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J Geriatr Psychiatry Neurol 2014 27: 56 originally published online 8 January 2014
DOI: 10.1177/0891988713516544

Journal of Geriatric Psychiatry and Neurology
2014, Vol. 27(1) 56-62

DOI: 10.1177/0891988713516544
jgpn.sagepub.com

Neuroimaging Findings in Late-Onset Schizophrenia and Bipolar Disorder

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Abstract

In recent years, there has been an increasing interest in late-onset mental disorders. Among them, geriatric schizophrenia and bipolar disorder are significant health care risks and major causes of disability. We discussed whether late-onset schizophrenia (LOS) and late-onset bipolar (LOB) disorder can be a separate entity from early-onset schizophrenia (EOS) and early-onset bipolar (EOB) disorder in a subset of late-life schizophrenia or late-life bipolar disorder through neuroimaging studies. A literature search for imaging studies of LOS or LOB was performed in the PubMed database. Search terms used were "(imaging OR MRI OR CT OR SPECT OR DTI OR PET OR fMRI) AND (schizophrenia or bipolar disorder) AND late onset." Articles that were published in English before October 2013 were included. There were a few neuroimaging studies assessing whether LOS and LOB had different disease-specific neural substrates compared with EOS and EOB. These researches mainly observed volumetric differences in specific brain regions, white matter hyperintensities, diffusion tensor imaging, or functional neuroimaging to explore the differences between LOS and LOB and EOS and EOB. The aim of this review was to highlight the neural substrates involved in LOS and LOB through neuroimaging studies. The exploration of neuroanatomical markers may be the key to the understanding of underlying neurobiology in LOS and LOB.

Keywords

late-onset schizophrenia, late-onset bipolar disorder, neuroimaging

Introduction

In recent years, there has been increasing interest in late-onset mental disorders. This increasing interest is not only because of a natural result of the growing number of elderly population but also because of the difficulty in diagnosing and establishing a treatment strategy for late-onset mental disorders. Indeed, the initial differential diagnosis of older patients with major psychiatric symptoms, such as paranoia, hallucination, or mood change, is important and difficult. Major psychiatric disorders such as schizophrenia or bipolar disorder significantly decrease the quality of life of patients and caregivers and increase the burden of health and social care services. Although late-life schizophrenia and late-life bipolar disorder can be significant health risks of older adults and a major cause of disability,[1,2] there have been few publications on these topics.

Advances in neuroimaging techniques and image analysis have led to success in determining the neural substrates of various psychiatric disorders. Over the past decade, many studies have used neuroimaging techniques to identify brain regions implicated in various psychiatric disorders. This article focuses on neuroimaging studies of patients with late-onset schizophrenia (LOS) or late-onset bipolar (LOB) disorder. Neuroimaging is a powerful tool to identify neuroanatomical markers and can be used in the determination of diagnostic and prognostic statuses of LOS and LOB in the elderly patients, not only for research purposes but also for clinical treatment.

Several investigators have observed differences in the structure of the brain between late-onset and early-onset psychiatric disorders (LOS vs early-onset schizophrenia [EOS],[3-12] LOB vs early-onset bipolar [EOB][13-16]) but there have been few verification studies. We will discuss whether, in a subset of patients with late-life schizophrenia or late-life bipolar disorder, LOS and LOB can be considered to be separate entities from EOS and EOB, respectively, through neuroimaging studies. Additionally, we will also discuss certain unique neuroanatomical markers of LOS and LOB in accurately diagnosing and treating these disorders.

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Methods

A literature search for imaging studies of LOS or LOB was performed in the PubMed database. Search terms used were: "(imaging OR MRI OR CT OR SPECT OR DTI OR PET OR fMRI) AND (schizophrenia or bipolar disorder) AND late onset." Articles were included that had published in English before October 2013. Additional publications that were not found in the original search were complemented by reviewing reference lists of all retrieved studies. We discriminated between late-onset mental disorders and late-life mental disorders. Studies about late-life schizophrenia or late-life bipolar disorder could be cited in the text of this article if it was necessary, and studies about LOS and LOB are presented in the tables.

Results

Volumetric Differences in Specific Brain Regions

Success in exploring alterations in brain structures in patients with psychiatric disorders has closely paralleled the development of neuroimaging techniques and advances in image analysis. Several investigators have observed alterations in the morphology and volume of brain structures and reductions in cortical thickness in patients with mental disorders and have described disease-specific neural substrates. Among neuroimaging studies of late-onset mental disorders, more studies have been done on late-onset depression compared to other late-onset disorders, and results that emphasize the abnormalities of frontosubcortical circuits[17] are likely comparatively consistent. Although there are relatively fewer neuroimaging studies about LOS and LOB, most studies report results about simple volumetric alterations.

Late-Onset Schizophrenia. Howard et al,[18] in an magnetic resonance imaging (MRI) study of 50 patients with late-paraphrenia (31 patients with paranoid schizophrenia and 16 patients with delusional disorder), reported that patients with late paraphrenia had larger lateral and third ventricles compared to controls. They did not distinguish between LOS and delusional disorder, and they found that the lateral ventricle volume in the delusional disorder group was much greater than those of the schizophrenia group. These results suggested that various geriatric mental disorders might have different neurobiology. Corey-Bloom et al[3] reported larger ventricles in an LOS group than in an healthy control group, which parallels the results of Howard et al. Further, they reported that the group with LOS had larger thalamic volumes than the group with EOS. Barak et al,[11] in a computed tomography (CT) scan study of 21 patients with very LOS-like psychosis (VLOSLP) versus 21 patients with EOS, reported that the VLOSLP group was characterized by more pronounced cerebellar atrophy than the EOS group. Sachdev and Brodaty[8] reported that the mean area of the corpus callosum in an LOS group was smaller than that in EOS and control groups.

Symonds et al[5] observed brain MRIs of 30 patients with EOS, 24 patients with LOS, 15 other patients with psychosis, and 41 controls. They examined volume loss, infarcts, lacunae, and white matter hyperintensities (WMHs). Results indicated that there were no significant differences in gross structural abnormalities between the EOS and the LOS groups. Sachdev et al[10] examined 20 patients with late-life schizophrenia, 5 patients with LOS, and 20 controls on MRI imaging. Patients with schizophrenia had smaller hippocampal and amygdala volumes than those of the controls, consistent with morphological findings in schizophrenia. However, the LOS group did not differ in hippocampus–amygdala volumes from the EOS group. Imaging studies that compared the LOS group with the EOS group are presented in Table 1.

Late-Onset Bipolar Disorder. Beyer et al[20] examined the caudate nuclei volumes of 36 older patients with bipolar disorder and 35 older controls and reported decreased volume in the LOB group compared with the EOB group. They also reported that the right caudate was smaller in the LOB group than in the control group. In a different study, Beyer et al[21] observed no difference in hippocampal volume between the EOB and LOB groups. Additionally, Huang et al[16] reported contrasting results that the left caudate was larger in patients with late-onset mania than those with early-onset mania. Further, they reported that the late-onset mania group had greater volumes in the left middle frontal gyrus and smaller volumes in the right posterior cingulate than that of the early-onset mania group. Imaging studies that compared LOB group with EOB group are presented in Table 2.

White Matter Hyperintensities and Other Vascular Risks

Periventricular and deep WMHs on T2-weighted image have been thought to be indicative of microangiopathy. Several investigators have suggested that frequency of WMHs is correlated with vascular risk factors,[23] cognitive function,[24,25] and various neuropsychiatric symptoms[15,26] as well as with normal aging. Therefore, extant studies suggest a relationship between late-onset mental disorder and WMHs.

Late-Onset Schizophrenia. Breitner et al examined the brain MRIs of 8 patients with late-onset psychosis and 8 healthy controls (HCs) and found that patients with late-onset psychosis had significant vascular lesions or leukoencephalopathy in temporoparietal and occipital areas.[27] Tonkonogy and Geller reported that WMHs were more frequent in those with late-onset psychosis than those with early-onset psychosis. However, others have reported that those with early-onset show ventricular enlargement and cortical atrophy compared to those with late onset.[19] Sachdev and Brodaty examined WMHs of LOS, EOS, and control groups and found that the LOS group had greater periventricular hyperintensity than that of the EOS and control groups. Additionally, they observed that the LOS group had more signal hyperintensities in the thalamus than did

Table 1. Comparison Between LOS and EOS Through Imaging Studies.

Investigator, Publication Year	Imaging Technique	Patient Groups (Sample Size)	Key Findings of LOG Compared With EOG	Cutoff Age of Late-Onset
Corey-Bloom et al[3], 1995	MRI (volumetry)	LOS (16) vs EOS (14) vs HC (28)	Larger thalamic volume	45
Sachdev et al[7], 1999	MRI (mid-sagital cross-sectional area)	LOS (25) vs EOS (24) vs HC (30)	Smaller corpus callosum	45
Sachdev et al[10], 2000	MRI (volumetry, hippocampus and amygdale)	EOS (20) vs LOS (4) vs HC (20)	No difference in hippocampus and amygdala	45
Symonds et al[5], 1997	MRI (volume loss, infarcts, lacunae, WMHs)	EOS (30) vs LOS (24) vs other psychosis (15) vs HC (41)	No difference	45
Tonkonogy et al[19], 1999	MRI (WMHs)	LOPP (13) vs EOPS (35)	More frequent WMHs (ventricular enlargement and cortical atrophy were more frequent in EOPS group)	
Sachdev et al[7], 1999	MRI (WMHs)	LOS (25) vs EOS (24) vs HC (30)	Greater periventricular hyperintensities	45
Rivkin et al[9], 2000	MRI (WMHs)	LOS (12) vs EOS (10) vs HC (42)	No differences in the WMH voulmes	45
Casanova and Lindzen[12], 2003	MRI (gray/white matter ratios)	LOS (13) vs EOS (13)	Alterations in gray/white matter ratio of the parahippocampal gyrus (preservation of gray matter and reduction of white matter)	40
Barak et al[11], 2002	CT	VLOSLP (21) vs EOS (21)	More pronounced cerebellar atrophy	60
Sachdev et al[4], 1997	SPECT	LOS (15) vs EOS (7) vs HC (27)	Lesser temporal perfusion	45

Abbreviations: LOG, late-onset group; EOG, early-onset group; MRI, magnetic resonance imaging; LOS, late-onset schizophrenia; EOS, early-onset schizophrenia; HC, healthy control; LOPP, late-onset paranoid psychosis; EOPS, early-onset paranoid schizophrenia; WMH, white matter hyperintensity; CT, computed tomography; VLOSLP, very late-onset schizophrenia like psychosis; SPECT, single-photon emission computed tomography.

Table 2. Comparison Between LOB and EOB Through Imaging Studies.

Investigator, Publication Year	Imaging Technique	Subject Groups (Sample Size)	Key Findings of LOG Compared With EOG	Cutoff Age of Late-Onset
Beyer et al[20], 2004	MRI (volumetry, caudate)	Older bipolar disorder group (36, EOB [12], LOB [13]) vs HC (35)	Decrease brain volumes	45
Beyer et al[21], 2004	MRI (volumetry, hippocampus)	Older bipolar disorder group(36, EOB [12], LOB [13]) vs HC (35)	No differences in hippocampus volumes	45
Huang et al[16], 2011	MRI (volumetry)	EOM (25) vs LOM (19)	Greater volumes of the left caudate and left middle frontal gyrus; smaller volumes of the right posterior cingulated; more comorbid cerebrovascular disease	45
Fujikawa et al[13], 1995	MRI	LOM (20) vs EOA (20)	Higher incidence of SCIs	50
Takahashi et al[14], 2008	MRI (WMHs)	LOM (29) vs EOM (23) vs HC (14)	More severe deep WMHs in bilateral frontal and the left parietooccipital area; no difference of periventricular WMHs	50
Tamashiro et al[15], 2008	MRI (WMHs)	LOB (10) vs EOB (49) vs HC (24)	Prevalence: greater WMHs in deep parietal region and basal ganglia; group-comparison of mean WMH scores: more severe WMHs in deep frontal and parietal region and putamen	60
Huang et al[22], 2012	MRI	Elderly patients with bipolar disorder (43)	SCIs were detected in 59.5% (N = 22) of 37 patients without a history of stroke 61.3% of 13 patients with LOB 46.7% of 30 patients with EOB	50

Abbreviations: LOG, late-onset group; EOG, early-onset group; MRI, magnetic resonance imaging; EOB, early-onset bipolar disorder; LOB, late-onset bipolar disorder; EOM, early onset mania; LOM, late-onset mania; EOA, early-onset affective disorder; SCIs, silent cerebral infarctions; WMH, white matter hyperintensity.

the HC group.[6] They also found greater periventricular WMHs in those with LOS than those with EOS.[7]

In contrast, Symonds et al did not find any differences in volume loss, infarcts, lacunae, or WMHs between EOS and LOS.[5] Further, Rivkin et al examined 12 patients with LOS, 10 patients with EOS, and 42 controls and found no differences in the WMHs volume among these 3 groups.[9]

Late-Onset Bipolar Disorder. Fujikawa et al observed the relationship between late-onset mania and silent cerebral infarctions using MRIs and found that the late-onset mania group had a higher incidence of silent cerebral infarctions than the early-onset affective disorder groups. They suggest that those with late-onset mania may have increased vascular risk of brain damage.[13] Using different approaches, Huang et al examined elderly patients with bipolar disorder. They observed 59.5% silent cerebral infarctions among patients without a history of stroke. Interestingly, they detected 61.3% silent cerebral infarctions in an LOB group and 46.7% in an EOB group.[22]

Takahashi et al examined the severity of hyperintensities in 29 patients with late-onset mania, 23 patients with early-onset mania, and 14 controls. Although the authors showed no difference in periventricular WMHs among the 3 groups, the late-onset group had more severe bilateral deep WMHs in the frontal areas and in the left parietooccipital area than did the early-onset group.[14] Others have also found evidence to support the relationship between vascular risk factors and LOB. Tamashiro et al observed more frequent WMHs in the LOB group than in the EOB group and controls in the deep parietal region and the basal ganglia.[15] Furthermore, they showed that those with LOB had more severe WMH scores relative to the other 2 groups in the deep frontal and parietal regions and the putamen.

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) can detect microstructural characteristics in the brain, allowing for inferences about the structural connections between brain regions.[28-30] White matter (WM) has the unique distinction of having a directional nature, which causes remarkable differences in diffusion within WM tracts. Therefore, by measuring the water diffusion tensor in WM, DTI can display microstructural alterations in WM of patients with psychiatric disorders.[31-33] Diffusion tensor imaging can be interpreted by measuring mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD), all of which reflect the integrity of the neural circuit.

Late-Onset Schizophrenia. In an early study, Casanova et al reported the preservation of gray matter and the concomitant reduction of white matter in affected parahippocampal gyri by observing significant alterations in the gray matter and white matter ratio in those with LOS.[12] Although this study was not focused on WM integrity in LOS, the authors observed a change in WM in patients with LOS.

Chen et al[34] measured FA in whole WM and reported significant loss of integrity in the left parietal and right posterior cingulum of those with LOS. Because findings of frontal and temporal connectivity disturbances are established in general schizophrenia,[35] the findings of Chen et al suggested the possibility of specific neural substrates involved in LOS.

Others, however, have not found any differences when assessing WM. For instance, Jones et al[36] reported no difference in FA and MD between VLOSLP and control groups.

Late-Onset Bipolar Disorder. To the best of our knowledge, no study has examined microstructural alterations of WM in patients with LOB. Haller et al analyzed DTI of patients with late-life bipolar disorder by assessing FA, AD, RD, and MD and found significant loss of integrity in the ventral part of the corpus callosum in patients with bipolar disorder.[37]

Functional Neuroimaging

Functional neuroimaging techniques, such as positron emission tomography (PET), functional MRI, and single-photon emission CT, have been widely used in psychiatry research. These techniques allow for brain function imaging in real time through indirect measures of neuronal activity. However, very few researchers focus on functional neuroimaging to explore LOS or LOB.

Late-Onset Schizophrenia. Sachdev et al examined 15 patients with LOS, 7 patients with EOS, and 27 controls and showed that the LOS group had significantly lower perfusion in the frontal and bilateral temporal lobes. They also observed less temporal perfusion in the LOS group compared to the EOS group and temporal and frontal cerebral blood flow abnormalities in LOS. However, these findings are similar to those found in schizophrenia, suggesting that they are not indicative of separate pathology in EOS.[4] Finally, Pearlson et al[38] examined quantitative D_2 dopamine receptor PET and observed elevated receptor density values for D_2 dopamine receptors, which they had previously found to be abnormal in EOS.

Conclusions

The primary aim of this review was to highlight the neural substrates involved in LOS and LOB based on extant neuroimaging studies of both major psychiatric disorders. Several neuroimaging studies indicate that LOS and LOB may be subtypes of each respective disorder. However, current data do not support consistent results of differences between early-onset and late-onset disorders. Larger studies of LOS and LOB should consider the neurobiology of each disorder and concurrently examine the neurobiological peculiarities unique to the late-onset subgroup of schizophrenia and bipolar disorder compared with the early-onset of each disorder. However, current evidence is mixed regarding the hypothesis that LOS or LOB has unique neurobiological characteristics from the early-onset of each of these disorders. Schizophrenia and

bipolar disorder are very complex diseases involving several neural substrates that affect onset and symptoms and do not have a definite pathogenesis. However, with the development of imaging techniques and analysis methods, a sufficient number of replication studies may be able to determine whether LOS and LOB are separate entities from EOS and EOB.

In the case of LOS, several studies suggested neuroimaging biomarkers of LOS that differed from that of EOS. For example, Cory-Bloom et al[3] observed thalamus enlargement in LOS, which is inconsistent with other findings in schizophrenia in general. Chen et al[34] reported loss of integrity in the left parietal and right posterior cingulum in LOS. Volume change or loss of integrity in specific brain regions can be interpreted in various ways, such as indicating the expression of a protecting factor, an aspect of pathophysiology, or a phenotype of disease progression delayed by late onset. Although there are not enough follow-up studies about volumetry or microstructural alteration in patients with LOS, comparative studies between EOS and LOS suggest different neurobiological markers and indicate a direction for future research.

With regard to LOB, 1 study found progressive increases of gray matter volume in the right caudate,[39] and another study reported larger left caudate nucleus volume in patients with bipolar disorder.[40] However, Beyer et al.[20] found a smaller right caudate in a late-life bipolar group than in a healthy control group. Additionally, Huang et al[16] reported a larger left caudate in patients with late-onset mania than those with early-onset mania. These findings indicate the necessity of investigating volume change in the caudate in late-life bipolar disorder depending on the chronicity of disease with longitudinal imaging studies. If there are volume changes in the caudate based on the chronicity of bipolar disorder, studies verifying volumetric differences in the caudate between LOB and EOB could be valuable. Further, a discussion about the clinical significance of volumetric differences between LOB and EOB is necessary. In this review, we summarized the close relationship between LOB and vascular risk, which has consistent support. Through the elaborate localization and quantification of WMHs in LOB, future studies should focus on the association between vascular risk and the neural circuitry of bipolar disorder.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by a grant from the BioGreen 21 Program (No. PJ009830012013), Rural Development Administration, Republic of Korea. This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A2042339). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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