Peculiarities of Geriatric Psychiatry: A Focus on Aging and Depression

Jerson Laks¹ & Elias Engelhardt²

¹ Institute of Psychiatry of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

² Institute of Neurology of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

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Correspondence

Jerson Laks, Av. Copacabana 749/802, 22050-001 Rio de Janeiro, RJ, Brazil.

Tel.: +55 21 2255 3454;

Fax: +55 21 2548 4510;

E-mail: jlaks@centroin.com.br

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SUMMARY

There is a debate on whether Geriatric Psychiatry stands for itself as a discrete specialty or whether it is an extension of clinical Geriatrics, Neurology, and Psychiatry. This review aims to outline some recent data and possible approaches to define peculiarities of Geriatric Psychiatry, focusing on certain characteristics that define the aging brain. Geriatric depression is discussed taking into consideration some data from translational research. The brain aging process is not uniform. Frontal areas show marked impairment in inhibiting irrelevant information in working memory as they age, and the recruitment of these areas occur differently than in young subjects. Executive functions also change in normal elderly. Geriatric depression is a general definition of a multidimensional disorder with multiple risk factors. Dysexecutive syndrome is considered as a key to the neuropsychology of geriatric depression, correlated with functional impairment in late life. Late-onset depression has a higher load of comorbidity, of cerebrovascular disease, and of some genetic factors that may be different from early onset depression. Also, there are at least four clusters of treatment outcomes that are common in geriatric depression, which mirror the neuropsychological and clinical profiles. Research and practice in Geriatric Psychiatry should focus on the interaction of various dimensions and risk factors rather than on attempting to find a single cause to the disorders. Some answers may be found in comorbidity issues, in white matter lesions, which are more common in the elderly, and in genetic factors that impact on the aging process.

Introduction

The ever rising cost of healthcare and the projections for the next five decades show that there will be a special impact on costs related to the populations which continue to grow increasingly old [1]. However, some but not all of the chronic diseases will eventually exert their effect on healthcare costs and on the nature of caregiving as the Baby Boomers come of age [2]. Psychiatric conditions, for example, show three peaks of costs along the lifespan, one of them over the age of 65. Psychiatric conditions, however, would have a lowered impact (–1%) on costs whereas heart diseases and diabetes would lead the rank [1]. Despite these facts, these economic projections do not take into account that psychiatric disorders in the elderly, mainly depression and dementia, carry a heavy load of comorbidities such as hypertension, heart diseases, and diabetes which may in turn be facilitated by these very same geriatric psychiatry disorders.

As dementia and depression are expected to be increasingly more common in the population, public health strategies to diagnose and treat these diseases are also expected to rely on data

generated by research in Geriatric Psychiatry. Also, it is reasonable to hypothesize that postgraduation in this field will possibly achieve a more important position because of the increasing demand for services. This review aims to outline some of the recent data and possible approaches to define the peculiarities of Geriatric Psychiatry, with a special focus on depression and on certain characteristics that are peculiar to this age range.

Defining the Field of Geriatric Psychiatry

The field of Geriatric Psychiatry has experienced a surge of publications in the latest years, with increasing interest being focused on dementia and depression. Yet, there is still a debate on whether Geriatric Psychiatry stands for itself as a discrete specialty or whether it is just an extension of clinical Geriatrics, Neurology, and Psychiatry [3]. A proper definition of Geriatric Psychiatry must thus include a comprehensive set of information based upon phenomenological, epidemiologic, and biomedical data. A number of different approaches to the subject might yield complementary and yet conflicting answers, given the relations of the many

factors involved in aging and diseases in the elderly. It is virtually impossible to build up a body of knowledge that covers the extensive array of genetic and environmental risk factors, together with the study of aging, neurodegenerative, and cerebrovascular disease processes, and medical comorbidity [4]. Moreover, some of these areas of knowledge are just starting to be understood, such as proteomics, and the few psychiatric-related studies in this field are still focused in comparisons rather than in functional and structural changes which may occur in aging and in depression, for instance [5]. In a way, Geriatric Psychiatry may be viewed as the psychiatry of survivors [3]. If this is true, there would be scarce sound and reasonable data to name a clinical picture as Geriatric Depression, rather than the fact that it has been found in an old person. All these factors posit the research and the practice of Geriatric Psychiatry as a difficult task even to be defined [4]. Indeed, it raises some concerns voiced by important authors like Blazer [3] that Geriatric Psychiatry should focus on the oldest old and apply the theoretical frame of frailty as a hallmark, together with health-related quality of life measures. Ultimately, psychiatric syndromes in the elderly exert a marked impact on daily function and independence, therefore they should be included as geriatric syndromes as well [3].

Recently, Sadavoy [6] has proposed that the scope of Geriatric Psychiatry can be defined with five key "C" elements, namely complexity, chronicity, comorbidity, continuity, and context. Complexity stands for the interaction of life experience, stress, personality, and psychological developmental factors, and core physiological and neuropathological processes which all have their role to contribute to neuropsychiatric diseases in the elderly. Next, many diseases, which start up in old age often become chronic and longstanding problems (chronicity). Continuity refers to the cumulative effect of all the issues cited in the complexity element, which occur over the life cycle. Context, in turn, presents the notion that every fact and disease cannot be separated from the situation in which it appears, enrolling again all the complex and intersecting array of variables involved in the matter.

The cost effectiveness of developing special services for geriatric patients in psychiatry is another relevant issue when positing Geriatric Psychiatry as a specialty. Complex and chronic as they may be, psychiatric disorders in the elderly need appropriate work ups and services to meet the need to treatment. Some characteristics of the elders may give clues as to how to organize services according to their needs. A wider and comprehensive approach to diagnosis and management of the various syndromes in Geriatric Psychiatry is also needed, which should cover then cognitive, behavioral, neuroimaging, functional, social, and clinical comorbidity issues [6]. This is in fact the way psychiatrists who care for older people organize their practice. A comparison of the medical practice in two inpatient services at the same hospital, one concentrated on young psychiatric patients which also cared for elderly patients and another specialized in Geriatric Psychiatry showed that only the Geropsychiatry unit used a comprehensive approach to diagnosis and treatment (including complete organic medical workups, structured cognitive assessment, aging sensitive aftercare referral, and monitoring of psychopharmacological side effects and blood levels) [7]. Although the cost effectiveness of this approach is questioned [7], Blazer favors this kind of practice arguing that a

comprehensive workup is time consuming rather than procedure consuming [3]. Compared to other age ranges, patients older than age 64 are almost twice as likely to be treated in hospital settings for mental disorders. Admission criteria are similar to those used for adults on a general psychiatric unit, but in the geriatric population, there is an added emphasis on suicide risk and the inability to care for self [8].

Differences between mentally ill geriatric and general adult population can also be drawn by examining some other cost effectiveness data on health service delivery. Length of stay in hospital is one of them. Older patients with serious mental illness often require longer length of hospital stays compared with younger adults [9,10]. Electroconvulsive therapy (ECT) and adverse reactions to drugs consistently increases length of stay. The average length of stay is almost 59% longer for patients experiencing such complications than for those without. Developing protocols for addressing medication side effects and interactions are needed. Falling while hospitalized, greater severity of psychiatric illness but not cognitive impairment have been associated with increased length of stay in hospitals [11]. Albeit a short stay *per se* is not enough to provide appropriate care, the cost effectiveness of a well-planned short stay is the best scenario to be sought. This has been the policy in developed countries in Europe and America. In Korea, a recent study showed that length of stay of psychiatric elderly patients is approximately 128 days, a figure which may be similar in other developing countries [12]. This length of stay may be more a sign of lack of specific protocols of treatment and of proper design of multilevel organized network in institutions which provide care as needed for the situation, such as day hospitals, outpatient units, intensive acute units in hospitals, and, ultimately, respite homes with trained caregivers. There are, however, huge differences in healthcare systems, resources, and health budgets between developed and developing countries which may explain the preference for prevention and family treatments in developing countries whereas developed countries must face the chronic cases and provide for more nursing homes and care settings [13,14]. Also, cultural disparities between countries, regardless of the economic status, may account for peculiarities in dealing with the psychiatric cases in the elderly. Family and community configuration vary widely from culture to culture and issues such as age and mental disease are stigmas in many cultures, sometimes clearly stated, sometimes hidden. All these aspects impact on the care of elderly with psychiatric illnesses.

An approach that could lead to an improved knowledge in the field of Geriatric Psychiatry would be the integration of basic and clinical neuroscience research. This is critical for understanding the variability in illness course, as well as for the development of prevention and intervention strategies that are more effective [4,7]. Translational research on how the brain ages and its relation to psychiatric disorders is one of the issues, which may lead to this path.

The Aging Brain and its Relation to Psychiatric Disorders

Defining normal mental and cognitive status during the aging process as something different from cognitive decline is a key issue

to establish what is particular to Geriatric Psychiatry. Indeed, it is very difficult to define what is healthy cognitive aging. The brain does not age in a uniform fashion. Some areas and circuits seem to be more sensitive than others to the passage of time, mainly the prefrontal areas and the dopaminergic subcortical system. As adults get older their brains become smaller and brain weight declines by at least 10% between the ages of 25 and 75 years. Magnetic resonance imaging (MRI) analyses have contributed to our understanding of several aspects of brain aging. Volumetric studies with MRI present more pronounced age-related volume reductions in the frontal lobes than in other brain regions, associated or not with similar changes of the temporal lobes [15,16]. Likewise, studies on aging have also shown that the gray and white matter (WM) volumes do not change at the same rate over the lifespan. Gray matter volume declines throughout adulthood and into old age at a more or less linear rate. In contrast, WM volumes actually may increase slightly until the fifth decade of life, after which there is a steep decline in WM volume [17,18].

There is also a considerable interregional variation on the effects of age on gray and WM volumes of the major cerebral lobes (frontal, temporal, parietal, and occipital). This is also true for the major sectors of the temporal lobe, including the hippocampus and amygdala. The gray matter decrease is most strongly associated with age in the frontal lobes, followed by the parietal and temporal lobes. The weakest effect of age is observed in the occipital lobes. The same profile is present in relation to the WM [17]. The recently developed MR diffusion tensor imaging (DTI) technique offers an opportunity to evaluate the brain WM microarchitecture in a quantitative manner, including the degenerative changes with normal aging. A detailed analysis of the WM with DTI is possible given two of its features—mean diffusivity and the fractional anisotropy (FA). Currently, the most widely used measure of anisotropy is DTI-FA that allows quantification, where the values obtained represent an average of the sampled fibers in a given region of interest (ROI). It is a highly sensitive but fairly nonspecific biomarker of neuropathology and microstructural architecture of WM and is generally considered a marker of its integrity. DTI-FA appears to be the most sensitive imaging parameter to determine age-related WM damage, and the strong relationship of such damage with this parameter suggests that axonal damage may be important in age-related cognitive decline. Regional DTI-FA measures were assessed from several regions of interest in each hemisphere and from the genu and splenium of the corpus callosum. DTI-FA showed lower anisotropy values in the anterior region (subcortical WM and genu), but not in the posterior region (subcortical WM and splenium), in elderly normal subjects compared to a sample of young subjects. The results may represent loss of integrity of anterior (frontal) WM fibers in the elderly subjects. These fibers constitute important intra- and interhemispheric tracts, components of neural networks that provide cognitive, behavioral, motor, and sensory integration. These findings suggest that WM alterations are variable throughout the brain and that particular fiber populations within prefrontal region are most vulnerable to age-related degeneration. The loss of integrity of the anterior segments of the studied fiber systems with aging, represents a disconnection process that may underlie frontal clinical manifestations found in elderly subjects [19,20].

These aging processes, which occur in the brain bring along cognitive and behavioral-related changes. Among the frontal-managed activities executive function (including planning, fluency, and cognitive flexibility) is one of the first to show a relative impairment with a relevant impact on functional tasks [21]. It is an established fact, for instance, that working memory declines with age, although there seems to be no difference on verbal tests in oldest old and younger old healthy persons [22–25]. There are also consistent data to affirm that older persons have a marked impairment in inhibiting irrelevant information in working memory [26,27]. This is probably related to the fact that as the dorsolateral prefrontal cortex ages it shows a different pattern of activation from that which occurs in young subjects. This leads to decreased speed of processing and diminished mental flexibility. Older adults seem to make earlier and more demands on the dorsolateral prefrontal cortex than young adults do [28,29]. Also, prefrontal areas from both hemispheres are recruited symmetrically in older adults as compared to the asymmetrical recruitment, which occur in young adults so as to carry out a number of cognitive tasks [30].

Differentiation of Mild Cognitive Impairment, Age-Associated Cognitive Impairment, Cognitive Impairment Not Dementia, and Normal Aging is an issue of lively debate. Some cognitive domains might be specifically impaired in mild cognitive impairment (MCI) subjects and these aspects could serve as differential markers to distinguish this condition from normal aging. Rodríguez et al. [31] found that individuals diagnosed as MCI performed significantly worse than healthy elderly in some neuropsychological subtests, mainly on variables related to memory, abstract thinking, and executive function. Erkinjuntti et al. [32] also observed impairment in memory, conceptual functions, and arithmetical skills in a sample of individuals presenting age-related cognitive changes. More recently, another study showed that memory, constructive ability, and abstract thinking were particularly impaired in MCI individuals compared to controls [33].

To sum up, cognition and mood show some slight changes in normal aging, mainly in executive functions and in conceptual tasks, which are related to different recruitment of prefrontal and temporal areas. This may provide some of the factors for the susceptibility to geriatric depression. As attentional processes and motivation are important aspects of the depressive syndrome which are also related to executive functions, the elderly might be more prone to depression as these mechanisms seem to be changed due to the aging process.

Geriatric Depression

Clinical Course, Predictors, and Psychobiological Factors

Depression in the elderly is a preferred focus of interest in Geriatric Psychiatry. Nevertheless, diagnosis of Geriatric depression is frequently underestimated, despite its importance as a risk factor for cognitive decline and dementia and as a predictor of a bleaker outcome in a number of medical conditions, such as diabetes, stroke, and heart disease [34,35]. A multidimensional approach is necessary to tackle this problem from a clinical, psychopharmacological,

and translational standpoint. Some studies show that depression in the elderly behaves in the same fashion as the one, which occurs in middle-aged subjects with regards to treatment outcomes lest the aged depressed patient does not hold any comorbid condition [36]. Clinically, however, geriatric depression may present with more anhedonia, apathy, and dysexecutive symptoms than those found in early onset depression [37,38]. Some common types of depression in the elderly, such as melancholic- and psychomotor-retarded depression, may be caused by a reduced dopamine uptake in the limbic system together with a diminished noradrenergic and dopaminergic binding in the thalamus and locus coeruleus as is found in Parkinson's disease patients [39,40].

The different profiles of clinical course and outcome show that we are dealing with a heterogeneous disorder, and there is a need to describe the clusters and subtypes so as to arrive to sound conclusions when genetic and clinical outcomes are studied. Some studies show that late-onset depression may present as either a dysexecutive syndrome, or a pseudodementia syndrome, or may also be a prodrome of dementia [41]. The dysexecutive syndrome may be also considered as a trait rather than a state in the currently depressed patient, since there are some data showing that remitted depressed subjects have some degree of attentional and dysexecutive impairments as measured by neuropsychological test [42]. Although the evidence is not restricted to elderly patients, age may provide a pronounced susceptibility to depression as far as the differential aging of the frontal lobes is concerned.

Awareness on the predictors and risk factors of depression in elderly subjects is important to plan for possible preventive measures and treatment strategies for those who are diagnosed with it. Both cross sectional and longitudinal studies show that higher scores on depression scales, cognitive decline, a shorter stay in nursing home, and comorbid heart disease [42–47] may be predictors of depression in the elderly. Also, a recent longitudinal naturalistic study on the outcome of treated depressed outpatients showed that baseline depression, baseline anxiety, and greater increase in anxiety were the variables most related to a bleaker outcome in treatment [36].

The data on comorbidity, however, may not be distinctive, but rather a coincidence of many other factors [28]. Depression is a risk factor for the development of clinical disorders, as well as clinical disorders may be risk factors for depression, both leading to mortality in the elderly [48]. Cerebrovascular disease caused by hypertension, hyperlipidemia, and diabetes is certainly one of the most distinctive factors between late- versus early onset depression [29]. Chronic and treatment resistant late-onset depression in the elderly has been shown to be associated with microangiopathic injuries in limbic, frontal, neostriatal regions, and subcortical WM areas [49,50]. Again, if the question to be answered in this article is what is distinctive of Geriatric Psychiatry, we are forced to answer that certainly comorbidity and "organicity" are key elements.

There is a multitude of interacting and intervening factors that mediate the final outcome of clinical depression in the elderly. Higher cortisol levels have been correlated both with depression and with the development of metabolic syndromes in young and older subjects, although some studies have shown negative results. These inconclusive results may be due to comparisons between heterogeneous populations and subsets of depressive patients. In

the elderly, low cortisol levels may reflect biological exhaustion or frailty, which would render a unique feature to this population. In these cases, patients have shown not to have metabolic syndromes [51]. Conversely, hypercortisolemic depression was associated with metabolic syndrome in a study, which was able to present data in which hypo- and hypercortisolemia was more evenly spread over depressed persons [52–54]. These features may be also related to neuroinflammation and proinflammatory factors in depression.

The nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have been implicated in a series of inflammatory and neurodegenerative diseases, as well as with depression. BDNF levels decrease with age but the distribution of serum NGF and BDNF is not normal in the population and has a negative correlation between serum BDNF levels and age in healthy old adults according to a large cohort from Berlin [55]. Also, there were no significant differences between the depressed and the healthy subjects with regard to BDNF levels, the same being found for NGF. When BDNF polymorphisms were searched in depressed elderly the Val66Met [56] but not the C270T polymorphism [57] was associated with late-onset depression. Interestingly, the Val66Met polymorphism is also linked to the development of WM hyperintensities which may be viewed as biomarkers for subtyping clinical depression in the elderly clinically and to predict pharmacological response [58].

APOE ϵ 4 carriers have been found with increased risks of developing Alzheimer's disease (AD) and are more susceptible to impaired recovery from trauma, although there is no link between this genetic profile and major depression in young subjects. Depression and APOE ϵ 4 genotype may be higher in women with AD but not in men [59]. Other studies, however, failed to support the assumption that APOE ϵ 4 genotype influences depression in AD [60,61]. Although Delano-Wood et al. [59] revealed that women who possessed the APOE ϵ 4 allele were almost four times more likely to be depressed in comparison to those who did not carry the allele, a more recent case control study [62] did not find such a relationship with a large dataset which searched for the role of APOE ϵ 4 in late-onset depression and in depression of AD [63]. However, another large study, which looked into the interaction of depression and APOE ϵ 4 as risk factors for dementia in men came to different findings. APOE ϵ 4 modifies the association between depression and dementia leading to a 7.1-fold higher risk in depressed men with APOE ϵ 4 as compared with the 1.6-fold risk for depressed men who do not carry the APOE ϵ 4 allele [64]. An interesting study designed to test the hypothesis of an impaired response to antidepressants in elderly patients with this allele showed that mirtazapine but not paroxetine actually had a better response in patients who were APOE ϵ 4 carriers [65].

Response to antidepressant treatments may be modulated by a series of interrelated factors. We have already mentioned how depressed elderly with WM lesions tend to be more resistant to remission than patients who do not show intense lesions as showed by FA. Interestingly, the serotonin transporter is encoded by a gene located in chromosome 17 and the most important polymorphism (5-HTTLPR) has two main alleles, namely S and L. Depressed elderly patients with SL genotype have more total brain lesions and WM lesions than depressed L and S homozygotes

[66]. The S allele of 5-HTTLPR polymorphism may attenuate the response of major depression to selective serotonin reuptake inhibitors [67]. Another study showed that remission in treatment with escitalopram and citalopram were lower in a group of depressed Caucasian elderly who were S carriers as compared to controls. This subset of patients also revealed lower FA values pointing to increased WM lesions in several frontolimbic areas [68].

The response to treatment may display many different outcomes, which mirror several possible clusters or subtypes of depression. Dew et al. [69] have described four clusters of outcomes to the treatment of depression in the elderly: one group has a marked and fast improvement with remission and a second group also shows remission although with longer duration to achieve this goal. The third cluster is constituted of patients who show response but not remission, whereas the fourth one is not respondent to the treatment. Of course, these are not subtypes of clinical presentation, but the clusters described may bring insights on which clinical presentations may predict these outcomes.

Conclusion

Research and practice in Geriatric Psychiatry should focus on the interaction of various dimensions and risk factors rather than on attempting to find a single cause to explain the disorders. Some of the answers may be found in comorbidity issues, in WM lesions, which are more common in the elderly, and in genetic factors that impact on the aging process. The study of the brain aging process together with the ensuing neuropsychological changes unique to the elderly may also help the clinical workup and provide some routes to better define Geriatric Psychiatry as a distinct practice and research field in Medicine.

Conflict of Interest

Jerson Laks has been a lecturer, worked as a consultant, and in clinical trials with Apsen, Eli Lilly, Glaxo SmithKline, Janssen-Cilag, Lundbeck, Novartis, and Wyeth-Whitehall. Elias Engelhardt has been a lecturer and a consultant for Janssen-Cilag, Novartis, and Wyeth-Whitehall.

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