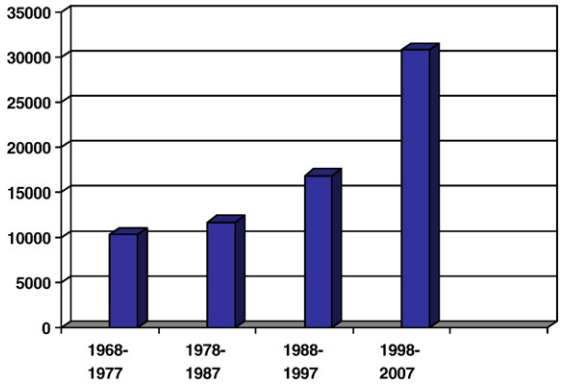

Fig. 1. Number of schizophrenia related articles in PubMed over the past four decades.

now deceased)[1] published a summary of generally accepted ideas or "facts" about the disorder (Wyatt et al., 1988) and this was expanded a decade later (Tandon, 1999). On the 20th anniversary of *Schizophrenia Research*, we once again undertake the task of updating our body of information about this enigmatic mental illness. As before, our principal objective is to summarize the current body of accepted "facts" about schizophrenia which can serve as the basis for further characterization of the disorder and building further understanding of its etio-pathophysiology.

2. Approach

There are several challenges in constructing such a succinct summary of established findings. How does one select the representative highlights from among the several hundred thousand papers and books published on schizophrenia? Currently approximately 5000 publications per year relating to schizophrenia can be found in PubMed when using schizophrenia as a keyword and this number has been growing exponentially over the past four decades (Fig. 1). Almost twice as many publications are not abstracted or indexed and several have not been translated into English. Sometimes abstracts of studies are available but detailed findings are not easily obtained. Even when detailed results of studies are reviewed, confounds and other methodological limitations are often not immediately apparent. Furthermore, until a study's results have been consistently replicated, its findings cannot be accepted as "fact", no matter how potentially important the findings might be. Additionally, unless the findings have also been assessed in conditions other than schizophrenia, their unique relevance to schizophrenia cannot be assumed.

2.1. Process

Even as the principal objectives and challenges in constructing a body of facts about schizophrenia are similar across these three endeavors over a span of 20 years, there are some noteworthy differences. In 1988, the original author (RWJ) collaborated with three colleagues in his institution to summarize their collective interpretation of existing information about schizophrenia in terms of the reproducibility of findings and their specificity for the disorder (Wyatt et al., 1988). In 1998, he collaborated with two of the current authors (RT and MSK) to compile a set of facts that in turn were considered by a body of 16 experts[2], whose collective opinion was then presented (Tandon, 1999).

While the basic process of development (consensus) and outline (inclusion of key findings with statement about their reproducibility and primary relevance to disorder) are retained, this iteration represents a substantial elaboration in two significant ways. First, considering the rapid burgeoning of "findings" in schizophrenia, we organize the facts in terms of their putative defined relevance for our understanding of the nature of schizophrenia, i.e. to the etiology, pathophysiology, clinical expression, or treatment of the disorder. Second, in comparison to the two previous summaries, there is substantially more discussion of each "fact" and this is reflected in the degree of detail contained within the table.

After the publication of our last summary of established findings in schizophrenia a decade ago (Tandon, 1999), we (MSK, RT, RJW) decided to substantially expand our effort for the next iteration to include a critical discussion of each "fact" with reference to its veracity, relevance, and critical unanswered questions along with a presentation of major conceptual models of schizophrenia specifically indexed to this body of facts. Primary areas of responsibility (MSK — neurobiology; RT — clinical features and treatment; RJW — epidemiology) were assigned and a five-year process of manuscript development formalized. The tragic death of our senior mentor (RJW) midway through

[1] Richard J. Wyatt participated substantially in the initial phases of manuscript development. He passed away in 2002.

[2] The sixteen experts who provided ratings for the 1999 version were Francine Benes, William T. Carpenter, Jr., Lynn DeLisi, Peter Falkai, Robert Freedman, Patricia Goldman-Rakic, Anthony Grace, John F. Greden, John M. Kane, Matcheri Keshavan, Peter Liddle, Robin Murray, John Olney, Rajiv Tandon, John Waddington, and Daniel Weinberger (Tandon, 1999).

this process (DeLisi and Nasrallah, 2002) necessitated a revision to our timeline and the addition of another senior researcher (HAN), who assumed primary responsibility for the treatment section. Over 100 pages of text compiled by RJW on the epidemiology of schizophrenia were reviewed and the material incorporated and updated for that section by RT. Over the past year, the process accelerated and versions of manuscript drafts were systematically refined via exchange of written materials and regular telephone conference calls among the three authors (MSK, RT, and HAN); the final Table of Facts represents our unanimous consensus. We conducted a comprehensive literature review utilizing schizophrenia and psychosis as broad search terms in conjunction with terms for specific areas; we screened over 6000 abstracts from which we culled approximately 2000 complete articles for review — we specifically reference about 300). Although we include some original studies, our list of references is tilted towards recent meta-analyses (Egger and Smith, 1997; Noble, 2006) and other systematic reviews.

2.2. Overall presentation

In order to provide a balanced discussion of each "fact" and consideration of sets of findings grouped on the basis of their putative relevance to our understanding of schizophrenia, we plan to submit more detailed material in five subsequent manuscripts (etiology, pathophysiology, clinical expression, treatment, and conceptual models) (Fig. 2). In this article, we introduce the series and discuss our approach towards developing a summary of established findings in schizophrenia and defining what they tell us about the nature of the disorder and its treatment.

As data about various aspects of schizophrenia have burgeoned, constructs around which these findings can be organized have become critically important. In the absence of such unifying hypothesized constructs, "our field might become inundated with undigested data that collectively do not make sense" (Tandon, 1999). Each theoretical framework, however, has to be subject to critical appraisal and address the questions of: (i) what is the need for the model; (ii) exactly what is the model; (iii) what "facts" does the model clearly explain; (iv) what other "facts" might the model potentially explain; (v) what "facts" does the model not explain; (vi) what "facts" is the model not consistent with; (vii) what cellular mechanisms might underpin the model; (viii) what currently unknown "fact" does the model predict; and (ix) is the model testable and what evidence would disprove the model. We will discuss major theoretical constructs indexed to our Table of Facts in terms of these issues in the last paper in the series.

2.3. Table of Facts

Table 1 represents our evaluation of the best established findings that we consider important when thinking about schizophrenia. Considerations in the

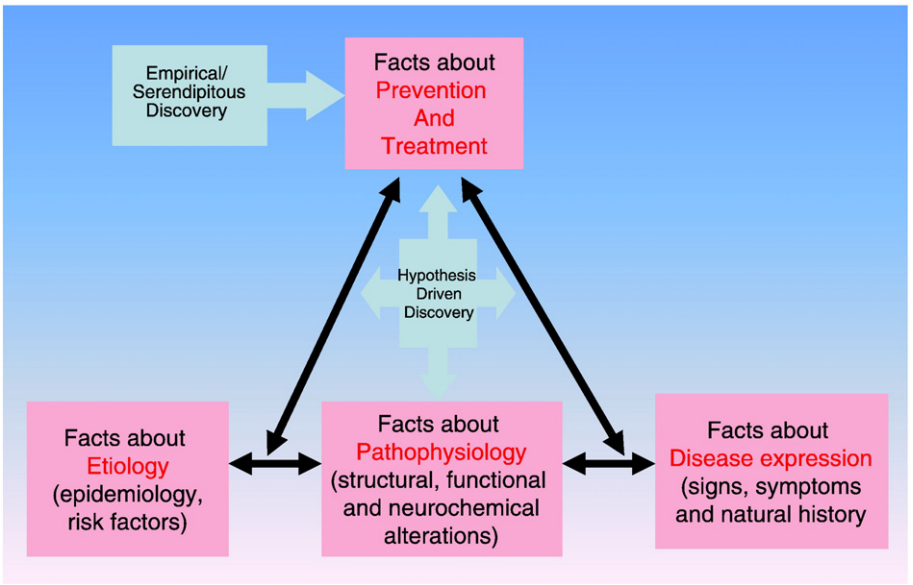

Fig. 2. Relevance of etiological, pathophysiological, clinical and treatment "facts" to our understanding of schizophrenia. Bidirectional arrows indicate that these facts inform each other, resulting in testable models that may generate new hypothesis-driven knowledge.

Table 1
Table of Facts

Fact	Reproducibility	Whether primary to illness	Durability of finding over time	Key questions	References
Epidemiology [etiology and service need]					
Annual Incidence = 8–40/100,000/year with relatively similar incidence across continents.	***	**	***	What specific causal factors (stress, social, substance abuse, nutritional, obstetric, toxins, infection, etc.) explain differences?	Sartorius et al. (1986), Jablensky et al. (1992), McGrath et al. (2004), Saha et al. (2006).
Higher incidence associated with urbanicity.	**	**	**		Lewis et al. (1992), Mortensen et al. (1999), Pedersen and Mortensen (2001), McGrath et al. (2004), Kirkbride et al. (2006), Amaddeo and Tansella (2006).
Higher incidence associated with migration.	**	**	**	Does a dose–response relationship exist?	Bhugra et al. (1997), Boydell et al. (2001), Cantor-Graae and Selten (2005), Fearon et al. (2006).
Lifetime risk = approximately 0.7%	**	**	**	Is the lifetime risk for developing the illness changing; if so, why?	Saha et al. (2005).
Greater lifetime risk in males	**	**	*	Do variations in diagnostic criteria or case ascertainment methods explain observed differences? What environmental and/or genetic factors explain the observed male–female difference?	Aleman et al. (2003), McGrath et al. (2004), Beauchamp and Gagnon (2004).
Descriptions have been fairly consistent over past century.	**	**	**	Is schizophrenia an 18th–21st century disease; if so, why?	Torrey (1980), Jeste et al. (1985), Ellard (1987), Hare (1988).
Point Prevalence = 2–10/1000 with pockets of high and low prevalence.	***	*	***	To what extent do differences in outcome contribute to observed differences in prevalence?	Robins and Regier (1991), Saha et al. (2005).
Higher prevalence among lower socio-economic classes.	***	*	***		Goldberg and Morrison (1963), Dohrenwend et al. (1992), Saha et al. (2005).
Schizophrenia is highly heritable and genetic factors contribute to approximately 80% of the liability for the illness.	***	**	***	How do genetic factors modify risk of illness-polygenic, major locus-rare allele, epigenetic?	McCue et al. (1983), Cannon et al. (1998), Cardno et al. (1999), Sullivan et al. (2003), Crow (2007), McClellan et al. (2007), Lencz et al. (2007).
There is genetic heterogeneity, with multiple chromosomal regions of small effect across the genome linked to illness liability.	***	*	*	Why is consistent identification of any specific susceptibility genes proving so hard	Risch (1990), Lewis et al. (2003), Harrison and Weinberger (2005), Owen et al. (2005), Munafo et al. (2005), DeLisi and Faraone (2006), Straub and Weinberger (2006), Gogos and Gerber (2006), Law et al. (2006), Sullivan (2007), Li and He (2007a), Toulopoulou et al. (2007), Gray and Hannan (2007), Li and He (2007b), Le-Niculescu et al. (2007), Kanazawa et al. (2007), Sanders et al. (2008), Shi et al. (2008).
Several environmental factors of small effect (e.g., cannabis abuse, winter/spring birth, prenatal infection and famine, obstetric and perinatal complications, social stress, older paternal age, etc.) are associated with an increased risk of developing schizophrenia.	***	**	**	Are these effects similar across different populations and if not, why not? Exactly how do these environmental and genetic factors interact in different populations? What neurobiological mechanisms mediate these effects?	Mednick et al. (1988), Norman and Malla (1993), Jones et al. (1994), Geddes and Lawrie (1995), Susser et al. (1996), McGrath and Welhalm (1999), Mortensen et al. (1999), Cannon et al. (2002), Malaspina et al. (2002), Brown et al. (2002), Corcoran et al. (2003), Davies et al. (2003), Caspi et al. (2005), Henquet et al. (2005), Semple et al. (2005), St Clair et al. (2005), Shaner et al. (2007), McGrath (2007), Byrne et al. (2007), Wohl and Gorwood (2007), Moore et al. (2007), Munk Laursen et al. (2007)
Neurobiology [pathophysiology]					
Total brain volume is reduced, and lateral and third ventricular spaces are larger.	***	**	***	How do we explain widespread changes — if specific networks, which ones are they?	Haug (1962), Johnstone et al. (1976), VanHorn and Macmanus (1992), Ward et al. (1996), Shenton et al. (2001), Harrison et al. (2003), Steen et al. (2006), Nesvag et al. (2008).
There is reduced grey matter volume in specific brain regions such as medial and superior temporal lobe structures, prefrontal cortex, and thalamus.	**	**	**	Which changes are primary? Which are compensatory? Are some byproducts?	Pakkeberg (1987), Suddath et al. (1990), Zipursky et al. (1992), Nelson et al. (1998), Wright et al. (2000), Zakzanis et al. (2000), Shenton et al. (2001), Davidson and Heinrichs (2003), Honea et al. (2005), Vita et al. (2006), Baiano et al. (2007).
There are structural alterations in cortico-cortical white matter tracts.	*	*	*	Are the white matter changes secondary to "primary" gray matter abnormalities?	Buchsbaum et al. (1998), Davis et al. (2003), Kanaan et al. (2005), Kubicki et al. (2007).
There is reduction or reversal of cerebral asymmetry.	*	*	**	Is this artefactual or etiologically relevant	Crow et al. (1989), DeLisi et al. (1994), Flaum et al. (1995), Somner et al. (2001), Dragovic and Hammond (2005).
There are enlargements of the caudate nucleus and other basal ganglia in response to treatment.	**	0	**	Exactly what are the clinical implications of these neuroleptic treatment-related effects	Chakos et al. (1994), Lieberman et al. (2005b) Scherk and Falkai (2006).
Structural brain abnormalities are present at illness onset.	**	**	**	Precisely when do which abnormalities occur and what is their pathological basis?	Lawrie and Abukmeil (1988), Pantelis et al. (2002), Vita et al. (2006).
They may progress in a subgroup of patients during course of the illness.	*	*	**		Gur et al. (1998), DeLisi (1999), Mathalon et al. (2001), Weinberger and McClure (2002), Ho et al. (2003), Sporn et al. (2003), Lieberman et al. (2001), Pantelis et al. (2002), Woods et al. (2005), Pantelis et al. (2005), Ho et al. (2007).

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Table 1 (*continued*)

Fact	Reproducibility	Whether primary to illness	Durability of finding over time	Key questions	References
Some structural brain abnormalities of milder degree are present among unaffected family members.	**	*	*	Are these markers of illness vulnerability ("endophenotypes")?	Lawrie et al. (1999), Boos et al. (2007), Keshavan et al. (2007).
There is decreased activity of the prefrontal cortex both in resting and cognitive challenge studies ("hypofrontality").	**	*	***	Are these "functional" abnormalities reversible and how are they affected by treatment?	Ingvar and Franszen (1974), Weinberger et al. (1986), Andreasen et al. (1992), Buchsbaum and Hazlett (1998), Hill et al. (2004), Glahn et al. (2005).
There are abnormal activation patterns in several brain regions during performance of various cognitive tasks in functional imaging studies.	**	*	*	What is their functional meaning?	Davis et al. (2005), Tost et al. (2005), Turner et al. (2006), Brunet-Gouet and Decety (2006).
There are reductions in *N*-Acetyl Aspartate (NAA) in the frontal and temporal cortex.	**	*	**	What is the time-course and exactly what does this mark?	Nasrallah et al. (1994), Steen et al. (2005), Abbott and Bustillo (2006).
There are reductions in phosphomonoesters (PME), which are precursors of membrane phospholipids, in prefrontal cortex.	*	*	**	What membrane or other chemical pathology do they track?	Pettegrew et al. (1991), Horrobin et al. (1994), Keshavan et al. (2000).
Post-mortem brain findings include absence of gliosis	**	*	**	Which of them reflect primary pathology, compensatory process, or residua?	Harrison (1999), Iritani (2007).
Reductions in neuropil, and	**	*	**		Keshavan et al. (1994), Selemon and Goldman-Rakic (1999).
Altered placement of neuronal elements in a variety of cortical and limbic structures.	*	*	**	Exactly what pathological process underlies them?	Akbarian et al. (1993), Harrison (1999).
There are alterations in sleep architecture such as delta sleep deficits and shortening of REM sleep latency.	**	*	**	Which of these are pathophysiologically relevant?	Chouinard et al. (2004) Monti and Monti (2005) Benson (2006).
There are smooth pursuit eye movement abnormalities in patients and, to a lesser extent, in unaffected relatives.	**	*	***	What neurobiological mechanism/s underlie these findings? Are these markers of illness vulnerability ("endophenotypes")?	Holzman et al. (1973), Fukushima et al. (1988), Holzman (2000), Gottesman and Gould (2003), Levy et al. (2004), Greenwood et al. (2007), Braff et al. (2007), Turetsky et al. (2007).
There are abnormalities in latencies and/or amplitudes of several event related potentials such as				What neurobiological mechanisms underlie these findings?	Geyer et al. (2001), Bramon et al. (2004), Braff et al. (2007), Greenwood et al. (2007), de Wilde et al. (2007).
P-50,	*	*	**		Bramon et al. (2004), Potter et al. (2006), Patterson et al. (2008).
P-300,	**	**	**	What is their clinical or cognitive implication?	Jeon and Polich (2003), Bramon et al. (2005a).
N-100, and	*	*	**	Are these markers of illness vulnerability ("endophenotypes")?	Waldo et al. (1988), Frangou et al. (1997), Gallinat et al. (2002).
Mismatch negativity (MMN).	**	**	**		Javitt et al. (1996), Umbricht and Krljes (2005).
Dopamine agonists exacerbate and dopamine-2 antagonists alleviate schizophrenic symptoms.	***	*	***	Exactly how is dopaminergic neuro-transmission related to pathophysiology?	Lieberman et al. (1987), Laruelle et al. (1996), Laruelle and Abi-Dargham (1999), Kapur et al. (2000), Guillin et al. (2007).
NMDA antagonists such as phenylcyclidine (PCP) induce symptoms similar to schizophrenia.	**	*	***	Precisely what, if any, is the nature of glutamatergic dysfunction?	Itil et al. (1967), Javitt and Zukin (1991), Olney and Farber (1995), Moghaddam (2002), Krystal et al. (2003), Coyle (2006), Stone et al. (2007).
There are abnormalities in central GABA neurotransmission.	**	*	**	Does this reflect core pathology or compensatory effort?	Volk et al. (2000), Wassef et al. (2003), Costa et al. (2004), Lewis and Hashimoto (2007), Benes et al. (2007).
There are abnormalities in several other neurotransmitter systems (e.g., cholinergic and serotonergic).	**	*	**	Do these changes reflect core pathology compensatory effort, or epiphenomena?	Freedman et al. (1997), Raedler et al. (2007), Abi-Dargham (2007).
There is hypercortisolemia and features of hypothalamo-pituitary-adrenal axis dysregulation.	**	*	**	Is there a heightened stress liability?	Tandon et al. (1991), Webster et al. (2002), Corcoran et al. (2003), Phillips et al. (2006), Yuii et al. (2007).
Clinical features [disease expression and identification]					
The nosological boundaries between schizophrenia and other psychiatric disorders are indistinct.	***	*	**	Is schizophrenia on a continuum with bipolar disorder? Exactly how is "nature carved at its joints"?	Kendell and Brockington (1980), Owen et al. (2007).
Although characteristic symptoms (e.g., avolition, 'first-rank symptoms', formal thought disorder) and course (deterioration) are described, none is pathognomonic and diagnosis is based on a profile of symptoms and course.	***	**	***	How is the entity "schizophrenia" best defined and operationalized to enable more meaningful study?	Bleuler et al. (1911), Kraepelin (1919), Mellor (1970), Kendell (1987), World Health Organization (1992), Peralta and Cuesta (2000), American Psychiatric Association (2000), Kendell and Jablensky (2003).
There is significant heterogeneity in neurobiology, clinical manifestations, course, and treatment response across patients.	***	*	**	How does one categorize "the many schizophrenias"? Is there anything that meaningfully binds this construct?	Robins and Guze (1970) Heinrichs (2004), Jablensky (2006).
Schizophrenia is a chronic and relapsing disorder with generally incomplete remissions.	**	**	***	In what ways is this course predictably modifiable? What neurobiological mechanisms underlie this course? How viable is the concept of recovery?	Bleuler (1972), Ciompi (1980), Harrison et al. (2001).

Schizophrenia is characterized by an admixture of positive, negative, cognitive, and mood symptoms.	***	**	***	Do these dimensions reflect distinct brain abnormalities?	Strauss et al. (1974), Liddle (1987), Carpenter et al. (1988), Owens et al. (2005).
The severity of different symptoms varies across patients and through the course of the illness.	***	**	***	How do these symptom dimensions relate to each other and to illness course?	Bleuler (1972), Ciompi (1980), Hafner and an der Heiden (1999), Harrison et al. (2001).
There is a generalized intellectual impairment.	***	*	**	What mechanisms underlie this impairment?	Aylward et al. (1984), Heinrichs and Zakzanis (1998), Laws (1999), Fioravanti et al. (2005).
There is specific impairment in a range of cognitive functions (such as executive functions, memory, psychomotor speed, attention, and social cognition).	**	*	**	Is this an expression of the illness or a risk factor for its development? What neurocognitive changes are central?	Saykin et al. (1991), Aleman et al. (1999), Achim and LePage (2005), Fioravanti et al. (2005), Lee and Park (2005), Henry and Crawford (2005), Hoekert et al. (2007), Sprong et al. (2007).
Cognitive impairments are present prior to onset of psychosis and persist during the course of the illness.	**	*	**	Why are these impairments so refractory to change? What is the course of different abnormal cognitive functions and what is their basis?	Bilder et al. (1991), Saykin et al. (1994), Reichenberg et al. (2005), Joyce (2005), Hoff et al. (2005).
Less extensive cognitive impairments are present in unaffected relatives.	**	*	**	Are these markers of illness vulnerability ("endophenotypes")?	Sitskoorn et al. (2004), Hughes et al. (2005), Whyte et al. (2005), Szoke et al. (2005), Snitz et al. (2006), Trandafir et al. (2006), Gur et al. (2007).
There is an increased prevalence of minor physical anomalies and dermatoglyphic abnormalities.	**	*	**	Do these indicate the timing of the neurodevelopmental insults?	Bramon et al. (2005b), Compton et al. (2007), Weinberg et al. (2007).
There is an increased prevalence of neurological abnormalities, including movement disorders and "soft" neurological signs.	**	*	**	Do these indicate the nature of the pathological process?	Bombin et al. (2005), Compton et al. (2007).
There is a higher occurrence of obesity and cardiovascular disease.	***	*	**	Are these associations indicative of shared etiological factors, pathophysiology, or some confound?	Carney et al. (2006), Leucht et al. (2007), Newcomer and Hennekens (2007).
There is a reduced occurrence of rheumatoid arthritis.	**	*	**		Oken and Schulzer (1999), Leucht et al. (2007).
There is a reduced occurrence of cancer.	*	*	**	Exactly how do these impact outcome?	Barak et al. (2005), Hippisley-Cox et al. (2007).
There is increased prevalence of cigarette smoking and other substance use disorders.	***	*	**	What is cause and effect? Precisely, how does this affect course and outcome?	Regier et al. (1990), de Leon and Diaz (2005).
There is increased suicidality.	***	*	***	What are the clinical correlates and	Fenton (2000), Hawton et al. (2005), Palmer et al. (2005).
There is some increase in violent behavior.	**	*	**	neurobiological mechanisms?	Swanson et al. (1990).
Onset of psychotic symptoms is usually during adolescence or early adulthood.	***	**	***	What is the neuron-biological basis?	Chapman (1966), Sartorius et al. (1986), Jablensky et al. (1992), Owens et al. (2005).
Age of onset is earlier in males.	***	**	***	What genetic, socio-cultural, hormonal, developmental factors, etc. contribute to these gender differences?	Seeman (1982), Angermeyer and Kuhn (1988).
There are significant premorbid impairments in a substantial proportion of patients.	***	**	***	Do these reflect early expression of illness or represent a marker of illness liability?	Jones et al. (1994), Keshavan et al. (2005).
There is an approximate doubling of age-standardized mortality.	***	*	**	Exactly what factors contribute to this?	Harris and Barraclough (1998), Brown et al. (2000), Osby et al. (2000), Lawrence et al. (2003), Daumit et al. (2006), Nasrallah et al. (2006), Parks et al. (2006), Leucht et al. (2007), Seeman (2007), Saha et al. (2007).
Poor outcome is predicted by male gender, early age of onset, prolonged period of untreated illness, and severity of cognitive and negative symptoms.	**	*	**	What are the implications for subtyping the illness and for treatment selection?	Loebel et al. (1992), Green (1996), Hafner and an der Heiden (1999), Perkins et al. (2005).
Outcome has improved modestly over the past century.	*	*	**	Might this be related to the effects of treatment or changes in diagnostic criteria?	Morrison (1974), Hegarty et al. (1994).
Prevention and treatment [reducing morbidity and mortality]					
Dopamine-2 antagonists ("antipsychotics") are the only effective therapeutic agents which are currently available.	***	*	***	What is the optimal nature of dopamine modulation for best therapeutic effect? Exactly how does dopamine D-2 blockade help?	Creese et al. (1976), Kapur and Remington (2001), Tuominen et al. (2005), Kapur et al. (2005), Tandon et al. (2008-this issue).
Clozapine is more effective than other agents for neuroleptic-refractory positive symptoms and suicidality.	**	*	**	Precisely what mechanisms underlie clozapine's greater efficacy in this group	Kane et al. (1988), Wahlbeck et al. (1999), Chakos et al. (2001), Meltzer et al. (2003), Hennen and Baldessarini (2005), Lewis et al. (2006), McEvoy et al. (2006), Tandon et al. (2008-this issue).
All other currently available antipsychotics are similarly efficacious across patients for positive symptoms.	**	*	***	Why are negative and cognitive symptoms so refractory to treatment?	Cochrane Collaboration (2008), Tandon et al. (2008-this issue).
Antipsychotics have limited efficacy on negative symptoms and cognitive deficits.	**	**	**		Carpenter (2004), Keefe et al. (2007), Goldberg et al. (2007), Tandon et al. (2008-this issue).
Extrapyramidal side-effects are not necessary for an antipsychotic effect and compromise benefit on cognitive, negative, and mood symptoms.	**	0	**	Why are the most potent D-2 blockers not the most effective in treating positive symptoms?	Kapur et al. (2000), Tandon et al. (2008-this issue).

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Table 1 (*continued*)

Fact	Reproducibility	Whether primary to illness	Durability of finding over time	Key questions	References
Antipsychotics vary widely in their adverse effect profiles.	***	0	***	How does one best individualize anti-psychotic treatment?	Lieberman et al. (2005a), Tandon et al. (2008-this issue).
Antidepressants are effective in treating depressive symptoms.	**	0	**	When and how should these agents be utilized?	Whitehead et al. (2003), Cochrane Collaboration (2008).
Electroconvulsive therapy may be effective.	*	*	***	Is this completely nonspecific?	Greenhalgh et al. (2005), Cochrane Collaboration (2008).
Transcranial magnetic stimulation (rTMS) can be effective.	*	*	0	Exactly what role should this play?	Aleman et al. (2007).
Family and patient psycho-education reduce relapse rates.	**	*	**	When and in what manner should this service be provided?	Hogarty et al. (1986), Bustillo et al. (2001), Cochrane Collaboration (2008), Pitschel-Walz et al. (2001), Pilling et al. (2002a), Lincoln et al. (2007).
Cognitive behavior therapy reduces psychotic symptoms.	**	*	*	How does one apply this to the "real world"?	Gould et al. (2001), Pilling et al. (2002a), Zimmermann et al. (2005), Turkington et al. (2008).
Social skills training improves outcomes.	**	*	**.	Why do gains not easily generalize?	Benton and Schroeder (1990), Hogarty et al. (1997), Bustillo et al. (2001), Pilling et al. (2002b), Xia and Li (2007).
Assertive community treatment reduces hospitalization rates.	**	*	**	What aspects of this package contribute to the better outcomes?	Bond (1995), Bustillo et al. (2001), Cochrane Collaboration (2008).
Cognitive remediation reduces cognitive deficits.	*	*	0	Can this translate to real-world functioning?	Pilling et al. (2002b), McGurk et al. (2007).
Early intervention in high-risk individuals with pharmacological and psychosocial treatments prevents development of schizophrenia.	*	*	0	Why are these benefits less extensive than might be expected? What are the trade-offs?	Olsen and Rosenbaum (2006), Phillips et al. (2007).
Early intervention during first episode of psychosis improves outcomes.	**	*	**	Is psychosis neurotoxic?	Wyatt and Hunter (2001), Perkins et al. (2005), McGlashan (2006).

0 to *** scale to used to score reproducibility, whether primary, and durability of each "fact".

1. Replicability.

0: very few studies or few — fair number of studies with contradictory findings.

*: Few studies with consistent replication or fair — many studies with inconsistent replication.

**: Fair number of studies with consistent replication or many studies with fairly consistent replication.

***:Many independent studies with consistent replication and no contradictory findings.

2. Whether primary to schizophrenia.

0: finding certainly because of some other confounding variable and definitely not related to schizophrenia.

*: finding possibly because of some other confounding variable but may be related to schizophrenia.

**: finding probably not because of some other confounding variable and likely related to schizophrenia.

***: finding certainly not because of some other confounding variable and definitely related to schizophrenia.

3. Long-term durability.

0: very new finding (<5 years) not in previous 2 versions of "facts" in 1998 and 1999.

*: relatively new finding (5–15 years). Not in 1988 version, but may have been noted in 1999 version.

**: fairly established finding (15–30 years). Listed in 1999 and may have been noted in 1988 versions.

***: long established finding, well-known for over 30 years. Listed in both 1988 and 1999 versions.

selection of the "facts" included in the table were relevance, breadth of coverage, ease of presentation, and overall balance. These seventy-seven "facts" are graded on a 0–3 scale with reference to their reproducibility, whether primary to schizophrenia, and long-term durability. In the last column, one or more critical issues relevant to each "fact" needing further study are listed. The basis for these ratings will be discussed in the four topic-specific papers in preparation. In addition to the specific organization of these findings under four headings (epidemiology, neurobiology, clinical features, and treatment), two additional changes from previous versions of the Table of Facts will be noted. First, recognizing that several "rock-solid" findings of yesteryear may be considered trivial or wrong today, we evaluate the longitudinal stability or durability over time of each "fact". Has this finding held up over time? Second, recognizing that many findings may not have been fully developed and their relevance to schizophrenia may not have been fully clarified, we enumerate one or more critical issues relevant to that "fact" that merit elaboration. What key questions need to be answered in order to further elucidate the "meaning" of the finding or better understand what that fact tells us about the nature of schizophrenia?

2.4. Discussion

Schizophrenia investigators and clinicians will be pleased to note that considerable progress has been made since 1988. Whereas many "facts" from 1988 have been confirmed, some have been refuted and several additional new "facts" have been discovered. Breakthrough advances in molecular genetics and neuroimaging have principally fueled many of the new discoveries. Many new hypotheses have taken form, our knowledge of the brain and how it interacts with the environment has evolved, and new ideas and techniques for exploring these hypotheses have appeared at a rapid rate.

As RJW noted in his materials for this paper, "as with any such review, our perspective depends on how we, the reviewers, approach the topic. It would, of course, be best if we could forewarn readers of our biases, but it is unlikely that we fully understand them ourselves. What is not apparent to us will undoubtedly be immediately clear to those readers who will judge our interpretations, omissions, and weighting of the data."

Nevertheless, we feel that we should acknowledge one important perspective. We will be using the term "disease" when referring to schizophrenia. This approach differs from that taken by the American Psychiatric Association's (2000) most recent Diagnostic and Statistical Manual (DSM-IV-TR) and the World Health Organization's (1992) International Classification of Disease (ICD-10), where schizophrenia is described as a "disorder." In contrast to the vagueness of the term disorder ("something is wrong"), disease implies a discrete entity with a specific etiology (even if unknown) and a discernible pathology (even if incompletely delineated) (Evans, 1976; Becker, 2005; Berganza et al., 2005; Steurer et al., 2006). We believe that there is sufficient evidence to call schizophrenia a disease related to brain abnormalities that are the final "common pathway" caused by an assortment of specific genetic and/or environmental factors. While many etiological factors and pathophysiological processes currently appear relevant to what we consider schizophrenia and it is almost certain that our construct of schizophrenia encompasses not one but several diseases, precise delineation of the constellation of distinct "individual diseases" that are part of this entity is not possible at present. We utilize the disease model because of the clarity it provides and its heuristic value.

How do we understand schizophrenia in 2008? We hope this summary of established findings will assist in better characterizing this enigmatic brain disorder and building further understanding of its etio-pathophysiology and developing more specific and effective treatments.

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Role of Contributors

Rajiv Tandon, Matcheri Keshavan, and Henry Nasrallah all participated in the conceptualization of the manuscript, development of its content, and the writing of the manuscript. They all accept complete responsibility for the manuscript.

Conflict of interest

None of the authors report any significant relevant conflicts of interest. This manuscript was not developed as part of Rajiv Tandon's current employment by the State of Florida, which is not responsible for its content.

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