As attention to hikikomori grows across cultures and countries, so does the importance of establishing a clear and consistent definition of the disorder. About a decade ago, preliminary diagnostic criteria[3] and a semi-structured diagnostic interview[4] were developed. Over the last decade, we and others in this emerging field of research have gained a wider breadth of experience in evaluating, treating and following up a series of individuals with hikikomori, as well as their family members, in Japan and beyond. This has led to an evolution in our biopsychosocial understanding of the disorder[4,5], and an acute awareness of the limitations of its earlier definitions. We believe it is time now to provide an updated proposal of diagnostic criteria for hikikomori, which is presented here.

Hikikomori is a form of pathological social withdrawal or social isolation whose essential feature is physical isolation in one's home. The person must meet the following criteria: a) marked social isolation in one's home; b) duration of continuous social isolation of at least 6 months; c) significant functional impairment or distress associated with the social isolation.

Individuals who occasionally leave their home (2-3 days/week), rarely leave their home (1 day/week or less), or rarely leave a single room may be characterized as mild, moderate or severe, respectively. Individuals who leave their home frequently (4 or more days/week), by definition, do not meet criteria for hikikomori. The estimated continuous duration of social withdrawal should be noted. Individuals with a duration of at least 3 (but not 6) months of social isolation should be classified as pre-hikikomori. The age at onset is typically during adolescence or early adulthood. However, onset after the third decade of life is not rare, and homemakers and elderly who meet the above criteria can also receive the diagnosis.

Four aspects of this revised definition of hikikomori bear emphasis. First, the behavior of staying confined to home – the physical aspect of withdrawing and remaining socially isolated – remains hikikomori's central and defining feature. However, the definition adds clarification as to what frequency of going outside home still qualifies as "marked social isolation in one's home". Second, the requirement for avoidance of social situations and relationships has been removed. In our interviews assessing individuals for hikikomori[5], they commonly report having few meaningful social relationships and little social interaction, but deny avoiding social interaction. Many clinicians often wonder about what distinguishes hikikomori from social anxiety disorder, and this lack of avoidance is one of the primary differences.

Third, distress or functional impairment should be carefully evaluated. While impairment in the individual's functioning is vital to hikikomori being a pathological condition, subjective distress may not be present. Our in-depth clinical interviews with people with hikikomori[4] have revealed that many actually feel content in their social withdrawal, particularly in the earlier phase of the condition. Patients frequently describe a sense of relief at being able to escape from the painful realities of life outside the boundaries of their home. However, as the duration of social withdrawal gets longer, most people with hikikomori begin endorsing distress, such as feelings of loneliness[4].

Fourth, we have removed other psychiatric disorders as an exclusion criterion for hikikomori. It is clear that this disorder tends to co-occur with other conditions[6,7]. In our view, the frequency of co-occurring conditions increases the importance of addressing social withdrawal as a health issue. It is possible that hikikomori (pathological social withdrawal) co-occurs with a variety of psychiatric disorders as a contributor to psychopathology, similarly to how catatonia and panic attacks are now listed as specifiers to several mental disorder diagnoses.

With advances in digital and communication technologies that provide alternatives to in-person social interaction, hikikomori may become an increasingly relevant concern. We hope that these simplified diagnostic criteria may help standardize evaluation and encourage cross-cultural comparison of hikikomori.

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The revised German evidence- and consensus-based schizophrenia guideline

The German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN) has just completed and published its revised national guideline on schizophrenia[1].

This guideline is evidence- and consensus-based according to the methodological criteria for clinical guidelines fulfilling the highest quality standard (S3) of the Standing Guideline Commis-

sion of the German Association of Scientific Medical Societies (AWMF)[2]. S3 standard is based on scientific evidence including systematic literature search and grading, evaluation and adaptation of available international high-quality guidelines, and a scientifically sound formal consensus by means of nominal group processes, structured consensus conferences and possible additional use of the Delphi technique[2].

For the revision process, the guideline was arranged into topic-specific modules, which were updated by members of the Steering, Expert and Consensus Groups of the Association. Thirty-eight stakeholders – including representatives from medical societies and other associations of the workforce from all fields involved in the diagnosis, treatment and care of schizophrenia, from patients' and relatives' advocacy groups, as well as more than 20 experts from different topic-related disciplines – were involved in the process.

Standardized operational procedures to deal with all potential financial and non-financial conflicts of interest were implemented. The guideline underwent several internal and external revision steps, including a public consultation phase, and was funded by the DGPPN without any public, ministerial or industry support. The guideline group produced a total of 162 recommendations and 8 statements. The document is freely available at the AWMF webpage (www.awmf.org), as a long (in German) and short (in German and English) version.

The guideline is structured in seven modules, covering all areas of diagnosis, treatment and management of schizophrenia. Module 1 describes the general principles of the management of schizophrenia, while module 2 focuses on differential diagnoses (including rare diseases such as autoimmune psychosis) and the detection of somatic comorbidities that may cause excess mortality. Module 3 describes the general aspects of treatment, focuses on developing course-specific treatment plans, and emphasizes the need for shared decision making.

Module 4 includes the available treatment interventions in schizophrenia. Submodule 4a covers all aspects of pharmacological and biological treatments, with a particular emphasis on side effect prevention and management. Submodule 4b focuses on psychotherapeutic and psychosocial interventions and family care. Submodule 4c gives recommendations for treatment under special clinical circumstances, such as comorbid mental illnesses (e.g., depression, post-traumatic stress disorder or obsessive-compulsive disorder), agitation and aggression, substance use disorders (tobacco, alcohol and cannabis), catatonia; childhood, adolescence and the elderly; pregnancy and breast feeding; as well as in people being at risk for psychosis. Submodule 4d covers issues of medical, social and occupational rehabilitation.

Module 5 refers to care coordination and is giving recommendations for an integrated cooperation of all service providers. Most importantly, the guideline group also produced recommendations for the necessary staffing of psychiatric hospital care to guarantee an optimal guideline-based treatment. Module 6 evaluates the cost-effectiveness of treatments, and Module 7 covers quality management in schizophrenia treatment and care.

The German guideline gives recommendations with different strengths (A: we recommend; B: we suggest; 0: it may be considered; KKP: good-clinical practice/expert recommendation), based on a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) terminology[3].

Examples of particularly important recommendations are the following[1]: a) to offer regular monitoring of physical health to all persons with schizophrenia; b) to evaluate and classify symptoms suggesting typical medical comorbidities in every patient with schizophrenia; c) to offer magnetic resonance imaging to every person with a first-episode schizophrenia; d) to offer acute and maintenance antipsychotic drug treatment using the lowest possible dosage to every person with schizophrenia; e) to select an antipsychotic drug mainly based on the side effect profile; f) to work out the duration of maintenance treatment on an individual basis, offering the possibility for an early discontinuation (e.g., to reduce side effect burden), but also for a long-lasting treatment in every disease stage (to reduce the relapse likelihood); g) to offer clozapine monotherapy as soon as the criteria for treatment resistance are fulfilled, and antipsychotic drug combination treatment only if adequate response is not achieved with monotherapy with three different antipsychotics, including clozapine; h) to offer electroconvulsive treatment in cases of catatonia; i) to offer psychosocial interventions, exercise interventions and/or metformin (or topiramate) for weight gain; j) to offer cognitive behavioural therapy (CBT), psychoeducation and family interventions to every person with schizophrenia; k) to develop crisis plans and advance treatment arrangements to avoid compulsory admissions; l) to offer primarily CBT rather than antipsychotic drugs to persons at risk for developing psychosis, and m) to wait for two weeks before switching antipsychotic drugs in case of depressive symptoms, but also to offer an add-on antidepressant in case of a significant depressive syndrome. These examples highlight the scope of the guideline content, but should not be used in clinical practice without consulting the original text.

Compared to the guidelines of the UK National Institute for Health and Care Excellence (NICE)[4], the German guideline is putting more emphasis on specific challenging clinical situations and has involved a broad spectrum of stakeholders, which adds to its representativeness and acceptance.

We are planning to submit the currently available major schizophrenia guidelines, including our own, to a systematic quality check by using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument, as has been done with former guideline versions[5].

For the future, we believe that an international high-quality "core guideline", based on best available evidence and "neutral" international consensus, should be developed by the WPA and other international associations and stakeholders. This guideline should then be adapted to the special needs of national health care systems by the national psychiatric and other associations and stakeholders. This would have the potential to improve overall care for patients with schizophrenia, to harmonize treatment across countries and to reduce guideline developmental costs per country.

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Schizophrenia as parasitic behavior manipulation: can we put together the pieces of an evolutionary puzzle?

It is a disturbing fact that a diagnosis of schizophrenia is still associated with a poor prognosis concerning quality of life and community functioning, and that life expectancy of people with this diagnosis is reduced by about 14.5 years compared to the general population[1]. Over the last decades, this has changed very little, despite intensive research into drug development and psychological therapy. This calls for fresh ideas concerning the etiology of the disorder to pave the way for novel treatment approaches.

Even though it is undisputed that schizophrenia is highly heritable, decades of research have failed to find a conclusive answer concerning its genetic biology. One of the few replicated findings is that genes pertaining to immunological competency play a significant role, particularly those involved in the major histocompatibility complex[2]. It is also unclear why predisposing genes have remained in the genepool, despite their detrimental effect on reproduction, thus rendering schizophrenia an "evolutionary enigma"[3].

Accumulating evidence suggests that some cases of schizophrenia are associated with a latent infection with *Toxoplasma gondii*, a protozoic agent known to affect warm-blooded animals[4]. In essence, individuals with *T. gondii* antibodies have a 2.7-fold elevated risk for schizophrenia compared to unaffected subjects, and the risk for schizophrenia associated with the infection by far exceeds the risk conveyed by any single gene putatively involved in the etiology of the disorder[4]. In light of figures suggesting that about two billion people worldwide are infected with *T. gondii*, and observations that the risk of infection with this agent relies on the genetic make-up of one's major histocompatibility complex[2], there is a clear need for studying these associations in greater detail.

The reproductive cycle of *T. gondii* is complex, with felines being the definitive host for sexual reproduction. The felines' feces contain oocysts, which can infect intermediate hosts by oral pathways. There, asexually produced bradyzoites travel to the brain, the heart and other organs, where they build cysts and remain for the host's lifetime. The reproductive cycle of *T. gondii* closes when felines feed on infected animals through predation.

T. gondii has the potential to actively manipulate the intermediate host's behavior for its own reproductive benefit. Rodents infected with *T. gondii*, for example, display decreased vigilance for predators. Strikingly, infected rats lose their innate avoidance of cat urine odor. Instead, they seem to approach locations expressing cat (urine) odor in a "suicidal" manner, thus increasing their risk of predation.

Experimental evidence from rodent studies suggests that the parasite manipulates the host's dopamine turnover and impacts on glutamatergic neural pathways, which is entirely consistent with the prevailing neurotransmitter models of schizophrenia[5].

But what about the behavioral manifestations of *T. gondii* infection in human hosts? Might schizophrenia be seen as a possible phenotypic expression of the parasite's manipulation?

In fact, most researchers believe that human infection is an "accident" of *T. gondii* exposure[4]. From an evolutionary viewpoint, however, it is possible to argue that genetically vulnerable early humans (and their ancestors) were as logic a target to become an intermediate host as rodents now are. The manipulatory action of *T. gondii* in humans could have aimed at their exclusion from the social community, because in gregarious species like *Homo sapiens* individuals bare the greatest risk of predation when isolated from the social group[6].

Following this line of reasoning, many "core" symptoms associated with schizophrenia support the idea that the disorder may be the phenotypic correlate of manipulation by *T. gondii* ultimately promoting social exclusion. For example, social cognitive impairments lead patients to believe that others have malevolent intentions, thus giving way to paranoid ideation causing social withdrawal or aggression against the perceived perpetrator, which ultimately promotes marginalization of the individual. Negative symptoms such as affective flattening, apathy or abulia cause rejection from others, and many patients fail to experience social interaction as rewarding[7]. Together, it is possible to hypothesize that the typical signs and symptoms associated with schizophrenia may have served in the past the parasite's biological interests, i.e. to increase the risk of predation for its host by forcing the individual to leave or be expelled from his/her social community.

Current therapeutic approaches to schizophrenia mainly depend on the anti-dopaminergic action of antipsychotic drugs. Interestingly, some antipsychotics possess anti-parasitic properties, due to chemical similarities to naturally occurring plant