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Aging of the body and the brain in schizophrenia

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Schizophrenia has long been recognized to be accompanied by greater physical morbidity and elevated mortality (Meyer and Nasrallah, 2009). Yet, it is only relatively recently that investigators have begun to fully explore the possibility that the schizophrenia syndrome affects not only the brain but the rest of the body as well. This multi-systemic view of the disorder was initially proposed in a review by Kirkpatrick and Galderisi (2008) who posed the question of whether schizophrenia was a disease of accelerated aging. By focusing the field on the notion that aging of both body and brain might be more rapid in people with schizophrenia compared to those without a serious mental illness, their review consolidated previous work and suggested studying the syndrome through a new prism.

This Special Issue begins with an updated review from Kirkpatrick and Kennedy (2018). The authors once again consider the complex relationship between disease and aging in schizophrenia, and whether it might qualify as a segmental progeroid syndrome, characterized by some but not all aspects of accelerated aging. In briefly reviewing progress in testing some of the hypotheses of their original article (Kirkpatrick and Galderisi, 2008), the authors note some areas in which evidence is consistently supportive of accelerated aging (e.g., glucose tolerance and insulin resistance, prolactin, inflammation, and oxidative stress) and others where the evidence is more mixed (e.g., cognition and telomere length). They highlight the need for more longitudinal studies, and emphasize the importance of accounting for potential confounds such as antipsychotic use, ethnicity, gender, socioeconomic status, lifestyle factors (e.g., sedentary lifestyle, smoking, diet), and body mass index in studies of accelerated aging in schizophrenia.

Furthermore, within the schizophrenia syndrome, subgroups may exist that are determined by clinical features, genetic or environmental risk factors, level of inflammation, or other factors. These subgroups may also differ in whether or not, or in what systems, accelerated aging occurs. The authors then considered seven inter-related mechanistic pathways thought to be involved in aging: epigenetic changes/DNA methylation, inflammation, proteostasis, including the mTOR signaling factor, adult stem cell function, metabolic changes, adaptation to stress, and macromolecular damage. Although some of these biomarkers have begun to be examined in schizophrenia, the article suggests studying these pathways in various cell types and with panels that can detect multiple players in the pathway. The review concludes by speculating on how a better understanding of the aging process in schizophrenia might lead to new lifestyle and pharmacologic interventions to slow aging and reduce morbidity and mortality.

The next article by Lee et al. (2018) discusses the most serious real life consequences of the postulated accelerated aging – i.e., premature mortality. The authors present data from a systematic review of longitudinal studies of mortality rates in schizophrenia. While the general population is living longer (almost a decade more since the 1970's), the troubling finding of this study is that patients with schizophrenia have not benefitted from this increase in longevity. Indeed, the mortality gap increased by 37% from pre-1970's studies; more recent longitudinal studies showed a three-fold elevation in mortality on average, and most individual studies also observed an increasing gap over the years examined. There may be biological as well as sociological explanations for the widening disparity in mortality rates. In the case of other health disparities, such as those due to race/ethnicity and socioeconomic status, targeted environmental and clinical interventions have been reported to reduce gaps in health outcomes. The Lee et al. (2018) article is important in that it raises awareness that the issue of heightened mortality in schizophrenia deserves continued attention and investment of resources aimed at reversing this disturbing and deadly trend.

Extending longevity in schizophrenia is a critical need that should be pursued with equal attention to improving the quality of life in the additional years. Cognitive dysfunction has become recognized as a core feature of the disorder, with longitudinal studies showing strong links to functional outcomes (Green et al., 2004). In the current issue, Harvey and Rosenthal (2018) examine the hypothesis of accelerated aging of cognitive performance and everyday functioning in schizophrenia. In this review of their own and others' work in this area, they observe that many features of cognitive performance, functional capacity, and functioning of people with schizophrenia resemble those of nonpsychiatric comparison participants who are 30 years older. Furthermore, there is some evidence from cross-sectional studies that the gradient of age-related changes is steeper among individuals with schizophrenia, suggesting both premature and accelerated cognitive

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aging. The pattern of cognitive deficits and changes is similar to that in typical aging, and does not resemble what is seen in pre-clinical or clinical Alzheimer's Disease. The authors emphasize that many longitudinal studies show parallel cognitive decline with age in people with and without schizophrenia, but note that there are subgroups who show steeper declines including those early in the course of the illness who have repeated relapses and chronic patients who are treatment resistant. In considering the role of metabolic and substance use comorbidities in the cognitive deficits of schizophrenia, the authors conclude that although these medical factors certainly worsen cognition and perhaps accelerate decline, the presence of cognitive dysfunction in persons with schizophrenia but without these co- morbidities suggests that they are not the sole drivers of premature and more rapid aging in patients. This paper sets the stage for studies of the possible biological underpinnings of altered course of cognitive and functional changes with age, which is the subject of several other articles in this Special Issue.

Consistent with the idea presented in the Harvey and Rosenthal review that there may be subgroups within the schizophrenia syndrome with better or worse trajectories of aging, Cohen and Murante's (2018) longitudinal study of performance on the Dementia Rating Scale (DRS) among community-dwelling older persons with early-onset schizophrenia identified several distinct patterns across an average follow-up period of almost 5 years. Although DRS performance was poorer in schizophrenia patients than in comparison participants, there were no cross-sectional differences in baseline DRS scores between individuals younger and older than 65, no significant overall decline in DRS scores from baseline to follow-up, and no evidence for greater decline over the study period for persons with baseline age older than 65. However, there was considerable heterogeneity of individual trajectories: 20% of patients showed substantial decline, 20% had substantial improvement, and the rest showed moderate or minimal positive or negative change in DRS scores. Among the 11 variables tested, only three were predictive of follow-up DRS scores. Specifically, DRS performance at follow-up was worse among non-White patients, individuals with lower baseline DRS performance, and those who had an increase in anxiety from baseline to follow-up. This study suggests that a minority of patients with early-onset schizophrenia may be at risk for accelerated cognitive aging, particular those with greater cognitive deficits to begin with, increasing anxiety with age, and those who are non-White. The authors speculate that interventions to decrease anxiety, remediate cognitive deficits, and treat metabolic comorbidities that are more prominent in non-White groups could stave off cognitive decline.

Clinical correlates of functional outcomes were the focus of Muralidharan et al.'s (2018) study of the relationship between thought, language, and communication (TLC) symptoms (i.e., thought disorder and alogia), age, and outcomes in a large sample of middle-aged and older community-dwelling patients with schizophrenia. In contrast to previous studies in institutionalized patients, which found that TLC deficits predicted only poorer social outcome, the current study of a community-dwelling sample showed that patients with greater degrees of alogia had worse performance on a social functioning capacity test and worse community functioning in many domains; more disconnected speech was associated only with worse occupational functioning. Since these relationships were observed after adjusting for several demographic and clinical measures and for cognitive performance, there appeared to be a role for alogia and thought disorder in functional outcomes above and beyond the known association with general cognitive deficits. Older patients had worse occupational and social community functioning than younger patients; since these age associations diminished when considering TLC measures in the model, there is some evidence that TLC deficits mediate the age associations with functioning. The authors suggest that interventions to reduce TLC deficits could be particularly useful in improving community functioning among older adults with schizophrenia.

Searles et al. (2018) present a thorough review of the potential role of steroidal hormones in sex differences in the course of schizophrenia. Women with typical age of illness onset generally have a more benign course of schizophrenia, but there is a second peak of onset for older women following menopause. This pattern suggests a hypothesis that the presence of estrogen may be protective, perhaps through estrogen's modulatory effects on dopamine. The authors review studies showing that frequency of relapse is greater and symptoms are more severe in women during times of relative estrogen depletion and that trials of estrogen therapy were effective in reducing symptoms in pre-menopausal women. The literature regarding older, post-menopausal women is sparse, but there are hints that estrogen treatments may improve functioning. Lindamer et al. (2001) found in a retrospective data analysis that older women with schizophrenia who had taken hormone replacement therapy had fewer negative symptoms, and a few trials of raloxifene (a selective estrogen receptor modulator) have shown symptom improvement, including gains in cognitive performance. The authors point out that the ability of estrogen to enhance dopamine function seems to be related to changes in the level of expression of the Catechol-*o*-methyltransferase (COMT) gene, and interactions of COMT polymorphisms with estradiol levels have been observed in healthy pre-menopausal women. Only a single study has examined the interplay of COMT genotype and estrogen levels (Papaleo et al., 2015), and the nature of the interaction was different from that in healthy individuals and in a direction that countered the idea of estrogen being protective in aging women with schizophrenia. Although estrogen treatment in healthy individuals may be associated with a high risk-to-benefit ratio, the authors argue that the balance may be tipped in favor of attempting such intervention for women with schizophrenia and deserves further study.

In addition to estrogen levels and COMT genotype, assessment of other blood-based biomarkers has begun to contribute to our understanding of the aging process in schizophrenia. Evidence is accumulating from cross-sectional studies that people with schizophrenia have greater systemic inflammation, cytotoxicity, and oxidative stress, and poorer metabolic health (Meyer et al., 2005), gene expression, and receptor/synaptic function compared to age-matched healthy individuals; in a minority of studies in this area, age was more strongly associated with biomarker levels in the schizophrenia than comparison group (Nguyen et al., 2018). Thus, there is consistent evidence of premature aging of many biological indices that are age-related and some evidence of accelerated aging. As reported in this issue, McKinney et al. (2018) set out to test whether a robust and multi-tissue index of biological aging based on DNA- methylation would indicate accelerated aging among patients with schizophrenia. They applied a validated algorithm (Horvath, 2013) to DNA-methylation data at 353 genomic sites contained in one brain and two blood datasets with samples from schizophrenia patients and healthy comparison individuals. The discrepancy between estimated biological age as determined by the DNA-methylation algorithm and chronological age was not significantly different in schizophrenia compared to healthy groups for any of the datasets. The findings are somewhat surprising since schizophrenia is clearly linked to premature mortality and the DNA-methylation measure of biological aging has been associated with mortality risk in the general population. The authors speculate that DNA-methylation age might be accelerated in other tissue types, brain regions, or cell types that were not examined here, or that other independent biological pathways might be more important in leading to the altered aging trajectories and premature death seen in schizophrenia. The possibility of some subgroups within the heterogeneous schizophrenia syndrome having advanced DNA-methylation age also cannot be ruled out since the datasets used in the study only contained limited clinical and medical information. Still, the negative findings based on large samples with a well-validated measure suggests caution in

making blanket statements about accelerated biological aging in all persons with schizophrenia, and are consistent with the heterogeneous pathophysiology of the disorder.

The final article by Palmer et al. (2018) looks at accelerated biological aging in schizophrenia from a markedly different angle – how a person with this illness can possibly avoid accelerated aging. The authors utilize a case-study approach to closely examine the clinical and biological characteristics of an exceptionally high-functioning woman with schizophrenia who is entering late life, in comparison with demographically similar typically- functioning women with schizophrenia and with non-psychiatric comparison (NC) women. In general, the index patient (IP) more closely resembled women in the NC group and out-performed or was healthier than women in the schizophrenia comparison group. In terms of working memory performance and brain response during an affective task, IP had better performance and greater activation than even the NC group. Remarkably, IP's levels of a number of blood-based markers of aging were healthier than those of two large NC and SZ groups from a separate study. The authors interpret these findings as being consistent with compensatory features that allow for exceptionally high level of functioning in IP, perhaps including biomarker levels that may help her avoid the usual premature morbidity and mortality seen in schizophrenia.

The articles in the Special Issue address a wide range of themes relevant to the hypothesis of accelerated biological aging in schizophrenia. Among these, it is important to emphasize that findings to date make it clear that serious mental illnesses are also serious physical illnesses. Research, healthcare systems, and societal structures need to adjust away from a narrow focus on brain pathology towards a broader whole-body approach that will enhance the wellness of individuals with schizophrenia. One possible positive result of such a shift would be a reduction in stigma that still negatively affects people with mental illnesses. Perhaps one day people with schizophrenia will be viewed like people with other chronic medical disorders such as cancer or diabetes, and no longer hear dismissive statements such as "it's all in your head." The articles in this issue also highlight a common theme in all types of schizophrenia research – that of heterogeneity. Just as onset, symptoms, and treatment response vary greatly among individuals with the same diagnosis, it is increasingly clear that the systems affected and pathways involved in accelerated aging may also be quite variable among subgroups of people with the schizophrenia syndrome. A challenge for the future is to identify meaningful and reliable biotypes with distinct trajectories of longitudinal changes and to discover early predictors of the course of aging. This will allow a more personalized approach to interventions aimed at reducing morbidity and mortality. This Special Issue focused on schizophrenia, but it must be noted that evidence for some degree of accelerated aging is also observed in other serious psychiatric disorders such as major depression (Wolkowitz et al., 2011), post-traumatic stress disorder (Lohr et al., 2015), and bipolar disorder (Rizzo et al., 2014). Future work will need to examine cross-disorder similarities and differences in the pathways and systems that show acceleration. Finally, although considerable progress has been made during the past decade, additional studies are needed to understand in detail the biological and environmental mechanisms of age-related deterioration in quality of health in schizophrenia. This would help lead to novel pharmacological and psychosocial treatment approaches which, if equitably applied, could enable people with schizophrenia to live longer and more fulfilling lives. They should finally catch up with the general population's recent gains in health and longevity.

Conflicts of interest

The authors declare no relevant conflicts of interest.

Contributors

Lisa T. Eyler was involved in data analyses, data interpretation and manuscript preparation.

Dilip V. Jeste was involved in data interpretation and manuscript preparation.

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