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An NIMH Workshop on Non-affective Psychosis in Midlife and Beyond: Research Agenda on Phenomenology, Clinical Trajectories, Underlying Mechanisms, and Intervention Targets

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Abstract

We present a review of the state of the research in the phenomenology, clinical trajectories, biological mechanisms, aging biomarkers, and treatments for middle-aged and older people with schizophrenia (PwS) discussed at the NIMH sponsored workshop “Non-affective Psychosis in Midlife and Beyond.” The growing population of PwS has specific clinical needs that require tailored and mechanistically derived interventions. Differentiating between the effects of aging and disease progression is a key challenge of studying older PwS. This review of the workshop highlights the recent findings in this understudied clinical population and the critical gaps in knowledge and consensus for research priorities. This review showcases the major challenges and opportunities for research to advance clinical care for this growing and understudied population.

Keywords

Schizophrenia; Aging; Cognition; Biomarkers; Treatment

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Introduction:

Schizophrenia spectrum disorders affect 24 million individuals across the world and are associated with significant disability, morbidity, and premature mortality (1). Most patients have onset of the disorder in late adolescence and young adulthood with about 25% emerging in middle age and beyond. Most research efforts have been directed towards a better understanding of the neurobiology and clinical needs of the younger age group. However, schizophrenia is a chronic disorder that can affect patients for decades. The majority of people living with the illness are in mid- to late-life and the burden of disease is greatest for these age ranges (2). Additionally, incident cases of schizophrenia, particularly in women, also present in middle age and beyond. Furthermore, it is projected that people with schizophrenia (PwS) aged over 60 years will constitute half of all schizophrenia cases by 2060 (3). Despite these increasing numbers, only a small percentage of the schizophrenia literature (~1%) is focused on this middle-aged and older patient population. The emphasis on the early stages of schizophrenia has overshadowed the need to take a lifespan approach to understanding the neurobiology, clinical presentation, and treatment needs of older people with schizophrenia.

To address these knowledge gaps, the National Institute of Mental Health (NIMH) sponsored a workshop on “Nonaffective Psychosis in Midlife and Beyond” held on February 19th-20th, 2022 involving over 30 experts on schizophrenia and aging including clinician scientists, neuroscientists, behavioral scientists, psychopharmacologists, and a person with lived experience. The goal of the workshop was to share the latest research findings, challenges, and opportunities for transformative research in this population through individual talks and panel discussions organized into five sessions: phenomenology/course/outcomes, cognition, regulatory/metabolic processes, accelerated aging, and treatment targets/intervention development. The workshop chairs (EEL, SF) and NIMH organizers selected and invited workshop presenters and moderators based on the body of their published literature and expertise. Following each of the five sessions, a moderated roundtable discussion was held around key workshop questions that were developed by the chairs and NIMH organizers (Supplemental Appendix A). The workshop was open to the scientific community and the public at large and was recorded (available at https://www.nimh.nih.gov/news/events/2022/workshop-nonaffective-psychosis-in-midlife-and-beyond). This paper synthesizes the evidence reviewed and the challenges identified in formulating a consensus future research roadmap for schizophrenia in mid- and late-life.

State of the Research

1. Clinical features of schizophrenia across the lifespan

1.A Phenomenology—Cardinal features of schizophrenia include positive and negative symptoms. Positive psychotic symptoms (in particular, visual, olfactory, tactile and auditory hallucinations) appear to dominate the clinical presentation of people who experience the onset of schizophrenia in mid-to-late adulthood (40 to 60 years – known as late-onset schizophrenia and >60 years - known as Very late-onset schizophrenia-like psychosis). By contrast, negative symptoms among older PwS (regardless of age at onset of psychosis) are mixed in terms of prevalence and course (4, 5). A key study by Ahmed and colleagues (6)

identified five key dimensions of negative symptoms (e.g., blunted affect, alogia, anhedonia, avolition, and asociality) and showed that negative symptoms in four independent US and European samples had similar severity in older and younger PwS, although their prevalence was highest in PwS over the age of 56 years. Across samples, negative symptoms were associated with male sex and having worse physical and cognitive functioning. Generally, however, the longitudinal evolution of psychopathology in schizophrenia remains unknown due to the lack of large-scale longitudinal samples.

There may be other phenomenological distinctions between older people who developed schizophrenia at a young age and people whose onset of psychosis was in mid-to-late life, though this topic is understudied. One Netherlands study reported one-year prevalence rates of 0.14% for late-onset schizophrenia and 0.05% for very late-onset schizophrenia among patients >60 years of age receiving mental health care (7). Onset of psychosis in late life is an indication for a thorough medical workup to exclude neurological disorders or delirium. Onset of psychosis in late-life is also strongly associated with sensory loss (8, 9), premorbid cardiovascular risk factors (10), and higher levels of peripheral inflammatory markers (10). While treatment guidelines for adults with late-onset schizophrenia have not been formally established, a few promising studies have shown good response among such individuals to certain antipsychotics (11, 12).

1.B Outcomes—Studies on recovery and remission typically focus on psychopathology with limited data on social functioning and quality of life. This represents a major knowledge gap as shown by Cohen and Reinhardt (13) who found five distinct outcomes in PwS based on the measure used; specifically 12% of the sample achieved stable clinical recovery; 23% of the sample fluctuated between clinical recovery and partial remission; 11% either attained persistent clinical remission or persistent community integration, but not both; 37% attained either clinical remission or community integration at only one point in time; and 18% never attained clinical remission or community integration. At present, we have no reliable predictors of long-term outcomes in schizophrenia which hampers personalized treatment planning.

1.C Neurocognition—Neurocognitive deficits are present in the premorbid phase of schizophrenia and appear to deteriorate around the onset of psychotic symptoms. However, studies on the longitudinal evolution of neurocognition in schizophrenia remain limited. There is robust evidence through registry studies that schizophrenia is a key risk factor for developing dementia. Compared to the general population, the prevalence of dementia among PwS from mid-life onwards is between 10–20 times higher (14) compared to the general population.

The Suffolk County Mental Health Project (SCMHP) stands out for its unique cohort of 628 patients who were enrolled as young adults during their first psychotic episode and have been followed longitudinally for 25 years. Using school records and neuropsychological testing from this sample, Jonas and colleagues noted declines in IQ roughly 14 years prior to the onset of psychosis, with continued decline leading to an average loss of 18 IQ points at 30 years post-onset (15). At Year 25, 12% of PwS had Clinical Dementia Rating (CDR) scale scores consistent with dementia, and 32% had CDR scores consistent with

mild cognitive impairment. If these declines continue, the SCMHP sample is projected to have high rates of dementia. The links between dementia and schizophrenia may reflect accelerated biological aging, increased cerebrovascular disease among PwS (16), or more severe psychopathology and subsequent treatment with antipsychotics.(17)

The role of disease chronicity in the absence of antipsychotic exposure on cognition has been uniquely explored in a cohort of PwS from Ningxia, China, a remote rural community where patients do not have regular access to psychiatric services and therefore minimal – if any – exposure to antipsychotics. The study investigators conducted cognitive assessments using an adapted version of the Matrics Consensus Cognition Battery (MCCB) in 197 individuals with untreated schizophrenia (mean age of 52.2 years and mean duration of untreated psychosis of 23.6 years) and 220 matched healthy individuals (18). Each year of untreated psychosis was associated with worse performance on executive functioning tasks, suggesting that illness chronicity is a risk factor for worsening cognitive dysfunction in schizophrenia. The mechanisms underlying cognitive decline in PwS remain unclear, and their association with treatment and risk factors related to lifestyle or physical comorbidity require further investigation.

1.D Social Cognition and Function—Social functioning is the engagement in social interactions and relationships, while social cognition is the ability to experience, and regulate one's own emotions and recognize those of others. Social functioning deficits have been reported up to 15 years prior to the onset of schizophrenia and show a steep deterioration in the 5 years preceding the first psychotic episode (19). In the SCMHP cohort, social functioning in 485 PwS was assessed in terms of education, employment, and independent living over 20 years, from their first psychotic episode to middle age; patients clustered into four subgroups with preserved, moderately impaired, severely impaired, and profoundly impaired social function that diverged early. However, the evolution of social functioning in patients beyond middle age remains understudied, and therefore, their social support needs remain unmet.

In parallel, a meta-analysis of 112 studies reported that PwS had significant impairments in social cognition involving the perception and processing of emotionally valanced information processing. Inter-study heterogeneity was large and not explained by age, education, or sex (20), suggesting a lack of standardization in how social cognition was measured in each study, rather than true intrinsic variability in social cognition among PwS. There was an effect of inpatient status on the severity of dysfunction in social perception, which was significantly worse during acute psychotic episodes. The pattern of longitudinal changes in social cognition is unclear. Cross-sectional studies suggest that deficits in social cognition remain stable in younger patients (below 35 years of age) (21). In the largest study on social cognition in schizophrenia to date, Velhorst and colleagues examined social perception and mentalizing in a sample of 993 individuals with psychosis, 1,219 unaffected relatives, and 543 healthy individuals. Although middle-aged individuals with psychosis (age 41–50 years) had worse performance on emotion perception, the level of age-related changes was similar to that of their relatives and of the healthy individuals. By contrast, mentalizing abilities showed minimal age-related changes across all diagnostic groups. Although conclusions about longitudinal changes are limited by lack of data particularly for

the older age groups, the existent literature largely supports the notion that deficits in social function and cognition, although present in schizophrenia, do not show greater deterioration than that observed in typical aging.

1.E Sex differences and Aging in Schizophrenia—Sex differences are present in multiple aspects of human physiology and behavior. In the context of schizophrenia, clinically relevant sex differences have been noted in age of onset and in antipsychotic sensitivity. Specifically, the incidence of schizophrenia in men peaks in early adulthood while women may have a second peak in late mid-life (22). As in the general population, depressive symptoms are more common in female than male patients while the opposite is the case with substance use (23). As a result of these differences, delays in accurate diagnosis of schizophrenia are longer in women than men (6 years vs. 2 years respectively), and women have reduced access to specialized early psychosis intervention services (24). Early psychosis programs are not typically tailored toward the needs of middle-aged or older women with incident schizophrenia as they tend to emphasize substance use treatment but not family relationships or childcare, which are often more directly relevant to women.

Research on psychosis treatment has largely ignored sex differences in drug sensitivity and drug metabolism. In a meta-analysis of 132 trials investigating the efficacy and safety of antipsychotics, only three studies discussed results by sex (25). This is an important omission as at least one randomized controlled trial has found that the blood levels of most antipsychotics (excepting quetiapine) were higher in women compared to men with schizophrenia despite receiving equal doses (26). Sex also impacts side effect profiles. The risk of breast cancers in females is increased by 150% after exposure to prolactin-raising antipsychotics for ≥5 years, compared to 1 year (27). The menopause transition and post-menopause are vulnerable periods for women with greater hospitalizations for psychosis and decline in antipsychotic effectiveness (28). There is early evidence supporting the role of estrogen modulating agents in augmenting treatment in women with schizophrenia.(29)

2. Brain Alterations in Schizophrenia across the lifespan

2.A Structural Brain Alterations in Schizophrenia—Brain structural alterations are a consistent correlate of schizophrenia. The Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium, which has conducted the largest meta-analyses of cross-sectional multi-site brain morphometry measures from approximately 2,000 PwS and 2,500 healthy individuals, has reported decreases in subcortical volumes (30) and multiple cortical regions among PwS (31).

Multiple research groups, mostly based in Australia, Europe, and North America, have examined longitudinal brain alterations following the first psychotic episode with significant inter-study variability in the results reported. A few key meta-analyses have identified several consistent findings. A meta-analysis of brain morphometric measures from 156 patients with childhood and adolescent onset (mean age at baseline 13.3–16.6 years) and 163 demographically matched healthy youth followed for 2.46 years revealed accelerated gray matter volume reduction in patients that was widespread but most pronounced in the frontal and occipital lobes (32). A similar pattern has been identified in patients with onset of

schizophrenia in young adulthood (31); although, the mean follow-up periods are typically 3–6 years. Reductions in gray matter volume have separately been shown to be associated with cognitive deficits in schizophrenia (33).

Homing in on specific brain circuitry has highlighted the importance of the anterior limbic system, which includes the hippocampus and medial prefrontal cortex. This system plays a critical role in global and episodic memory and emotional and reward processing (34) and is sensitive to processes related to both aging and schizophrenia. Volume reduction in anterior cornu ammonis of the hippocampus is a brain alteration that presents early in the course of schizophrenia, while abnormalities in other hippocampal subregions are present in chronic patients (35). Further, at least one study has shown that intrinsic hippocampal activity, as inferred from cerebral blood volume, is lower in untreated patients with first episode psychosis compared to healthy individuals but normalizes with antipsychotic treatment (36). As noted in previous sections, there remains a major gap in terms of longitudinal cohort studies that extend beyond young adulthood and studies that target patients with disease onset in mid- or late life.

2.B BrainAGE and Schizophrenia—Advances in machine learning applications to neuroimaging data have enabled the examination of the rate of brain aging in each individual as inferred by their Brain-Age-Gap-Estimation (BrainAGE). This metric quantifies the difference between the biological and chronological age of the brain with higher values indicating accelerated brain aging (37). BrainAGE is of particular interest in schizophrenia research given that this disorder is associated with age-related decline in neurocognitive function and higher rates of dementia in later life as already discussed. Multiple studies have documented higher brainAGE in patients with first-episode and chronic schizophrenia (38–40), with an average increase of 4 years as reported in the largest study to date that involved 2,598 healthy individuals and 2,803 patients with schizophrenia, aged 17–73 years (40). However, the longitudinal evolution of the pace of brain aging in schizophrenia remains uncharted. One study by Schnack and colleagues (38) showed a continued increase in brainAGE in PwS during the first 5 years post-onset that was associated with measures of clinical severity in terms of positive symptoms and number of hospitalizations. Conversely, there is some evidence that lifestyle interventions, and particularly aerobic activity, that are generally known to enhance brain health can also improve brain function in PwS (41). Although promising, the generalizability and real-world efficacy of these clinical trials are limited by small sample sizes, short follow-up of only a few weeks to months, and the inclusion of young participants.

2.C Sleep Spindles and Sleep-disordered Breathing in Schizophrenia—Sleep is one key biological process that links schizophrenia to age-related cognitive deficits. Sleep disturbances are common among PwS and older adults (42). In the general population, reductions in slow wave sleep and sleep spindles are associated with worse memory consolidation, mild cognitive impairment, and brain atrophy, though some of these relationships are age-dependent (43). Similarly, PwS have reductions in sleep spindles that are correlated with memory consolidation deficits (44). Increasing spindle density with eszopiclone among PwS was insufficient in enhancing memory consolidation, as PwS have

shown concomitant abnormal temporal coordination of spindles and cortical oscillations that resulted in worsening of memory performance (45). Novel approaches including pink noise to increase sleep spindles and impact memory are being studied (46).

Another understudied area of sleep research among PwS is obstructive sleep apnea (OSA), a disorder where airway collapse during sleep leads to intermittent hypoxia and downstream oxidative stress and inflammation. OSA has rising incidence and severity with older age, and independently predicts risk for cognitive impairment and dementia (47). Several studies have shown that the gold standard treatment for OSA, continuous positive airway pressure (CPAP) therapy, can improve processing speed, vigilance, attention, and executive functioning (48) among subgroups of OSA patients – depending on age, OSA severity, sleepiness, and specific treatment modality. PwS are two to three times as likely to have untreated OSA, and early studies have suggested that OSA contributes to further cognitive deficits among PwS (49). One small pilot study reported that CPAP treatment improved overall cognitive functioning for six PwS (50). Further research on OSA to improve cardiovascular and cognitive risk is warranted for PwS.

3. Dysregulation within Biological Pathways in Schizophrenia

3.A Mitochondrial function in Schizophrenia—Energy metabolism in the brain has a critical role in synaptic transmission, information processing, apoptosis, and spinal pruning (51). Abnormalities in mitochondrial function (key for cellular energy production) within the brain, such as the dorsolateral prefrontal cortex (DLPFC), may contribute to schizophrenia-related cognitive dysfunction. One postmortem study identified 871 differentially expressed genes in the DLPFC of PwS, pointing to a coordinated downregulation of genes related to mitochondrial energy production (52).

Imaging techniques, such as phosphorus (^{31}P) magnetization transfer (MT) spectroscopy can examine *in vivo* bioenergetics among PwS. Consistent with the postmortem findings of mitochondrial abnormalities, a 20–22% reduction in the rate of new ATP synthesis in medial frontal (53) and elevated *in vivo* brain lactate levels in the anterior cingulate assessed with 7Tesla ^{1}H-MRS (54) have been reported in PwS when compared to healthy individuals. The bioenergetic dysfunction in schizophrenia consists of dysregulated brain energy metabolism and evidence of oxidative stress as measured by spectroscopy, resulting in the inability to sustain normal brain circuit function secondary to impaired synaptic function, plasticity, and energy homeostasis (55). These findings are intriguing, there is need for future work to replicate these findings in broader subgroups of PwS.

3.B Extracellular Vesicles: A novel approach to molecular investigations in schizophrenia—Extracellular vesicles (EVs) found in biological fluids include exosomes (product of exocytosis from endosomes) and microvesicles (vesicles that are produced through the plasma membrane, which are involved in inter-cellular communication and removal of waste products). EVs from neurons and astrocytes can provide a “liquid biopsy” of the brain as they are accessible through a peripheral blood draw. The value of EVs was first demonstrated in studies in Alzheimer’s disease that have shown that neuronal EV-derived levels of amyloid beta-42, phosphorylated tau, and insulin resistance biomarkers

were elevated in patients (56, 57). The use of EVs in the study of schizophrenia is recent, but available evidence on neuronal EV-derived biomarkers suggests abnormal mitochondrial homeostasis (58), brain insulin resistance (59, 60), and a mitophagy deficit in patients in the early stages of psychosis (61). EVs are currently being considered in terms of their potential for targeted delivery of therapeutic biological agents, although this approach has yet to be applied to schizophrenia.

3.C Systemic Biomarkers of Aging in Schizophrenia—Baker and Sprott defined a biomarker of aging as a "biological parameter that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age than will chronological age"(62). A literature review of systemic aging biomarkers in schizophrenia found that nearly 75% of the 42 included articles reported abnormalities in biomarkers of inflammation, cytotoxicity, oxidative stress, metabolic health, gene expression, and receptor/synaptic function; 29% of these studies (predominantly on synaptic function and gene expression) showed a differential age-related decline, supporting the hypothesis of schizophrenia-related accelerated aging in some biological processes (63).

Cross-sectional studies have consistently reported increased levels of proinflammatory cytokines and chemokines among PwS, which are associated with clinical outcomes, though not necessarily with age (64). Exploratory studies using broad proteomics surveys and microbiome analyses have also highlighted differences in metabolic and inflammatory protein levels, and microbiome profiles in schizophrenia (65).

4. Developing and Testing Innovative and Personalized Treatments

4.A Pharmacological treatment development – D1 receptor stimulation—Reduction in striatal dopamine transmission remains the key pharmacological target for most medications used in schizophrenia. However, decreased cortical dopamine transmission has also been observed in schizophrenia and is postulated to contribute to neurocognitive deficits (66). Drugs that act as agonists for stimulating the D1 receptor (the main dopamine receptor in the cortex) may be a potential complementary treatment approach (67). The development of D1-targeted therapeutics has met with several challenges. The heterogeneity of D1 expression across PwS affects response and is partially related to prior exposure to typical antipsychotic medications, age, and chronicity of illness (68, 69). A very small dose is needed to reverse cognitive impairment (70) with different response from partial agonists and constant stimulation. Bioavailability of drugs also impacts effectiveness, e.g., catecholamine-type drugs have poor oral bioavailability and thus very limited D1 occupancy.

Newer agents that include non-catecholamine based compounds may hold the promise of better pharmacokinetics, bioavailability, and blood-brain barrier penetration, producing higher occupancy with fewer side effects. The kappa opioid receptor system is a promising target due to its ubiquity and modulation of GABA, glutamate, serotonin, and dopamine neurotransmission. A meta-analysis of 30 early studies on pan-opioid antagonists, mainly used as adjunctive treatment, in schizophrenia showed an overall beneficial effect of medium effect size on positive and negative symptoms (71). The same study also found that symptomatic improvement with pan-opioid drugs was weaker in patients treated with

higher doses of traditional antipsychotics. However, it was notable that the improvement in positive symptoms was of similar magnitude to the improvements reported with traditional antipsychotics that are used as monotherapies, despite the opioid antagonists being used in most studies as adjunctive treatment. Recent studies of dopamine-related treatments have used neuromelanin-sensitive MRI scans as a proxy of dopamine release in the striatum (71) and PET radiotracers to assess kappa opioid receptor binding, aiming to target these treatments for PwS who are most likely to benefit..

4.B Pharmacological treatment development – Cannabidiol—Cannabidiol (CBD), one of 140 cannabinoids present in the extract of the cannabis plant, has also been explored as a potential antipsychotic. In contrast to tetrahydrocannabinol (THC) which can induce psychotic symptoms in healthy individuals and worsen psychosis in patients, CBD is non-intoxicating, does not induce psychotic symptoms, and blocks the psychotomimetic effects of THC (72). One study reported that CBD is non-inferior to the antipsychotic amisulpiride (73) in reducing psychotic symptoms in PwS. Among individuals at clinical high risk of psychosis, a single dose of CBD attenuated activation of the bilateral striatal areas, midbrain, and medial temporal cortex compared to placebo, suggesting that CBD may ameliorate some of the abnormal neural activation underlying psychosis (74). A meta-analysis of CBD trials in adults aged 50 years or older found that CBD had similar tolerability as placebo (75). However, no studies of CBD in older individuals with psychosis have been conducted, and it is unknown whether CBD will be either effective or tolerable in this clinical population. Clarification of CBD targets using neuroimaging and other approaches, dose-finding for identifying effective and safe CBD dosing, and investigation into the molecular mechanisms underlying its antipsychotic effects are still warranted, given its potential for modulating receptor targets outside of CB1 receptors.

4.C Interventional treatment development – Neuromodulation—Neuromodulation is being increasingly used to treat multiple psychiatric disorders. Electroencephalogram (EEG) studies have shown that *theta-gamma coupling*, a phenomenon by which the amplitude of gamma oscillations is modulated by the phase of theta oscillations, may represent cognitive reserve, and predict working memory performance among PwS (76). Using transcranial magnetic stimulation (TMS) and EEG, researchers found that they could increase theta-gamma coupling with associated changes in plasticity in the prefrontal cortex (77) in healthy individuals and transient improvement in working memory in patients with early Alzheimer's disease (78). Direct current stimulation is another neuromodulation method that can increase theta-gamma coupling and enhance working memory in young healthy individuals (79). A further neuromodulation approach that uses alternating current stimulation has also been shown to increase theta-gamma coupling and working memory in older healthy individuals who had baseline impairments in both (80). Future studies will be necessary to evaluate the usefulness of neuromodulation for the treatment of the clinical and cognitive symptoms of in middle aged and older people with schizophrenia.

4.D Psychological treatment development – Cognitive remediation—Cognitive remediation is arguably one of the few treatment approaches that has been tested in older

PwS. Cognitive remediation targets the cognitive rather than the clinical symptoms of schizophrenia and may lead to greater gains in overall social function when combined with other interventions such as skills training. Cognitive remediation in very chronically ill and institutionalized PwS (who tend to be older) seems to lead to gains in functional skills and cognition similar to those in younger patients (81).

According to a recent large-scale meta-analysis, the response to cognitive remediation was best predicted by premorbid education rather than age (82). The ACTIVE trial randomized 2,800 older individuals (mean age 73 years) to one of four cognitive training conditions: processing speed, memory, reasoning, and a control condition. All conditions resulted in short-term improvements in cognitive ability, and gains observed in processing speed and reasoning were sustained at 10 years follow-up (83). Importantly, those who received processing speed training with booster sessions had half the risk for developing dementia in the next 10 years compared to the control group (84). Future studies should focus on older PwS with baseline impairments, model the completion of real-world tasks, and examine the potential to prevent decline into dementia.

4.E Combined pharmacological and psychological treatments—Pairing pharmacological and psychological interventions may provide another treatment avenue in schizophrenia. One study that combined memantine with auditory discrimination and training showed improved performance in both PwS and healthy individuals (85). Another study has paired guanfacine with cognitive training, with significant improvement in individuals with schizotypal personality disorder (86). Studies combining psychosocial and drug treatments may be of particular value in older PwS.

5. Research Gaps and Future Directions

The review of the data presented in the preceding sections underscores the lack of studies in older PwS as the major challenge (Table 1). Most of the studies in PwS cover the first decade or so post-onset which typically coincides with young adulthood. Information on the neurobiological features of chronic patients who have reached mid and late adulthood and on those who experience late life onset of psychosis is sparse. These gaps leave many unanswered questions, particularly with respect to the interactions between disorder-specific mechanisms, aging processes, and medical comorbidity. The development of services for people at high-risk for psychosis and for patients with first-episode psychosis has established the principle of stage-specific service delivery, but regrettably, this has not been applied to the needs of older patients.

Schizophrenia is a risk factor for dementia in late life, invoking the possibility of accelerated aging in PwS. The evidence for this is arguably more convincing for brain aging, with multiple studies documenting accelerated neuroimaging changes and cognitive decline in PwS compared to the general population. Studies have documented alterations in aging processes, including energy metabolism and inflammation in schizophrenia which may accelerate the pacing of biological aging in this patient population. The role of antipsychotic medication remains unclear as the degree of exposure is commonly associated with disease severity.

Significant sex differences in the clinical presentation of schizophrenia involve the preponderance of affective symptoms in women and the over-representation of women who experience the onset of schizophrenia in mid-life or later. Women may be particularly at risk in later life. Estrogens may play a significant role in modifying the clinical severity of schizophrenia, increasing the risk when levels are low or fluctuating and enhancing response when prescribed as adjunct treatment. Regardless of age, men and women differ in their sensitivity to antipsychotics and in the metabolism of antipsychotic drugs. This issue is insufficiently addressed in the literature despite its immediate translational value in optimizing medication dosing in the two sexes.

Recent work has highlighted the importance of the social environment and social determinants of health on clinical trajectories and outcomes of PwS. Such studies have been typically conducted in western countries with an over-representation of patients of European ancestry. This approach restricts our understanding of the interaction between environmental and disorder-related processes and potentially prevents the identification of risk or protective factors that may be unique to specific socioeconomic contexts. Studying PwS across the globe will provide invaluable perspectives on clinical challenges and treatments.

Studies of PwS beyond early adulthood, particularly using longitudinal designs, is desirable as it would enhance our understanding of disease trajectories and their modifiers. Challenges with such designs are mainly logistical and involve the need for sustainable funding beyond the typical duration of research grants and investment in recruiting and retaining the large sample of patients that are needed for the meaningful (i.e., valid, and reliable) stratification of patients according to disease trajectories and the modeling of the complex and multiple determinants of those trajectories.

A major, and arguably most significant, challenge for psychiatry in general and schizophrenia specifically is the absence of a cohesive model for the pathogenesis of the clinical and cognitive symptoms of the disorder. As outlined in previous sections, many systems appear dysregulated in PwS, but none seems to capture the core pathophysiology of the disorder. This issue is further compounded for PwS in mid and late adulthood when additional problems arise from mechanisms related to aging and to chronic antipsychotic exposure to non-disorder specific risk factors such as limited social support networks, lack of employment opportunities, and difficulties in accessing services that meet the complex patient needs. Therefore, efforts aiming at providing more mechanistic insights and how these relate to the inter-individual variation in patients' presentation are paramount and emphasize the need for interdisciplinary collaboration and comprehensive and longitudinal characterization of PwS.

The workshop consensus for key research areas included promising mechanistic research areas – including abnormalities in sleep architecture and sleep-disordered breathing, metabolic pathways, peripheral, and brain aging. Future studies should examine predictors of cognitive changes and recovery. Treatment development should be targeted for this population, examining key underlying mechanisms and considering safety concerns for older PwS. Studies must consider cohort effects that specifically impact older generations of PwS, e.g., lower frequency of second-generation antipsychotic exposure prior to the year

2000 that could limit generalizability of findings to younger cohorts of PwS. Recruitment for studies on older PwS may require multiple sites and larger samples to consider the compounded heterogeneity of schizophrenia and aging. Traditionally, studying older PwS has had several key barriers—including lack of funding, diagnostic challenges, recall bias and cognitive deficits that affect accurate ascertainment of past history, lack of infrastructure for longitudinal follow-up, and lack of support for higher risk research (87). Limitations of the current review include the restricted body of research literature on this population that also impacts the ability to tease out cohort effects and sex differences, lack of formal Delphi approach to develop the consensus research areas, and circumscribed breadth of the workshop that focused on only five domains and included a modest number of experts. The workshop and current review did not examine psychosocial interventions for middle-aged and older PwS, though such interventions are important for future research development and have great potential to impact the quality of life and functioning for this population.

In summary, middle-aged and older people with schizophrenia are a growing population with specialized needs. Focused research is needed to better understand the phenomenology of older PwS with young adult-onset and late-onset schizophrenia, sex differences in older PwS, trajectories of symptoms and cognition, underlying biological mechanisms, and key considerations for treatment development and personalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The data has not been previously presented orally or by poster at scientific meetings.

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Table 1:

Broad framework for future studies

Samples	Broad age ranges Powered to look at sex differences Diverse by race and ethnicity Diverse by including other countries, especially underdeveloped nations
Structure	Consortia to share data by pooling datasets, testing for reproducibility, harmonizing common assessments, providing quality checks on data
Design	Longitudinal design with multiple-year follow-up Outcomes that reflect multifaceted recovery outcomes Consider key predictors of longitudinal trajectories
Analysis	Modeling trajectories across time Data-driven approaches Separate impact of schizophrenia from aging
Innovation	Utilize technology to enable scalability, feasibility, usability Personalized to schizophrenia itself Consideration of aging processes
Intervention	Mechanistically driven and targeted approach with biomarkers of response Precision medicine approach to account for heterogeneity of patient population
Key research areas	Predictors of cognitive changes, negative symptoms, positive symptoms, and recovery Biomarkers of brain and peripheral changes Sleep dysregulation Metabolic pathways Aging processes in brain and periphery Novel mechanisms for targeted treatment development