Neurocognitive and neurophysiological endophenotypes in schizophrenia: An overview

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Abstract

Schizophrenia (SCZ) is a severe psychotic disorder that affects up to 1% of the US population and it is associated with progressive impairment in social functioning and cognition. Nonetheless, despite its high burden, the pathophysiology of SCZ, including the genetic and biological mechanisms underlying the development and manifestation of the disorder, remains largely elusive. Endophenotypes are subtypes of biological markers that are more closely related to the genetic vulnerability for a disorder (e.g., SCZ). Recently, research on endophenotypes has identified several parameters that may prove useful in shedding light over the underlying neurobiology of SCZ. In this article, we provide an overview of the most established SCZ endophenotypes in the domains of neurocognition (attention deficits, working and verbal declarative memory dysfunctions) and neurophysiology (pre-pulse inhibition, anti-saccade impairment, event-related potential deficits) along with some novel, sleep-based measures (reduced sleep spindles and sleep slow waves). We also discuss recent conceptual advances in the field that may lead to novel, personalized treatment interventions for patients affected by this devastating mental illness.

Keywords

Introduction

Schizophrenia (SCZ) is a severe, major psychiatric disorder encompassing a wide range of behavioral and cognitive dysfunctions. SCZ affects approximately 1% of the US population [1] and ranks among the 15 leading causes of disability worldwide [2]. Typically, a subthreshold prodromal phase is followed by a first psychotic break - characterized by auditory hallucinations, delusional thoughts, disorganized speech - occurring during late

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adolescence or early adulthood. Afterwards, patients often experience a chronic-relapsing clinical course that leads to progressive impairmentin social functioning and cognition [3]. Despitethe availability of antipsychotic compounds that can effectively treat psychotic symptoms [4], the need for prolonged, often lifetime pharmacological treatment, associated with a wide variety of potential side effects, has a high impact on patients' lives and contributes to the substantial global burden of SCZ. Furthermore, a treatment-resistant form of SCZ still accounts for about one third of cases worldwide [5]. Persistent clinical and social impairments observed in patients are largely due to an incomplete understanding of the core pathophysiological mechanisms of the disorder. This has generated considerable research effort, both at the basic and translationa level, aimed at characterizing the neurobiology of SCZ.

A leading approach to unveil the biological underpinnings of SCZ involves the identification of genetic factors implicated in the risk and development of the disorder [6]. In this context, genetic research initially focused on twin studies to establish the heritability (h^2) of SCZ. H^2 is the proportion of variance explained by genetic factors and provides a measure of the genetic influence in certain characteristics (i.e., height) or disorders (i.e., SCZ). The main findings of those twin studies included an estimated heritability of 81 % for SCZ [7] and a concordance rate of 33 % for SCZ in monozygotic twins [8]. These findings, however, provide no direct information in terms of risk prediction at a single subject level. Recent advances in genome sequencing methods have provided novel insights onto heritability as well as on specific genes associated with SCZ. Genome-wide association studies (GWAS) of common genetic variants have suggested a heritability of 60–70 % for the SCZ spectrum [9]. These studies considered differences in allele frequency of single nucleotide polymorphisms (SNPs) and were able to initially identify specific genes associated with susceptibility for developing SCZ, including those located on chromosome 6p22.1, i.e. the region coding for the major histocompatibility complex (MHC) [10]. More recently, a multi-stage GWAS analysis on more than 35,000 + SCZ cases and 110,000+ controls reported 108 loci significantly associated with the disorder, 83 of which had never previously been reported [11]. Those loci comprised genes that are involved in glutamatergic transmission (such as DRD2) as well as genes responsible for immune responses, including MHC-related loci. Although promising, common SNPs identified with GWAS studies only reached statistical significance when comparing large SCZ and control cohorts, raising concerns over their relevance at the individual subject level. Indeed, most identified SNPs increase risk less than 1.1-fold above general population risk [12]. Furthermore, the difference between patient and control samples in the frequency of alleles associated with SCZ risk is typically no more than 2%. Next-generation sequencing (NGS) studies identify genetic variants, including copy number variants (CNVs), that occur in only 1 – 2% of patients with SCZ diagnoses [13]. It has been therefore challenging to find genetic features that are shared across large groups of patients with this disorder.

To establish the influence of genetic factors on the pathophysiology of SCZ, another research approach involves measuring so called "endophenotypes", i.e. biological factors that are expressed along the path from the genotype to the phenotype and are believed to be involved in the pathological mechanisms of a disorder. Since the concept of endophenotype was introduced in psychiatric literature by Gottesman and Gould's seminal work [14], this

line of research has rapidly developed. Endophenotypes are a subtype of biological markers characterized by the following specific criteria: 1) association with a disease; 2) heritability; 3) 'state-independence', i.e. being present regardless of illness phase; 4) co-segregation with the illness; 5) presence in unaffected relatives of patients at a higher degree than in the general population. These criteria aim to identify objective, quantifiable biological measures associated with a clinical diagnosis (e.g., SCZ). As such, an ideal endophenotype should point to a dysfunction in an identifiable brain circuit associated with the genetic vulnerability for the disorder. It must be pointed out, however, that the apparent association between an endophenotype and the pathophysiology of a specific brain disorder may result from endophenotype-related genes being in linkage equilibrium with genes providing risk for the syndrome [15]. Furthermore, putative endophenotypes may be indexing secondary or tertiary features that are consequences of the primary pathophysiology. Altogether, these potential pitfalls may affect the validity of isolated endophenotypes as pathophysiologically relevant markers of psychiatric disorders.

Several different candidate endophenotypes of SCZ have been proposed [16,17], from cognitive sciences, to neurophysiology and sleep research. In this article, we provide a brief overview of the most established neurocognitive and neurophysiological SCZ endophenotypes along with some novel, sleep-based measures. For each measure, we highlight the putative specificity for SCZ (or lack thereof) by reporting, when available, findings in other psychiatric syndromes. Particularly, we will focus on overlaps between SCZ and affective psychoses, which has been extensively studied under the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) initiative [18,19]. We also summarize potential future directions for endophenotype research, which may shed new light onto the pathophysiology of SCZ and related psychiatric disorders, eventually leading to novel treatment interventions for patients affected with this devastating mental illness.

Neurocognitive endophenotypes

SCZ is commonly associated with a progressive decline across multiple neurocognitive domains. Cognition regulated by temporal and prefrontal cortical areas is primarily affected, resulting in declarative and working memory deficits, impaired verbal learning, and altered executive functions [20–22]. These cognitive disturbances have a dramatic impact on patients' quality of life, leading to increased disability and poor functional outcome [23,24]. Furthermore, increasing evidence indicates that specific cognitive dysfunctions may represent putative endophenotypes of SCZ. A multi-site initiative (Consortium on the Genetics of Schizophrenia, COGOS) examined the genetic underpinnings of neurocognitive biomarkers in families with high rates of SCZ, identifying measures pertaining to attention, working memory and verbal declarative memory as candidate endophenotypes [25]. Moreover, data from the NAPLS consortium reported the predictive role of discrete neurocognitive deficits in populations at clinical high risk for SCZ and related psychotic disorders [26], confirming a role as putative endophenotypes for these cognitive measures. In the following section, we present key findings pertaining to the most established neurocognitive endophenotypes of SCZ.

Attention deficits

Deficits in attention have been observed in SCZ since the first descriptions of the disorder [27]. The inability of SCZ patients to sustain focused attention has been studied extensively, thanks to the development of reliable assessment tools, such as the Continuous Performance Test (CPT) [28]. CPT-DS (degraded stimuli), which focuses on perceptual attention, requires the identification of a blurred number or letter [29], whereas CPT-IP (identical pairs), which is associated with higher working memory load, involves the identification of the same stimulus in consecutive trials (B. A [30].). In patients with SCZ, deficits in CPTs appear to be trait-like (i.e., unrelated to the presence of clinical symptoms) [31] and are unaffected by medication status [32]. Consistently with the endophenotype criteria, attention deficits are also reported in offspring of SCZ probands, including in children who would eventually develop a disorder within the SCZ spectrum [33]. It is worth noting, however, that attention deficits are a common feature among several psychiatric populations, including euthymic bipolar patients [34].

Working memory (WM) dysfunction

WM refers to the ability to retain short-term, goal-oriented information needed for the execution of a specific task [35]. Methods used to quantify WM deficits include the Letter-Number Sequencing (LNS) task from the Wechsler Memory Scale III [36]. The LNS task involves showing to a participant a series of letters and numbers (2–8 total), which should be repeated in the order they were presented (forward condition), or in ascending/ alphabetical order (reorder condition). SCZ patients, regardless of their clinical state, perform significantly worse than healthy controls in LNS tasks [37]. Unaffected first-degree relatives (FDRs) tend to perform better than SCZ probands, but significantly worse than the healthy population [38]. Thus, a role for WM deficits as SCZ endophenotype appears plausible [39,40]. Notably, genetic studies have shown that polymorphisms of catechol-o-methyl transferase (COMT) genes and D1 dopamine receptors [41], both of which have been implicated in SCZ, are involved in regulating WM function, thus strengthening the theoretical framework linking WM deficits to the neurobiology of SCZ. While spatial WM deficits appear fairly specific for SCZ, this is not the case for performances in numeric tasks, that appear equally affected in Bipolar Disorder [42].

Verbal declarative memory (VDM) deficits

VDM refers to a subtype of long-term memory that reflects the ability to recollect events occurred to the subject (episodic memory), or facts learnt by the subject (semantic memory). Dysfunctions of VDM are associated with encoding deficits, higher rates of forgetting, and inability to recall words. VDM impairments have been found in patients with SCZ [43] and appear to be largely independent from medication status, duration of illness, and positive symptoms, although a significative association with negative symptoms has been reported [44]. VDM deficits are also present, to a lesser degree, in unaffected FDRs of SCZ probands as well as in subjects at high risk for developing psychosis [45], thus suggesting an association between VDM dysfunctions and the genetic risk of developing SCZ. However, VDM is known to be reduced in a number of psychiatric syndromes, including affective disorders [46].

Neurophysiological endophenotypes

Neurophysiological parameters closely reflect the activity of underlying neuronal circuits, thus representing ideal biomarkers for psychiatric disorders. Here, we will provide an overview of neurophysiological measures most consistently found to be altered in SCZ, which have also shown to be linked to the genetic risk for this disorder (i.e., neurophysiological endophenotypes). Specifically, we will first present well-established neurophysiological endophenotypes measured during wakefulness, which comprise Pre-Pulse Inhibition, Oculomotor anti-saccades, Mismatch negativity, and P300. We will then discuss novel candidate endophenotypes recently observed during sleep in SCZ, which including sleep slow waves and sleep spindles. Furthermore, we will highlight known overlaps between SCZ and other psychiatric disorders, including affective psychoses (for a review on this latter topic see [47]).

Pre-Pulse Inhibition (PPI) deficits

PPI is defined as the physiological dampening of a startle response to a loud tone, when such tone is preceded by a less intense auditory stimulus (i.e., the 'pre-pulse') [48]. In animal studies, PPI has been found to originate from a small cluster of neurons in the nucleus reticularis pontis caudalis of the reticular formation [49]. The startle response, assessed with electromyo-graphic recording of the orbicularis oculi muscle, is significantly less attenuated by exposure to a pre-pulse in patients affected by SCZ relative to healthy controls [50–52]. In those patients, PPI deficits tend to be stable over time and are unrelated to their clinical state [53]. Furthermore, PPI deficits were found in unaffected FDRs of SCZ probands, suggesting a link between PPI deficits and the genetic loading for SCZ [54–56]. Atypical antipsychotic medications can ameliorate PPI deficits, as established both in animal models and in SCZ patients [57,58]. However, PPI impairments are not exclusively found in the SCZ spectrum, having been reported in obsessive-compulsive disorder, attention deficit disorder, and Huntington's disease [51]. PPI was recently investigated in a large group of patients affected by SCZ and affective psychoses under the B-SNIP initiative, where it showed no significant differences between each set of probands and healthy controls [59].

Oculomotor anti-saccade (AS) impairment

The term 'saccade' defines a quick, simultaneous movement of both eyes from one point of fixation towards another one, so that the image of a previously peripheral target may be captured by the fovea. AS represents the ability to suppress a saccade towards a visual stimulus, and voluntarily direct the gaze towards the opposite direction. During AS tasks, subjects are asked to fixate a central target and, whenever a flashing stimulus appears on one side of the screen, they are prompted to look to the opposite side. Physiological mechanism underlying AS are complex and appear to depend on competitive stimulus selection in the superior colliculus [60]. Patients suffering from SCZ show longer latencies to correct eye movements in AS tasks, when compared to HC [61], which likely reflects a lack of inhibitor control [62]. Studies in unaffected FDR of SCZ probands have reported an intermediate degree of AS deficits in those individuals [63]. However, AS tasks require participants' active engagement, attention and motivation. Therefore, deficits in cognitive domains, including attention and visuomotor coordination, may affect the reliability of AS

measures, especially in acutely ill patients [64]. Furthermore, AS deficits were reported in other psychiatric disorders and particularly in affective syndromes [65,66]. Recently, a B-SNIP study in a large sample of patients showed that AS impairment are present across affective and non-affective psychoses and are associated with a non-coding region on chromosome 7 [67].

Mismatch negativity (MMN) deficits

Event related EEG potentials (ERPs), such as MMN and P300, have played a major role in psychiatry research, particularly in SCZ. MMN refers to the negative shift in scalp EEG potential recorded 50–200 ms after the presentation of a deviant stimulus embedded in a series of repetitive stimuli (i.e., oddball task). MMN is independent from attention and is thought to reflect automatic memory processing at lower level of awareness [68]. While the neural mechanisms underlying MMN still need to be fully elucidated, recent evidence suggests a contribution of lateral inhibition [69]. Deficits in MMN have been consistently reported in patients with SCZ [70,71] and appear to be relatively specific for this disorder [72]. MMN responses are reduced in unaffected relatives of SCZ patients [73] and in at-risk individuals, where they appear to have a role in predicting transition to full-blown psychosis and SCZ [74,75]. Interestingly, MMN abnormalities appear to be relatively specific for SCZ, being absent in patients with affective disorders (Umbricht 2003 Biol Psych) and obsessive-compulsive disorder [76]. Furthermore, MMN deficits is associated with poor functioning and disability in SCZ patients [77] and was recently found to discriminate remitters versus non-remitters [78], thus indicating a putative prognostic value and related potential clinical applications.

P300 deficits

The P300 is a positive evoked EEG potential recorded about 300 ms after a deviant, infrequent stimulus is presented in an oddball task, while the subject focuses attention on detecting these infrequent stimuli (e.g. if asked to keep count of them). More complex paradigms include a 3-stimuli setting – a frequent stimulus, a deviant non-target stimulus, and a deviant target stimulus – where deviant stimuli elicit so called P3a and P3b responses, respectively. P3a is believed to originate from stimulus-driven frontal attentional mechanisms, while P3b is thought to be related to temporoparietal activity associated with attention [79]. Deficits in P300 have been extensively studied in SCZ, and both a reduced amplitude and an increased latency of the P300 have been consistently reported [80]. Furthermore, the same P300 parameters are also abnormal in FDRs of SCZ patients, when compared to healthy controls [81]. In a recent study by the NAPLS consortium, P300 for deviant auditory target stimuli predicted transition to psychosis in at-risk individuals, as opposed to P300 for deviant non-target stimuli [82]. It should however be pointed out that altered P300 is not a finding limited to the SCZ spectrum, having also been reported in patients with Bipolar Disorder and their unaffected FDRs [83]. Data from the B-SNIP study suggest that P3b amplitude deficits may be specific to schizophrenia, while reduced P3a amplitude may be a shared feature across psychotic disorders [84]. Interestingly, a recent study reported that P300 amplitude and P300 latency were not related with each other, thus suggesting different biological factors underlying abnormalities in this same domain of information processing [85].

Sleep endophenotypes: Sleep slow waves and sleep spindle impairment

In clinical settings, sleep disturbances are commonly observed in SCZ patients [86], including early course patients and individuals at clinical high risk for psychosis [87]. These observations have generated great interest in assessing the implication of sleep in the pathophysiology of SCZ and related disorders. While initial research was primarily directed towards investigating abnormalities in sleep architecture (i.e., the basic structural organization of sleep), with inconsistent findings (for a review, see [88]), more recent work has focused on sleep-specific EEG rhythms, including slow wave and sleep spindles. Slow waves are 0.8–1 Hz, large amplitude oscillations which dominate the deepest stage of non-rapid eye movement sleep (NREM N3) and are primarily generated and coordinated within the cortex [89]. Sleep spindles are 12–16 Hz, waxing and waning oscillations that characterize NREM N2 sleep. Spindles are initiated within the thalamus and are regulated by thalamo-cortical circuits, specifically by the synchronous firing of GABA-ergic, parvalbumin positive interneurons located in the thalamic reticular nucleus [90]. Spindle and, to lesser extent, slow wave abnormalities have been established by several sleep EEG studies in patients of SCZ, including medication-naïve and first-episode psychosis individuals, and alterations in spindle and slow wave have been also recently reported in FDRs of SCZ probands, as detailed below.

A decrease in slow wave power [91] and other slow wave parameters [92] has been reported in SCZ patients during sleep, although other sleep studies found no difference between SCZ and control samples [93–96]. In-depth reviews of these findings are available elsewhere [97,98]. Furthermore, our group recently found that reduced slow wave density was present in first-episode psychosis patient and correlated with the severity of their positive symptoms [99]. We have also established that FDRs of SCZ probands had decreased slow wave amplitude and slopes, when compared to age and gender matched individuals with no family history of SCZ [100]. While future studies are needed to replicate these findings in large groups of FDRs and to further explore their genetic underpinning, this work indicates that slow wave abnormalities may represent a putative endophenotype for SCZ.

Sleep spindle power and several other spindle parameters, including amplitude, duration, density, and integrated spindle activity (ISA), were found to be reduced in chronic SCZ patients relatively to HC [101]. Sleep spindle deficits were unaffected by antipsychotic medications [93] and were also reported in early course SCZ [102] and first-episode psychosis patients ([99] [103],). Furthermore, recent work from our and other research groups reported impaired spindle parameters in healthy FDRs of patients affected by SCZ relative to individuals with no family history of SCZ [100,102,104], consistent with a candidate endophenotype of SCZ. However, one study has questioned the specificity of sleep spindles deficits for SCZ, showing reduced fast spindles density and frequency in a cohort of patients affected by Bipolar Disorder in euthymic phase [105].

Spindle parameters have also been correlated with cognitive measures, such as intellectual ability (e.g. IQ) [106] in the general population, and are thought to mediate procedural and declarative memory consolidation and learning in animal models and in humans [107–110]. Furthermore, reduced sleep spindles were associated with diminished overnight learning in SCZ [96] and with impaired cognitive abilities in psychotic disorders and unaffected FDRs

of SCZ patients [102]. Altogether, these findings suggest that spindles deficits are related to the cognitive impairment of SCZ patients and their FDRs. Thanks to advances on the genetic bases of sleep spindle activity [111], the theoretical framework linking risk SCZ genes (i.e. CACNA1I, a Ca + channel that regulate the spindle oscillation) to specific neural dysfunctions (i.e. reduced sleep spindles) and clinically relevant behavioral features (i.e. cognitive impairment) is testable and will inform future studies investigating sleep spindles as a treatable neurophysiological endophenotype linking genetic risk to impaired cognition in SCZ [112].

Conclusions

Heterogeneity in clinical presentation inherently affects both nosology and research of major psychiatric disorders, including SCZ. Current classification systems [113,114], which are based on behavior rather than neurobiology, indeed provide a partially validated framework that mental health professionals can use to deliver reproducible diagnoses and share research results. Nevertheless, the implicit imprecision of such classification systems can affect researchers' ability to gain a deeper understanding on the neurobiology underlying behavioral phenotypes [115]. The aim to fill this gap and "deconstruct" SCZ and other major psychiatric disorders into biologically validated constructs – genetically informed and testable in translational animal models – has generated extensive efforts to identify reliable endophenotypes. Here, we provided an overview of the most established candidate endophenotypes for SCZ in the domains of neurocognition and neurophysiology. We also presented emerging sleep-based putative electrophysiological endophenotypes of SCZ that have recently been proposed by our and other research groups. In this last section, we will briefly discuss how the growing knowledge on endophenotypes may springboard future studies to progress our current understanding of the pathophysiology of SCZ. How this might reveal shared abnormalities across major psychiatric disorders, which may then set the stage for tangible advances in treatment, will also be addressed.

Although potentially relevant in shedding light on the pathophysiological mechanisms of psychotic disorders, the co-occurrence of endophenotypes within and across these disorders remains largely uninvestigated. The majority of research studies investigating this issue has focused on the co-occurrences of different cognitive measures [116–118]. A recent study investigated the associations between P300, ventricular volumes on brain imaging, and several cognitive measures in a large cohort of patients affected by psychotic disorders (including SCZ) and in unaffected FDRs [85]. P300 amplitude was related to measures of working memory but not to VDM. Nevertheless, more research is needed in order to clarify the co-occurrence of endophenotypes in psychotic disorders, including sleep endophenotypes, and identify common pathways to help narrowing the biological heterogeneity of psychotic disorders.

Future work should employ existing and novel endophenotypes to enrich genetic studies of SCZ. This may provide insights on the overlap in genetic vulnerability between SCZ and a specific endophenotype [17]. For example, a recent GWAS study that aimed to elucidate genetic correlates of AS deficits in psychotic disorders identified several genetic variants associated with both psychosis and AS deficits [67]. A similar approach could be

employed to explore the relationship between genetic variants associated with increased risk for SCZ (e.g. CACNA1I, which regulate Ca + Channels expression in neurons of the reticular thalamic nucleus, the sleep spindle pacemaker) and the sleep endophenotype (e.g. reduced sleep spindles) in SCZ probands and FDRs.

Another future application involves combining several endophenotypes to characterize genetic risk for SCZ and related psychiatric disorders. In this regard, in a recent, elegant study Clementz et al. identified three neurobiologically distinct 'biotypes' of psychosis by characterizing a number of endophenotypes (neurocognitive, imaging-based, EEG-based) in subjects diagnosed with SCZ and other types of psychosis, including Schizoaffective Disorder and Bipolar Disorder with psychotic symptoms [119]. Biotype 1 showed weaker responses to sensory stimuli; Biotype 2 had higher neural activity during auditory stimulation tasks; Biotype 3 appeared closer to healthy subjects in most tasks results. Interestingly, these biotypes did not overlap with diagnoses based on current classification systems. Moreover, authors recently showed that frequency patterns of intrinsic activity (IA, or "ongoing high-frequency", i.e. the neural activity recorded between evoked stimuli, could successfully discriminate Biotype 1 (low IA) and Biotype 2 (high IA), and that IA correlated with the level of active psychotic symptoms, again regardless of DSM-5 diagnosis [120]. By applying a similar approach to unaffected FDRs, future studies could reveal how genetic risk translates into neurobiological and neurocognitive abnormalities that may require targeted interventions in patients.

The observation that some endophenotypes are shared across psychosis spectrum disorders is consistent with the idea that these measures may promote conceptual advances in psychiatric nosology. Specifically, future research on endophenotypes in psychiatry should encourage a shift from phenomenological diagnosis-based paradigms to neurobiology-driven subtyping of psychiatric populations. Endophenotypes should therefore be investigated not just as correlates of specific clinical diagnosis, but primarily as neural traces associated with distinct, transdiagnostic dimensions of psychopathology (e.g. anhedonia, irritability, anxiety), as recently proposed by Beauchaine et al. [121]. In this perspective, endophenotypes would represent markers of genetic vulnerability to basic behavioral traits that, when interacting, give rise to complex clinical patterns, as reflected by the heterogeneity of current diagnostic categories.

Along these lines, recent data from the B-SNIP study showed a degree of overlapping of clinical, neurocognitive, neurophysiological and imaging derived measures across affective and non-affective psychoses [67,122–124]. In accordance with such evidence, Keshavan et al. recently proposed a valuable four-step approach aiming to deconstruct clinically diagnosed syndromes and redefine psychiatric nosology with a "bottom-up", biomarkers informed, disease definition [125]. This approach, while pointing towards a dimensional reconceptualization of psychiatric diagnostics, may also inform the clinical routine performed within the current diagnostic framework. For example, biomarkers and endophenotypes may help identify subtypes of clinically diagnosed syndromes (e.g. subtypes of SCZ) based on biological features. Consistent with this assumption, Chand et al. [126] recently reported two distinct forms of SCZ identified by machine learning techniques applied to brain imaging data. These two biologically informed "clinical subtypes" of

SCZ may then be targeted by more effective pharmacological and non-pharmacological interventions in the clinical practice. Altogether, advances in our current theoretical framework on the role of endophenotypes in psychiatry are well in line with the Research Domain Criteria Initiative [127] and may have significant impact in clinical settings in the foreseeable future. Indeed, the use of endophenotypes to identify subgroups of patients across and within psychiatric diagnoses (e.g. Biotypes of psychosis in SCZ) may lead to new advances in precision medicine in psychiatry. The shift towards brain circuitry from diagnostic criteria may pave the way for the development of targeted therapies to address specific neurobiological vulnerabilities. This will be particularly relevant for patients impaired by symptom domains that are resistant to currently available treatments, such as cognition in SCZ.

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