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SPECIAL ARTICLE

Psychiatric neuroimaging research in Brazil: historical overview, current challenges, and future opportunities

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The last four decades have witnessed tremendous growth in research studies applying neuroimaging methods to evaluate pathophysiological and treatment aspects of psychiatric disorders around the world. This article provides a brief history of psychiatric neuroimaging research in Brazil, including quantitative information about the growth of this field in the country over the past 20 years. Also described are the various methodologies used, the wealth of scientific questions investigated, and the strength of international collaborations established. Finally, examples of the many methodological advances that have emerged in the field of *in vivo* neuroimaging are provided, with discussion of the challenges faced by psychiatric research groups in Brazil, a country of limited resources, to continue incorporating such innovations to generate novel scientific data of local and global relevance.

Keywords: Brain imaging; magnetic resonance; PET; SPECT; Brazil

Introduction

In the past few decades, Brazilian psychiatry research has taken a leading role among medical specialties in the country[1] and achieved international recognition.[2-4] Since it was first introduced in the 1990s, psychiatric neuroimaging research has made important contributions to such growth, and is now established as a major field of neuroscientific investigation in psychiatry in Brazil.

Methodological advances relating to *in vivo* neuroimaging continuously emerge, and it is essential to incorporate such innovations to studies investigating questions of relevance to psychiatry. From that perspective, the present article provides a historical overview of psychiatric neuroimaging research in Brazil, followed by a discussion of the challenges and opportunities that lie ahead.

The concept of neuroimaging as a subspecialty in psychiatric research and the establishment of psychiatric neuroimaging research teams

Over the past 40 years, a growing number of studies worldwide have applied neuroimaging methods to evaluate pathophysiological and treatment aspects of psychiatric disorders.[5,6] First, the field has benefited from its access to mainstream neuroradiological techniques, including structural magnetic resonance imaging (MRI), which is used to evaluate brain volumes and macroscopic lesions,[7] as well as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), which are used for the assessment of brain metabolism with ^{18}F-fluorodeoxyglucose (^{18}F-FDG PET) and regional cerebral blood flow (rCBF SPECT) respectively.[8,9] Moreover, leading research institutions worldwide have also gained access to increasingly more sophisticated imaging methods for dynamic brain activity mapping during cognitive, emotion-provoking, or motor tasks using functional MRI (fMRI),[7] and to molecular imaging using PET, SPECT, and magnetic resonance spectroscopy (MRS).[8,10] Although routine diagnostic applications of neuroradiological methods in clinical psychiatry have not yet emerged (a topic that is outside the scope of this article), brain imaging has become an essential field of psychiatry research.

In addition to the usual methodological planning associated with scientific investigation (i.e., study design, power calculations, definition of criteria for sample recruitment, choice of symptom assessment scales, etc.), neuroimaging research involves 1) choosing suitable equipment and defining strict protocols for data acquisition, quality control, and storage; 2) preprocessing routines using computational methods (for instance, removal of extracerebral tissue from structural MRI datasets and image inhomogeneity correction); 3) image processing steps, such as spatial normalization of datasets to anatomical templates, smoothing, correction for partial volume effects (in the case of PET or SPECT datasets), among others; 4) extraction of quantitative indices from images, such as regional brain volumes (in case of structural MRI), quantification of interregional correlations and anticorrelations (in case of connectivity

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investigations using fMRI), etc.; and finally, 5) applying contemporary, well-validated statistical approaches for data inference at both the individual and group levels.[11]

Following the steps described above, two main paths have been used by researchers worldwide in their efforts to generate relevant, novel data from neuroimaging investigations in psychiatry, both of which are being applied not only in large academic health centers, but also in specialized research institutes dedicated to the study of brain disorders. In the first of these two models, knowledgeable clinical research groups interested in questions pertaining to a specific area of psychiatry (e.g., mood or anxiety disorders, psychosis, etc.) use their expertise to devise original hypotheses that are best testable with neuroimaging methods. To achieve their goals, such psychiatric research groups typically liaise with teams of imaging experts from the same or other academic environments (neuroradiologists, physicists, and nuclear medicine physicians).[12,13]

In the second model, psychiatrists, psychologists, and other mental health professionals develop a deeper and broader interest in neuroimaging research, and they themselves establish specialized groups dedicated to brain imaging.[14-16] Most of these psychiatric neuroimaging research groups worldwide have focused on the systematic investigation of a few disorders of interest, while a minority has explored psychiatry more broadly. Close and fruitful collaboration with neuroradiology experts, physicists, radiopharmacists, and other imaging professionals is still crucial in this model to ensure access to imaging equipment and state-of-the-art methods for acquisition of brain data; however, study design, appropriate selection of data acquisition and image processing methods for the specific questions being asked, and interpretation of research results in light of previous neuroimaging knowledge that cuts across boundaries of different fields of psychiatry are typically reserved for the group of mental health researchers. In Brazil, there have been a few such initiatives to date, which will be described in the next section of this article.

Whichever of these two paths is chosen, the inclusion of computer scientists in the teams is absolutely essential, either as full-time investigators hired to work specifically in the psychiatric neuroimaging lab or as collaborators based in external academic computer science departments. Such professionals master the use of the software suites most commonly used in brain image processing (several of which are available as freeware but relatively complex), implement the information technology infrastructure necessary to run such software, propose innovative image analysis methods, and provide support to psychiatrists and other mental health researchers after they have been trained to use software to process data from their own studies. It should be noted that the wealth of neuroimaging research applications has driven the establishment of entire computer science groups or departments entirely devoted to this field in academic institutions.[17]

A concise history of psychiatric neuroimaging research in Brazil and its impact

During the late 1980s and 1990s, a number of Brazilian psychiatrists working abroad led the development of several quantitative, controlled psychiatric neuroimaging investigations using computed tomography,[18,19] structural MRI,[20] rCBF SPECT,[21,22] task-related fMRI,[23] and molecular imaging with SPECT.[24,25]

In regard to controlled studies carried out entirely in Brazil involving samples affected by psychiatric disorders, the first quantitative neuroimaging publications in international peer-reviewed journals date from the early 2000s (Figure 1).[26-29] These papers reported the findings of studies carried out at the Laboratory of Psychiatric Neuroimaging housed in the Clinics Hospital, University of São Paulo Medical School (HCFMUSP), set up in 1997. Supported by a state funding agency (Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP), this laboratory was established by the Institute of Psychiatry at HCFMUSP (IPq-HCFMUSP) in partnership with the nuclear medicine division and the neuroradiology research group at the HCFMUSP Institute of Radiology (InRad-HCFMUSP).[30] In 2003, the Laboratory of Psychiatric Neuroimaging was incorporated as one of the 62 official facilities participating in the HCFMUSP network of Laboratories of Medical Investigation (LIM 21), and has since performed its activities following the second model described in the previous section of this article (Figure 2A for number of publications from 2000 to the present date). Table 1 shows how LIM 21 uses MRI, PET, and SPECT technologies to investigate pathophysiological and treatment aspects of several psychiatric conditions. Such broadness stemmed from a vision that, given the large size of the University of São Paulo (USP), a lab dedicated to a subspecialty of key relevance to psychiatry should not be limited to support research performed by the laboratory's leaders, but rather should serve as a platform for collaborations with other research groups. Additionally, it should be noted that other leaders at IPq-HCFMUSP have coordinated neuroimaging research initiatives independently from LIM 21 in areas of MRS applied to mood disorders and psychosis,[31-34] morphometric MRI in mood disorders, obsessive-compulsive disorder, and psychosis,[35-37] functional imaging studies in obsessive-compulsive disorder,[38-40] and psychiatric manifestations of neurological disorders.[41-43]

A specialized psychiatric neuroimaging lab was also set up at the Federal University of São Paulo (UNIFESP) in 2004, with support from FAPESP and other funding agencies. Since then, this group has conducted a significant number of SPECT and MRI studies evaluating samples of patients with psychiatric conditions including psychosis,[44,45] mood disorders,[46] post-traumatic stress disorder (PTSD),[47,48] personality disorders,[49] and neuropsychiatric features associated with Parkinson's disease,[50,51] as well as more recently leading large-scale studies of childhood/adolescent brain development (Table 1).[52-54] This group is a branch of the Interdisciplinary Laboratory of Clinical Neuroscience (LiNC), a broader neuroscience initiative at UNIFESP devoted to the application of neuroscientific techniques in psychiatric research. This effort has provided impetus to a number of innovative neuroimaging studies at the interface with other neuroscience areas, mainly molecular genetics.[55]

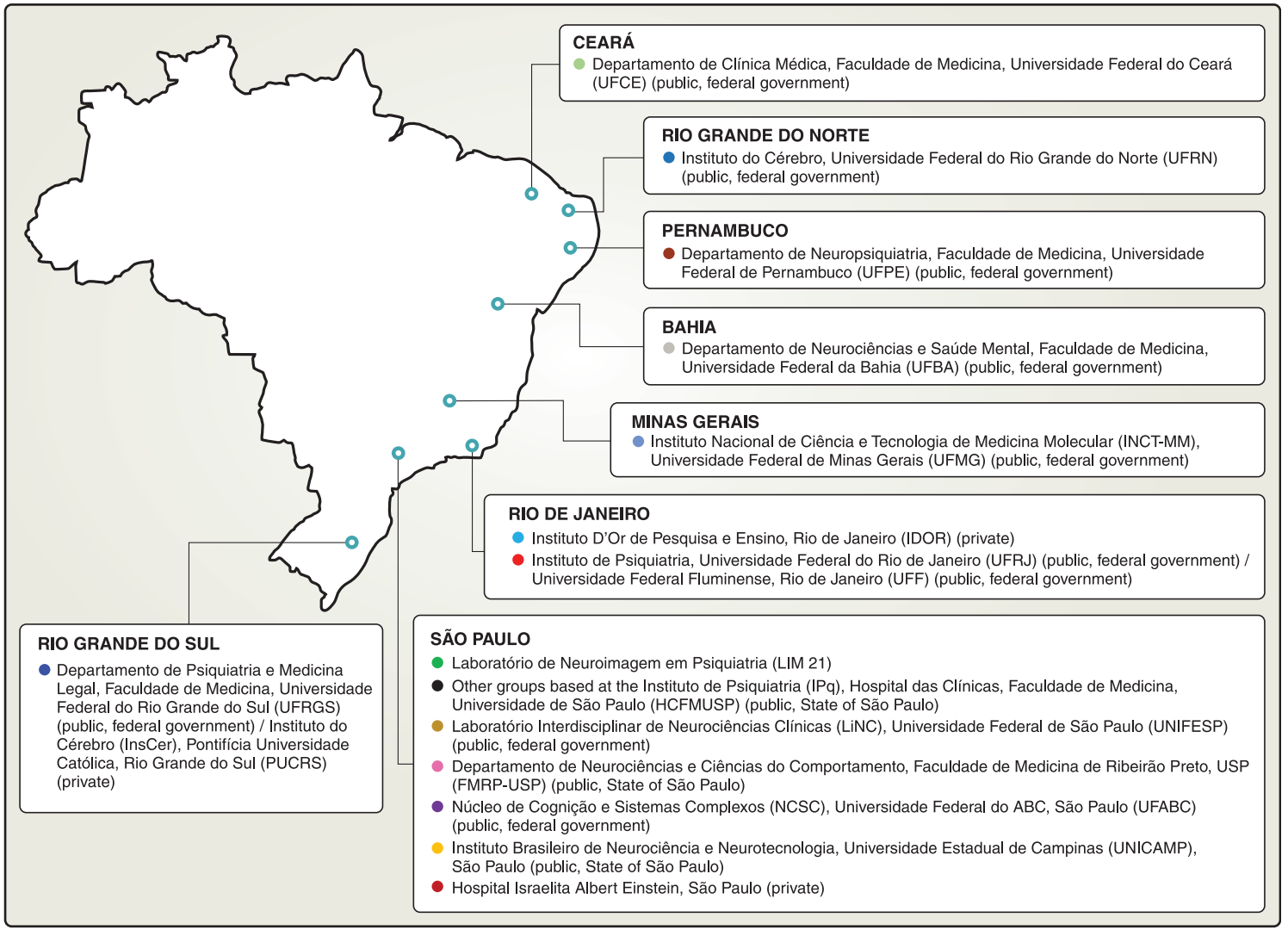

Figure 1 Geographic distribution of research groups conducting psychiatric neuroimaging studies in public and private institutions in several Brazilian states. The fields of interest of each group are listed in Table 1.

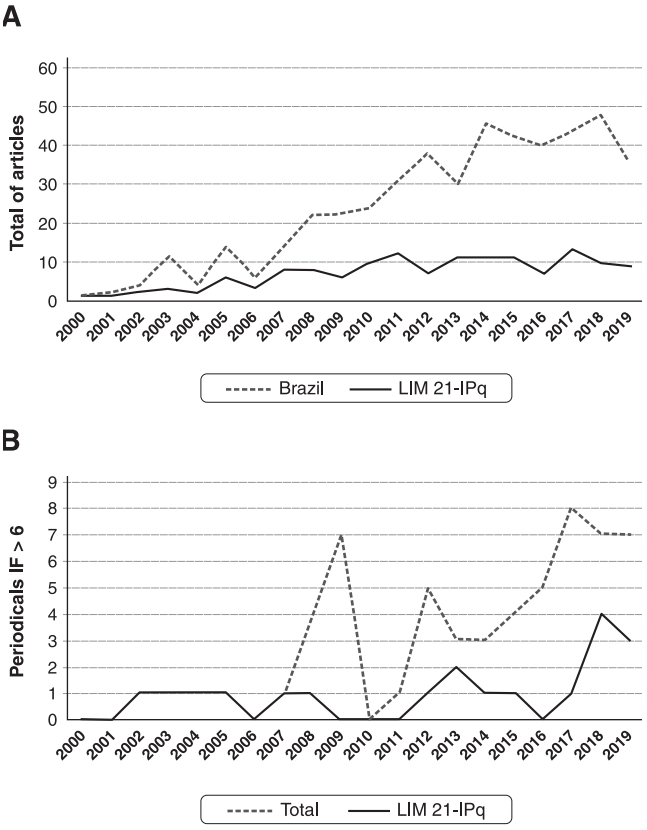

Figure 2 A) Total number of PubMed neuroimaging papers related to psychiatry published from the year 2000 onwards with participation of researchers based in all centers in Brazil (dotted line) and specifically Laboratory of Psychiatric Neuroimaging (LIM 21) at HCFMUSP (solid line), which contributed to 29.5% of the overall articles published to date. Details for the types of publications are provided in Table 2. The methods used to select publications (up until September 2019) are outlined in the online-only supplementary material. Neuroimaging papers published when researchers were working as members of research groups based in other countries were excluded, as were nonneuroimaging papers. B) Yearly number of papers published in the fields of psychiatry or neuroscience in journals with the highest impact factors (IF) (greater than 6, as calculated by Clarivate Analytics) by Brazilian groups (dotted line) and specifically by LIM 21 at the HCFMUSP (solid line). Journals were as follows: American Journal of Psychiatry (n=10); Biological Psychiatry (n=7); British Journal of Psychiatry (n=3); Cerebral Cortex (n=4); JAMA Psychiatry (formerly known as Archives of General Psychiatry) (n=6); Journal of Neurology, Neurosurgery and Psychiatry (n=1); Journal of Neuroscience (n=2); Lancet Psychiatry (n=1); Molecular Psychiatry (n=4); Neuropsychopharmacology (n=10); Neuroscience and Biobehavioural Reviews (n=6); and Schizophrenia Bulletin (n=3).

At the Department of Neuroscience and Behavioral Sciences at USP's Medical School at Ribeirão Preto (FMRP-USP), current leaders in psychiatry were trained in neuroimaging research during their doctoral studies[56] and as postdoctoral fellows in Brazil[57] or abroad.[58,59] With links to the local Center of Imaging Sciences and Medical Physics at FMRP-USP, this multidisciplinary team has since conducted neuroimaging investigations, with leadership in the following topics: frequency and clinical correlates of neurodevelopmental markers in neuropsychiatric disorders[60]; MRI studies in anxiety disorders[61-63] and postpartum depression[64,65]; neuropsychiatric features associated with neurological disorders[66,67]; and pharmacological studies evaluating brain functional and structural imaging correlates of the use of cannabinoids[68] and a number of other drugs (Table 1).[69,70]

Still in São Paulo, computer scientists and research associates founded the Center for Cognition and Complex Systems (NCSC) at the ABC Federal University (UFABC) in 2009. This prolific computer science group focuses almost entirely on innovative image processing and statistical methods applied to the analysis of neuroimaging data across several fields of interest to psychiatry (Table 1), working in collaboration with clinical psychiatrists from other Brazilian centers.[71-74]

Outside São Paulo, scientists based at the Federal University of Minas Gerais (UFMG) Department of Mental Health led the establishment of a PET imaging lab – the main facility at the National Institute of Molecular Medicine funded by the National Research and Technology Council (Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq) in the context of the Brazilian National Institutes of Science and Health (Institutos Nacionais de Ciência e Tecnologia) in 2008. This team has since conducted a number of ^{18}F-FDG PET studies,[75,76] as well as structural MRI investigations of bipolar disorders in collaboration with LIM 21 in São Paulo (Table 1).[77,78]

In the state of Rio Grande do Sul, knowledgeable clinical and basic science research groups based at the Federal University of Rio Grande do Sul (UFRGS) and the Pontifical Catholic University (PUC) have adopted the first model outlined in the previous section of this article, testing original hypotheses in a number of psychiatric neuroimaging studies carried out in collaboration with teams of imaging experts either from the local Clinics Hospital of Porto Alegre (HCPA), the PUC-based Brain Institute (InsCer), or São Paulo-based centers. These groups have contributed to the development of the field of psychiatric neuroimaging in Brazil by leading studies on attention-deficit/hyperactivity disorder (ADHD),[79-81] child and adolescent development,[82,83] psychosis,[84] mood and anxiety disorders,[85-87] and autism (Table 1).[88]

The same collaborative model has been applied by research groups based at other universities in Brazil. In the state of Rio de Janeiro, notably, psychiatrists based at the Federal University of Rio de Janeiro (UFRJ) have been involved in a number of original MRI studies on psychiatric disorders including PTSD,[89] obsessive-compulsive disorder,[90-92] and ADHD,[93] often in collaboration with radiologists and basic neuroscientists from the privately funded D'Or Institute of Research and Education (IDOR). The IDOR group pioneered the use of task-related fMRI in studies performed entirely in Brazil in the early 2000s.[94,95] They have since led a series of sophisticated studies in healthy subjects evaluating aspects of emotional processing and social behavior,[96,97] as well as MRI studies on samples of subjects with major

Table 1 Distribution of psychiatric neuroimaging publications by Brazilian research groups using different modalities from the year 2000 onwards

Field of interest	Morphometric MRI	DTI	White matter hyperintensity/other brain lesions	Task-related fMRI	Resting-state fMRI	^{18}F-FDG PET	rCBF SPECT	MRS	Molecular imaging – PET*	Molecular imaging – SPECT†	Pattern classification
ADHD in youth	● ●	●		●	●		●	●		● ●	
ADHD in adults and old age	● ● ●	●		● ●	● ● ● ● ● ●						● ● ● ●
Anxiety disorders	● ● ● ● ● ●			● ●	● ●			● ● ●			●
Autism	● ● ●				● ●						● ● ●
Drug abuse and dependence	● ● ●				●						
Gender identity	●										
Impulse control and gambling disorders	●										
Mood disorders – youth		●			● ● ●						
Mood disorders – adults	● ● ● ● ● ● ● ● ●	● ●	●	●	● ●		●	● ● ● ● ● ●		● ●	● ● ● ●
Mood disorders – old age	● ●	● ● ●	● ● ●								
Obsessive-compulsive disorder	● ● ● ● ●	● ●		● ● ●	● ● ● ● ●		●	● ●			● ● ●
Personality disorders	● ● ● ● ●										● ● ● ●
Post-traumatic stress disorder	● ● ●			●						●	
Psychotic disorders	● ● ● ● ● ● ● ● ● ● ● ●	● ●	●	●				● ●			● ● ●
Psychiatric symptoms in neurological disorders	● ● ● ● ● ● ● ●			● ●	●		●	●		● ● ●	
Pharmacological studies (cannabinoids, antidepressants, BDZ)				● ● ●			●	● ●			
Psychedelics	● ●			● ●	● ●		● ●	● ●			
Brain development in youth	● ● ● ●	● ● ● ●		●	● ● ● ●						● ● ● ●
Brain aging and dementia	● ● ● ● ● ● ● ● ● ●	● ● ●	● ● ●	● ●	● ●	● ●	● ●	● ●	●		● ● ●
Emotional processing and social behavior in healthy subjects	● ● ●			● ● ● ● ● ● ● ● ●	● ● ●						
Yoga and meditation	● ●			● ●	● ●						

^{18}F-FDG = ^{18}F-fluorodeoxyglucose; ADHD = attention-deficit/hyperactivity disorder; BDZ = benzodiazepines; DTI = diffusion-tensor imaging; fMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; PET = positron emission tomography; rCBF = regional cerebral blood flow; SPECT = single-photon emission computed tomography.

* Studies using carbon-11 labeled Pittsburgh compound B (^{11}C-PiB) for the visualization of cortical amyloid plaques.

† Studies using technetium-99m labeled TRODAT (^{99m}Tc-TRODAT) for the visualization of striatal dopaminergic terminals.

● Laboratório de Neuroimagem em Psiquiatria (LIM 21), Instituto de Psiquiatria (IPq), Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HCFMUSP).

● Other research groups based at HCFMUSP, São Paulo (IPq and others).

● Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), Universidade Federal de São Paulo (UNIFESP).

● Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, USP (FMRP-USP).

● Núcleo de Cognição e Sistemas Complexos (NCSC), Universidade Federal do ABC, São Paulo (UFABC).

● Departamento de Psiquiatria e Medicina Legal, Universidade Federal do Rio Grande do Sul (UFRGS) / Instituto de Cérebro (InsCer), Pontifícia Universidade Católica, Rio Grande do Sul (PUCRS).

● Instituto D'Or de Ensino e Pesquisa, Rio de Janeiro (IDOR).

● Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro (UFRJ) / Universidade Federal Fluminense, Rio de Janeiro (UFF).

● Instituto Nacional de Ciência e Tecnologia de Medicina Molecular (INCT-MM), Universidade Federal de Minas Gerais (UFMG).

● Departamento de Neurociências e Saúde Mental, Universidade Federal da Bahia (UFBA).

● Departamento de Clínica Médica, Universidade Federal do Ceará (UFCE).

● Instituto do Cérebro, Universidade Federal do Rio Grande do Norte (UFRN).

● Departamento de Neuropsiquiatria, Universidade Federal de Pernambuco (UFPE).

● Instituto Brasileiro de Neurociência e Neurotecnologia, Universidade Estadual de Campinas (UNICAMP), São Paulo.

● Hospital Israelita Albert Einstein, São Paulo.

depression[98] and personality disorders.[99,100] Additionally, in Rio de Janeiro, neuroscientists from the Fluminense Federal University (UFF) have conducted studies investigating neuroimaging features associated with emotional processing in healthy humans[101-103] and subjects with psychiatric disorders,[104] often in collaboration with colleagues from the IDOR and UFRJ. In regard to other Brazilian states, a group from the Federal University of Bahia (UFBA) undertook MRI studies of bipolar disorder in collaboration with other centers.[105-107] At the Federal University of Rio Grande do Norte (UFRN) Brain Institute, physicists and neuroscientists have pioneered neuroimaging investigations of humans using the psychedelic drug ayahuasca,[108,109] and have established collaborations with other groups in Brazil[110] and abroad.[111] Psychiatrists from the Federal University of Ceará (UFCE) have also collaborated in original studies of mood disorders with other groups in Brazil[34] and abroad.[112,113] Finally, groups of psychiatrists based at other public universities in different states in Brazil have regularly published well-cited systematic reviews and meta-analyses on several neuroimaging topics.[114-125]

There are two additional Brazilian research centers dedicated primarily to neurophysiology and neurology that deserve to be mentioned here. At the privately funded Albert Einstein Israelite Hospital in São Paulo, a group of neuroradiologists and neuroscientists has conducted a series of MRI investigations evaluating interventions of potential interest to psychiatry using yoga-based and other meditation methods.[126,127] They have also performed fMRI studies on emotional processing[128-130] and liased with psychiatrists from UNIFESP in SPECT investigations.[51] Finally, the State University of Campinas (UNICAMP) in São Paulo houses the Brazilian Institute of Neuroscience and Nanotechnology, funded by FAPESP. With noteworthy scientific output in epilepsy, this group has also performed a few investigations on psychiatric disorders including autism[131] and mood disorders[132] in association with local groups of psychiatrists, and conducted several MRI studies on mild cognitive impairment (MCI) and Alzheimer's disease (AD).[133-135] Studies of healthy aging, MCI, and AD are relevant in this context because they are at the interface between psychiatry and neurology; neuroimaging investigations in this field have been carried out by groups at HCFMUSP,[136-138] FMRP-USP,[139] and UNIFESP[140,141] in the state of São Paulo, as well at the UFMG,[142] UFRJ,[143,144] and the Federal University of Pernambuco (UFPE).[145]

A map of Brazil showing the official names and location of each of the institutions cited above is provided in Figure 1.

Table 2 and the graph provided in Figure 2A show the growth of psychiatric neuroimaging studies in recent decades in Brazil, as expressed by the total number of publications from 2000 onwards (n=478). Of these papers, 61.3% directly addressed psychiatric disorders across the life span, with the remaining publications covering brain aging, AD, and MCI (21.1%), emotional processing and social behavior in healthy humans (6.9%), brain effects of drugs in healthy subjects (4.6%), brain development in children and adolescents (4.4%), and studies of yoga and meditation practices (1.7%). Table 2 also indicates the high proportion of original studies and meta-analyses relative to literature reviews. The methods that were used to identify those publications are outlined in the online-only supplementary material.

Most Brazilian research groups mentioned above have regularly collaborated with each other. Additionally, in many of their initiatives, international collaboration has been of critical relevance. As shown in Table 2, to date 50% of psychiatric neuroimaging publications involving Brazilian groups have co-authors from non-Brazilian institutions. Of 478 papers, over 70% were led by researchers based in Brazil (first or senior authors), while the remaining publications were led by scientists from foreign institutions with Brazilian co-authorship. Most international collaborations have been established with researchers from the United Kingdom (UK) and United States, but several other countries are represented, including Germany, Australia, Canada, the Netherlands, Spain, Italy, France, China, Japan, Turkey, Sweden, Denmark, and Switzerland, as well as Argentina and Chile in South America. Additionally, a Brazilian physician with undergraduate and psychiatric training at USP in the 1990s (Jair C. Soares) moved soon thereafter to the United States to become a world leader in psychiatric neuroimaging research. As such, he has opened the doors of his research labs to several Brazilian students over the years.[146-148] Finally, other psychiatrists and computer scientists with doctoral or postdoctoral neuroimaging research training in Brazilian universities now hold academic positions in North America and Europe, providing additional opportunities for continued collaboration with scientists in Brazil.[149-151]

There is also evidence of a progressive increase in the international impact of psychiatric neuroimaging studies in Brazil. As shown in Figure 2B, the number of

Table 2 Characteristics of psychiatric neuroimaging publications from Brazilian research groups from the year 2000 onwards

Characteristic	n (%)
Total number of papers	478 (100.0%)
Review papers vs. original publications and meta-analyses	69/409 (14.4%/85.6%)
Publications in international vs. Brazilian periodicals	428/50 (89.5%/10.5%)
International co-authorship: yes/no	248/230 (51.9%/48.1%)
Leadership by Brazilian scientists* vs. international leaders	346/132 (72.4%/27.6%)

Numbers reflect the total psychiatry-related neuroimaging papers available in PubMed published from 2000 onwards with the participation of researchers based in Brazil (up until September 2019). The methods used to select publications are outlined in the online-only supplementary material.
* Scientists based in Brazil placed as first or senior authors.

neuroimaging papers published in high-impact journals (i.e., impact factor above 6, as calculated by Clarivate Analytics) was higher in the 2010s than in the 2000s. As we discuss in subsequent sections of this article, such an increase is substantially explained by a growing number of local studies using large-sized samples and the recent participation of Brazilian groups in international consortia, in addition to the publication of expert reviews in highly cited periodicals.

The synthesis provided herein indicates that psychiatric neuroimaging research in Brazil has grown steadily over the past few decades, with a sizeable international impact. As a whole, the field has flourished to a relatively greater degree in the state of São Paulo than in other Brazilian states. This is possibly related to the existence of more funding opportunities in São Paulo (via FAPESP) and a relatively greater availability of *in vivo* imaging equipment for research applications. For instance, in four of the São Paulo-based academic institutions mentioned herein, new 3 Tesla MRI equipment were simultaneously installed in the context of a large-scale program launched by FAPESP in 2004.[152] Additionally, the persistence of experienced São Paulo-based psychiatrists and other mental health professionals may have served to maintain a high level of motivation and nurture a local sense of empowerment to overcome technological challenges.

Recent neuroimaging advances applicable to psychiatric research

Technical neuroimaging developments are unfolding at the present time at a pace that is quicker than ever. This presses research groups to swiftly incorporate such innovations, providing exciting opportunities for novel investigations. Selected key examples of incremental innovation recently incorporated in MRI and PET research studies in Brazil are described below.

New approaches for the extraction of quantitative neuroimage indices

In conventional neuroimaging study designs, statistical tests are applied on mean group data after extracting quantitative information from individual imaging datasets (for instance, volumetric measures using structural MRI data or local brain uptake of radiotracers in PET or SPECT studies). Quantitative data from images are usually extracted with regions of interest of predefined anatomical borders placed on selected brain portions, or using automated voxel-based methods.

One fascinating aspect of brain research is the fast-paced incorporation of computational techniques capable of extracting novel and varied quantitative indices from neuroimaging datasets using traditional, readily applicable data acquisition protocols. One recent example is given by new, automatic processing methods for surface-based analyses of structural MRI data, which allow for the decomposition of regional brain cortical volumes into its two components, namely, cortical thickness and cortical area. These two cortical surface phenotypes, which are not directly correlated with each other,[153] are formed over separate time frames and through different mechanisms during brain development[154] and have distinct patterns of genetic heritability.[155,156] Recent automated MRI processing methods also allow reproducible measurements of the degree of local cortical gyrification (which is directly related to the development of neuronal connectivity at early periods of cortical maturation),[157] regional brain shape and texture,[158] and subfield volumes of brain structures of key relevance to psychiatry, such as the hippocampus.[159] The separate measurement of these MRI-based indices in neuroimaging studies opens exciting opportunities for the generation of data on the type and timing of structural brain abnormality associated with various psychiatric disorders and for the investigation of the correlations between brain imaging indices and genetic and environmental variables, history of treatment exposure, and other disease-related factors.

An increase in the number of neuroimaging investigations using the above-mentioned automated processing methods is expected, given their progressive availability. However, there is also a highly critical need to apply systematic quality control procedures in such MRI studies to detect occasional errors in cortical delineation and volume measurements that require either correction or the exclusion of participants.[160]

Innovative methods of data acquisition

PET and SPECT devices are highly adaptable to incorporate image acquisition protocols to quantify the brain distribution of new radiopharmaceuticals of interest to psychiatry.[161] In Brazilian facilities providing an on-site cyclotron together with experienced teams of radiopharmacists and physicists, new PET probes have been incorporated for research purposes in recent years, such as Pittsburgh compound B labeled with carbon-11 (^{11}C-PiB) for the mapping of extracellular amyloid plaques formed by amyloid β-peptide (Aβ) in the cerebral cortex (see Figure 3),[162] and ^{18}F-FDG PET for the evaluation of brain metabolism. The LiNC group at UNIFESP has also pioneered studies using ^{99m}Tc-TRODAT to evaluate the density of striatal dopaminergic terminals with SPECT.[80]

Concerning MRI, several new image acquisition methods of interest to psychiatry have been incorporated in studies led by Brazilian research groups in the past few years, including diffusion tensor imaging (DTI) for investigations of the microstructural integrity of white matter fibers and tracts, with acquisition of diffusion-weighted imaging (DWI) data (which measures the motion of water molecules within minute tissue portions),[163] and resting-state fMRI methods for the investigation of intra- and internetwork patterns of functional connectivity in the brain at rest.[164] There is continuous innovation in MRI acquisition methods. A very recent example is the acquisition of DWI data using a ''multishell'' imaging approach, which relies on a high angular resolution diffusion imaging (HARDI) protocol[165] combined with data acquisition with more than one electromagnetic field strength.[166] This allows the use of new mathematical models to generate quantitative indices of gray matter microstructure at the

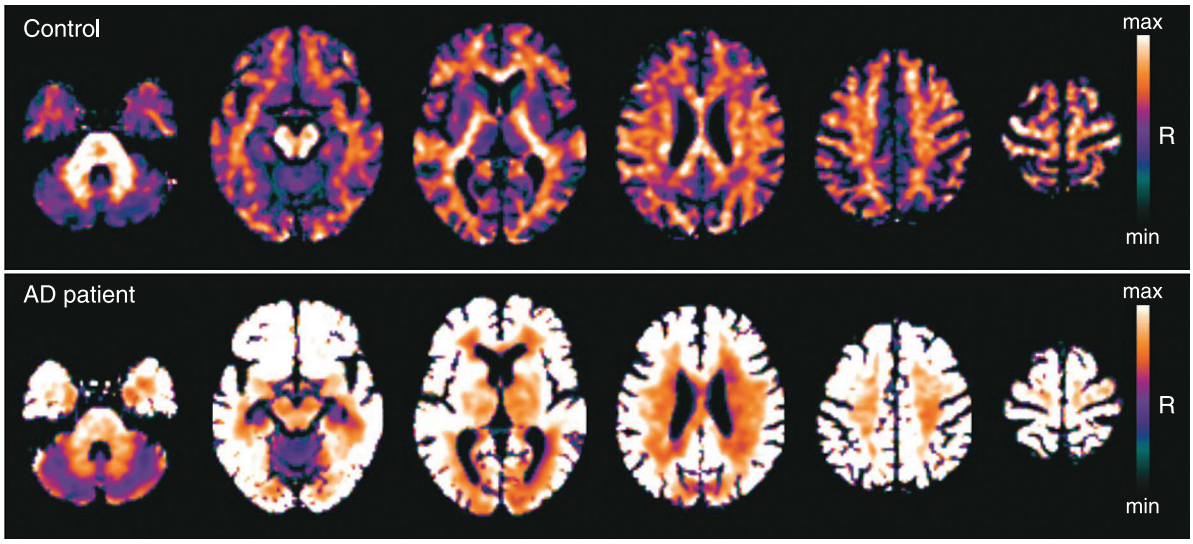

Figure 3 Positron emission tomography (PET) images acquired after intravenous injection of Pittsburgh compound B labeled with carbon-11 (^{11}C-PiB) to map the anomalous deposition of extracellular amyloid plaques formed by amyloid β-peptide (Aβ) in the cerebral cortex. Top panel: transaxial slices from a usual ^{11}C-PiB PET dataset obtained from a healthy elderly volunteer, with very low tracer uptake in the cortex relative to white matter uptake. Bottom panel: ^{11}C-PiB PET data from a patient suffering from dementia compatible with Alzheimer's disease (AD), with increased tracer uptake in the frontal, temporal, parietal, and cingulate cortices. Both datasets underwent automated processing typically employed in quantitative neuroimaging research studies, including spatial normalization to a standardized anatomical template (using the Statistical Parametric Mapping program) and correction for partial volume effects based on information from volumetric magnetic resonance imaging (MRI) datasets obtained from the same individuals. The original, preprocessed PET images were obtained in collaboration with scientists from the Centro de Medicina Nuclear, Instituto de Radiologia, Hospital de Clínicas, Faculdade de Medicina, Universidade de São Paulo, under the leadership of Dr. Daniele de Paula Faria and Prof. Carlos A. Buchpiguel.

level of axonal and dendritic projections (neurites) in techniques such as neurite orientation dispersion and density imaging (NODDI)[167] (Figure 4). MRI studies using NODDI now provide unique opportunities for the *in vivo* mapping of dendrite pathological changes and other neurite abnormalities that were only previously accessible using *post-mortem* histological techniques.[168]

Finally, the applicability of other *in vivo* imaging methods is also growing, most notably functional near infrared spectroscopy (fNIRS). This method, which provides measures of cortical brain activity with superior temporal resolution, high portability and low cost, has been recently used by Brazilian groups in studies of affective processing[170] and other areas of potential interest to psychiatry.[171] The fNIRS technique will probably become an important neuroimaging resource in environments with limited research funding opportunities. Additionally, it offers exciting opportunities by making use of reliable wireless devices that are suitable for implementing brain-computer interfaces and bedside investigations.

The need for large samples

In recent years, significant concerns have been raised regarding the validity and reproducibility of biomedical research.[172] Particularly, it has been stressed that studies commonly have small sample sizes and consequently low statistical power, thus reducing the chance of detecting a true effect and reducing the probability that a statistically significant result has an accurate effect size.[173] Furthermore, replication studies are seldom performed and frequently have sample sizes similar to those of the original investigation, again jeopardizing the ability to determine whether a given finding is actually true or not. There is a frequent association between small-sized samples and inferior quality of study design, selective data analysis, inability to properly treat nuisance factors, and imprecise reporting of outcomes, with all these factors further undermining the validity and reproducibility of results.[173] Such fierce criticism has led to questions regarding the ethics of conducting studies with small samples,[173] since unreliable research may waste scarce resources and mostly produce false findings.[172] Fortunately, recent guidelines have been published with the aim of maximizing the validity and reproducibility of the results of biomedical studies, which will hopefully lead to better-quality research.[173-175]

These considerations are also relevant to brain imaging research. It is currently clear whenever possible, psychiatric neuroimaging investigations should include large samples. In Brazil, the first initiative related to this issue consisted of a collaboration between neuroimaging researchers and epidemiologists from the USP and the UK in Europe, who conducted a population-based structural MRI investigation of first-episode psychosis (FEP) patients recruited by active surveillance of mental health services located in the city of São Paulo.[176,177] In addition to allowing the identification of over 100 FEP patients with little exposure to psychopharmacological treatment in a relatively short period of time, the epidemiological design

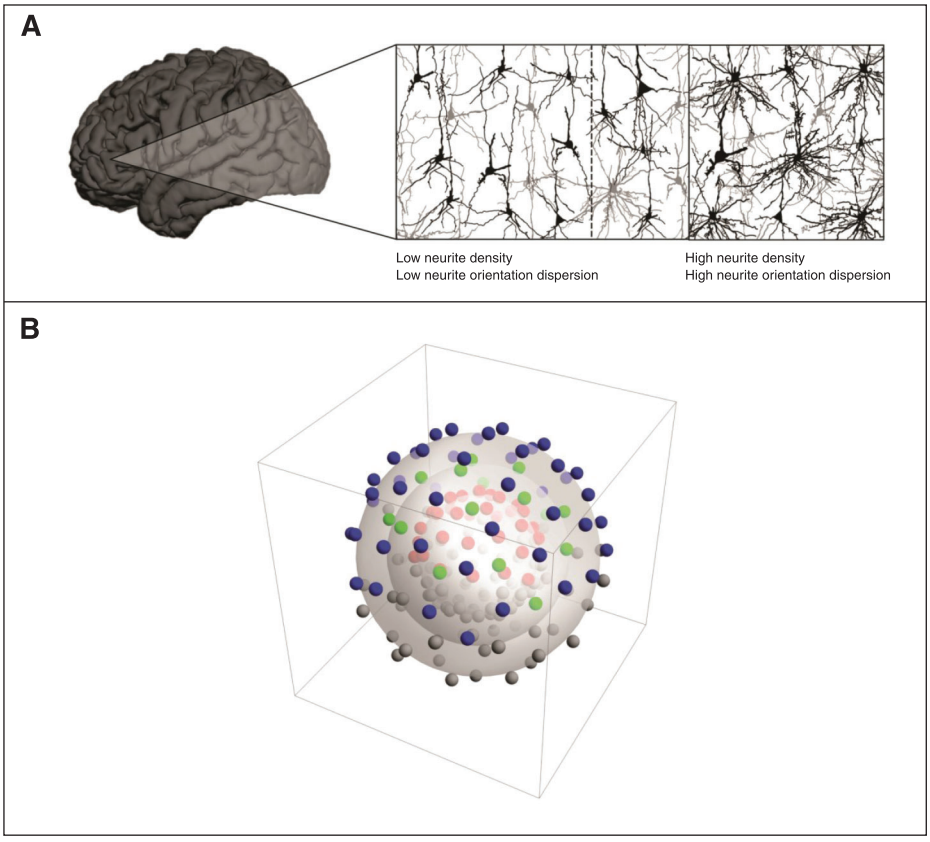

Figure 4 A) Illustrative depiction of neurite density and orientation dispersion (arborization) of dendritic trees within the cerebral cortex. Brain cortical variations in such microstructural gray matter indices, which may be present in patients with psychiatric disorders, can now be assessed using neurite orientation dispersion and density imaging (NODDI).[167] NODDI requires multishell/high angular resolution diffusion imaging (HARDI) acquisitions using magnetic resonance imaging (MRI). Please note that the figure is only meant for illustration and does not represent the actual spatial resolution achieved by NODDI (adapted from Genç et al.,[169] licensed under Creative Commons Attribution 4.0 International License). B) 3D schematic representation of a multishell encoding scheme generated using a gradient tool available at the Multiple Acquisitions for Standardization of Structural Imaging Validation and Evaluation (MASSIVE) website (http://www.massive-data.org/). The gradients (colored dots) are magnetic field pulses that sensitize diffusion in a particular direction; by doing this, MRI scans can obtain information related to the dispersion of water molecules for each voxel. The colored dots show each randomly defined gradient direction. For each shell, there is an operator-selected parameter called the b-factor that defines gradient strength and duration. In this example, each gray circumference represents one of the shells: the inner one has a b-value of 1,000 s/mm^2 (gradients represented in pink); the outermost one has a b-value of 3,000 s/mm^2 (dark blue gradients); and, in between, a shell with a b-value of 2,000 s/mm^2 (green gradients). The grey dots represent the diametrically opposite end of each gradient, i.e., the line (not shown) linking a colored dot to a grey dot is the gradient axis. This representation exemplifies how MRI acquisition protocols can be designed to measure the dispersion and orientation of water molecules to generate quantitative indices of gray matter microstructure at the level of neurites with NODDI.[167]

of that study provided an opportunity for recruitment of next-door neighbors who were included in a healthy control group strictly matched for socioeconomic status with the FEP sample.[176] The strategy of recruiting large subject samples for neuroimaging studies has since become frequent in Brazil. In addition, MRI databanks are now available, acquired from large cohorts of schizophrenia patients,[44,178] children and adolescents,[52] and elderly subjects from circumscribed urban areas.[179]

In addition to large-sized, single-site neuroimaging studies, the strategy of conducting mega-analyses of multisite neuroimaging data has also been explored in Brazil. Such initiatives combine data from multiple studies using uniform image preprocessing and analysis procedures. In the first effort of this kind in Brazil, our research group performed a voxel-based morphometry investigation of gray matter volume deficits in a sample of 161 schizophrenia patients and 151 healthy controls combining structural MRI data from four previous studies carried out at USP.[180] With the greater power afforded by combining data from several studies, we showed that FEP patients display only subtle volumetric deficits relative to controls in a circumscribed fronto-temporal-striatal network, while chronic schizophrenia patients present a much more extensive pattern of regional gray matter volume decrement relative to controls.[180]

The combination of samples from several different Brazilian neuroimaging studies has also paved the way for exciting opportunities to take part in international consortia in recent years. The most notable of these

international consortia is Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) (http://enigma.ini.usc.edu), which brings together an international research network intended to produce meta- and mega-analyses of neuroimaging and genetic data evaluating dozens of psychiatric disorders and other medical conditions.[181] Such a large-scale initiative inevitably leads to the inclusion of subjects with a much higher degree of clinical and demographic heterogeneity than single-site or local multiple-site collaborations. Prospective meta-analyses are carried out by ENIGMA teams in which cohorts, hypotheses, and analyses are selected based on certain criteria before any actual result is known.[182] This flexibility in data analysis is suitable to address data heterogeneity and thus offers advantages over traditional meta-analyses based on previously published results. A series of recent ENIGMA papers including thousands of subjects have shed light on features of brain abnormalities associated with psychiatric disorders – including for instance widespread reductions in cortical thickness and area among (mostly chronic) schizophrenia subjects relative to controls,[183] thinner cortices in frontal, temporal, and parietal regions with no associated abnormalities in cortical areas of bipolar disorder patients relative to controls,[184] and cortical thickness changes in direct proportion to the use of psychopharmacological agents such as antipsychotics.[183] Brazilian research groups have recently taken part in ENIGMA studies on schizophrenia,[183] bipolar disorder,[184,185] major depression,[186] ADHD,[187] obsessive-compulsive disorder,[188] autism,[189] and brain structural variations in normal individuals.[190]

One final aspect related to the need for large samples in neuroimaging investigations regards the complex management of databases (not only for images but also for demographic data, clinical details, and neuropsychological characteristics of study subjects). It has become mandatory for neuroimaging research groups to incorporate the use of secure, open-source applications, such as Research Electronic Data Capture (REDCAP),[191] to capture and manage clinical data, and XNAT to store and organize imaging data.[192] Such aspects of data management are also critical to allow the necessary integration of imaging datasets with information on peripheral biomarkers acquired from the same subject samples. The adequate integration of neuroimaging and peripheral biomarker datasets is essential to support the testing of hypotheses evaluating the relationship between neuroanatomical and molecular abnormalities in mental disorders.

New statistical approaches

After the development of voxel-based image analysis methods, neuroimaging researchers have struggled with the statistical problems associated with multiple comparisons, given that the unbiased, whole-brain voxel approach involves up to thousands of statistical comparisons conducted on the same imaging databank, even when one single hypothesis is being tested. This problem has become more complex as a result of improvements in imaging equipment that allow acquisition of data with greater spatial resolution and voxels of reduced size (but increased number), increased use of multimodal neuroimaging protocols (as discussed below), and planning of multiple hypotheses to be tested using the same databanks. Although the problem of multiple statistical testing may be minimized with data smoothing, specialized computer science groups have demonstrated that both traditional brain analysis methods (i.e., voxel-based morphometry)[193,194] and techniques developed more recently (surface-based analyses) may still yield results with unacceptably high levels of false-positive results,[195] particularly with the use of small smoothing filters on phenotypes, such as cortical area and volume. This problem might be tackled with the use of more stringent statistical thresholds, but this conversely leads to higher and unacceptable false-negative rates (i.e., reduction in statistical power).

More recently, a promising strategy to overcome the multiple testing dilemma involves the use of nonparametric, permutation analysis methods.[195] These approaches, which demand few assumptions about the data,[196] involve in simple terms computer-based randomization of the actual study data over several times and subsequent testing of the probability that a true difference between groups or conditions is statistically greater than the randomized data distribution. This simple but elegant statistical approach accommodates study designs that include nuisance factors and offers an optimal control of false positives[196] without reducing study power, as it allows for the use of regular statistical thresholds with any smoothing filter.[195] Future studies will demonstrate whether earlier research findings in the psychiatric neuroimaging field obtained using conventional statistical testing methods with suboptimal control for false positives will be confirmed by strategies that are better suited to cope with multiple testing problems, such as permutation statistics.

Also aiming to overcome drawbacks of univariate and multiple statistical testing as well as to bring neuroscience findings to the level of individual subjects, other researchers in the field of neuroimaging have employed multivariate statistical models using artificial intelligence (AI) in the last decade.[197] AI could be roughly defined as the attempt to emulate natural human intelligence in computer systems, i.e., inserting higher-order cognitive functions (such as learning, reasoning, and self-correction) into machines. Such methods are of interest to psychiatry given their potential to inform individual diagnostic classification, as well as to predict clinical outcomes and responses to therapeutic interventions. In other words, in addition to being a robust means to help reveal neurobiological aspects of psychiatric disorders, AI methods might in the future be used in the development of clinical tools to aid mental health professionals in decision-making (e.g., improving diagnostic accuracy or choosing the right medication) based on reliable biological information.[197,198]

One of the branches of AI, machine learning (ML), has been intensely used in recent neuroimaging studies. ML consists of creating mathematical models sensitive to patterns in natural data that can be generalized. In other words, the main goal/focus of ML is to find patterns in

data by training a computational model so that it can accurately predict outcomes when subsequently inputted with previously unseen data. Given a specific dataset, two main steps are involved in model generation: first, parameters are defined by training the model with part of the data; then, the model is tested against another sample from the original dataset.[197] The most common ML methodology used in neuroimaging studies is support vector machine (SVM), which consists of a discriminative classifier defined by a hyperplane (multidimensional plane) that can differentiate groups; such a hyperplane is the output of an algorithm that has been presented to a training dataset.[199] In neuroimaging investigations, SVM is used as a classification tool to assign an individual to a specific category (for instance, to differentiate patients with a given psychiatric diagnosis from healthy controls or between patients with good vs. poor prognosis over time). The hyperplane is defined using information from one or multiple imaging modalities to generate a signature that differentiates groups with the greatest possible accuracy.[198,200] Psychiatric neuroimaging groups in Brazil have been involved in ML studies of brain aging and dementia,[151,199,201] mood disorders,[200] ADHD,[163] personality disorders,[202] obsessive-compulsive disorder,[203] autism,[74] and schizophrenia-spectrum disorders.[177,204] In general, the neuroimaging signatures identified in ML studies evaluating psychiatric disorders have not produced clinically meaningful indices of diagnostic accuracy.[163,177,200] However, some studies do indicate that objective, ML-based information may in the future be used to influence treatment decisions in some mental disorders if current findings are replicated and extended in future studies with large, population-based samples evaluated prospectively.[163] If used in large patient samples, ML-based analyses also allow the definition of neurobiological signatures that rely on imaging indices in combination with other sources of information, such as peripheral biomarker data and neurocognitive test scores.

Imaging multimodality as the rule

With the wealth of available imaging protocols and the relatively short times taken to acquire each type of MRI- or PET-based information, multimodality is becoming the rule in psychiatric neuroimaging investigations.[205] By combining different MRI and PET modalities, neuroimaging research groups now have the opportunity to document interrelationships (or independence) between different types of brain structural, functional, and molecular abnormalities in the same samples of subjects with psychiatric disorders and produce a hierarchical view of the features that most significantly discriminate subjects with a given psychiatric condition from unaffected controls.

For instance, in a study led by our psychiatric neuroimaging group in which we acquired both morphometric MRI and DTI data from the same sample of adult ADHD subjects and healthy controls, the application of the same image processing and statistical inference methods to the two modalities revealed abnormalities in ADHD patients compared with controls mainly affecting white matter microstructure, involving fronto-parieto-temporal circuits.[206] More recently, using an expanded sample evaluated with ML-based analysis methods, we confirmed that DTI indices were the features that contributed most prominently to the neuroanatomical signature that best discriminated ADHD patients from controls.[163]

Challenges and opportunities in our low- to middle-income environment

As illustrated along this article, experienced research groups in Brazil must strive to keep up with the hectic pace of technological innovation in the field of neuroimaging. This is crucial to allow our psychiatric neuroimaging research labs to remain in a favorable position to contribute original investigations of potential impact.

Investment in highly innovative equipment for use in research (rather than clinically) is a complex endeavor which has been restricted almost entirely to a few centers in the Southeast and South of Brazil. At HCFMUSP in São Paulo, for instance, there has been recent investment in infrastructure and research staff to put to work an MRI system of ultrahigh magnetic field strength (7 Tesla) awarded by FAPESP as well as two PET systems for preclinical molecular imaging studies, awarded by the federal government-funded Financiadora de Estudos e Projetos (FINEP) and FAPESP.

However, it is reassuring to confirm that MRI and PET systems used predominantly for clinical purposes may be suitable for a number of state-of-the-art research applications in humans, with few adjustments. In recent years, such arrangements have been useful for imaging studies carried out in different Brazilian centers, where psychiatric neuroimaging groups have liaised with radiologists and nuclear medicine physicians who are open to allocating equipment time for research despite intense clinical demand. However, it will be challenging to keep up with the need to upgrade equipment for such research applications. For instance, the use of 3 Tesla MRI equipment is now almost the rule in brain imaging research. Even though brain MRI datasets acquired with 1.5 Tesla continue to be included in mega- and meta-analyses carried out by large consortia,[183-190] it is progressively more difficult to publish single-site psychiatric neuroimaging studies in highly visible scientific journals with data acquired using equipment of such lower magnetic field strength (which is still the predominant kind of MRI system in most clinical radiology services in Brazil).

Additionally, from now onwards, it will not make sense to devise unimodal neuroimaging studies with modestly sized samples that simply attempt to replicate original findings from studies carried out in other countries. Careful definition of specific research objectives will acquire extreme importance, with the formulation of hypotheses that have never been proposed before or that would only be testable in specific populations that live in low-middle income environments. Even in such ''environment-specific'' neuroimaging studies, subject samples must be diligently recruited and examined in relatively short timeframes to minimize the risk of equipment and data acquisition protocols being considered of inferior quality

by the time the results are submitted for publication. One particularly important strategy is to encourage close collaboration between neuroimaging labs and research groups with profound interest in specific areas of psychiatric care and privileged access to special patient populations. For instance, our psychiatric neuroimaging team was recently contacted by the specialized group dedicated to ADHD in adults also based at IPq-HCFMUSP (Programa de Deficit de Atenção e Hiperatividade no Adulto), which had started the recruitment of a unique cohort of never-treated, elderly patients with ADHD symptoms but no other cognitive deficits. This collaboration led to the publication of the first neuroimaging study of elderly individuals with ADHD worldwide, in which we used structural MRI to document regional brain volume deficits in these ADHD patients relative to elderly controls, as well as significant correlations between ADHD symptoms and volume variations in cortico-striatal-cerebellar circuits.[207]

Brazilian neuroimaging research groups should also seize as many opportunities as possible to take part in international multigroup collaborations, as exemplified by the consortia mentioned in the previous section of this article. Our expertise to acquire and store neuroimaging databanks from large-sized samples places Brazilian groups in a privileged position to share unique data from low- and middle-income environments. Moreover, these collaborations may optimize the extraction of meaningful information from our samples, which are frequently submitted to a limited and insufficient number of analyses, thus remaining underused. Additionally, recent experience has shown that our participation in international, prospective meta-analytic investigations is a powerful means of further internationalizing research activities, fostering regular communication and networking with experts from other centers, and supplying high-quality online training for research staff. Specifically, such liaising offers vast opportunities for the assimilation of technology developed abroad, which can then be adapted and improved based on our own local needs. The open-source software ethos that is currently present in the neuroimaging community favors decentralized collaboration among researchers and may help biomedical publications to achieve a higher level of transparency, hopefully through auditability of both data and methods. Additionally, it is relevant to mention that organizers of international neuroimaging consortia are often keen to make way for Brazilian experts to share or take the lead on the testing of new hypotheses using large neuroimaging databanks acquired from subjects recruited in different parts of the world.[208] Finally, the field of neuroimaging will rely increasingly more heavily on AI-based methods, and recent initiatives to create centers of excellence in AI[209,210] have the potential to further increase the relevance of neuroimaging research in Brazil.

One final point: we carry out research with populations frequently subjected to socioeconomic adversities

As in several other areas of neuroscience research, contemporary neuroimaging studies have provided compelling evidence that previous or current adversities, such as low socioeconomic class, low levels of educational attainment, and history of childhood maltreatment, may all reflect on interindividual variations in brain imaging measurements.[211] Investigations carried out in low- and middle-income environments must document individual information on such clinical and demographic variables, and there is a great need for neuroimaging studies evaluating specific populations subjected to adversities. These neuroimaging studies are relevant not only to increase global knowledge about the range of brain impacts derived from such conditions, but also to generate information that may be of local public health relevance.

Only a few structural MRI and fMRI investigations of this kind have been carried out in Brazil to date. One study mapped the effects of violence on anterior cingulate volumes in adults with PTSD,[47] while one other documented abnormalities in regional brain activity and functional connectivity patterns in preadolescents exposed to violence in an urban environment.[212] One additional structural MRI study of adults with bipolar disorder identified significant correlations between history of childhood maltreatment and lower volumes of brain regions that modulate emotional behavior.[78] Finally, a recent fMRI investigation of a large-sized population-based sample of children and adolescents reported variations in resting-state functional connectivity as a function of the quality of the family environment, involving brain regions critical to emotional processing.[213]

Neuroimaging findings have also been reported from a community-based sample of cognitively unimpaired elderly individuals recruited in an economically disadvantaged catchment area of São Paulo. Reductions in both regional brain volumes[179] and glucose metabolism[214] were found in direct proportion to the degree of cardiovascular risk, which is known to be significantly greater in elderly subjects with disadvantageous socioeconomic backgrounds. Additionally, silent brain infarcts were highly frequent in that sample and significantly associated with lower levels of previous education.[215] In an additional MRI study on an expanded sample of cognitively healthy elderly individuals, variations in regional brain volumes were detected that depended on the level of previous educational attainment, supporting the notion that education may exert subtle protective effects against aging-related brain changes, in accordance with the concept of cognitive reserve.[216]

The above concept of cognitive reserve is also usually invoked to explain interindividual differences in the degree of neuropathologic burden across individuals with amnestic MCI or mild AD who present comparable levels of cognitive impairment. Recent neuroimaging studies with AD and amnestic MCI samples carried out elsewhere have indicated that compensatory effects of cognitive reserve may be best documented when using sophisticated probes for specific AD-related molecular pathology indices (such as the accumulation of cortical amyloid plaques) rather than overall measures of advanced neurodegeneration (such as brain atrophy as detected with MRI).[217] However, it is interesting to note that all contemporary neuroimaging investigations of cognitive

reserve performed in other environments have recruited AD or MCI patients with 6 years of education or above.[217] This is in contrast with our own experience of carrying out neuroimaging studies with elderly populations in Brazil, as a substantial proportion of our subjects have lower levels of educational attainment.[215] With our recent validation and implementation of PET imaging with ^{11}C-PiB for *in vivo* imaging of cortical Aβ plaques,[162] it will be possible to assess groups of AD and MCI individuals with levels of education lower than those of all studies evaluating cognitive reserve in the international literature to date. This should allow us to directly ascertain *in vivo* whether elderly individuals with very low levels of education develop symptoms of dementia at a degree of cortical Aβ load that is lower than those of groups with similar levels of cognitive decline but significantly higher educational attainment and therefore greater levels of cognitive reserve. Investigations of this kind may provide clues to explain how poor educational attainment may influence increased rates of AD and earlier emergence of clinical signs of dementia in low- and middle-income countries.[218]

Concluding remarks

In this article, we aimed to demonstrate how Brazilian neuroimaging research in psychiatry has achieved world-class excellence. Across various Brazilian academic centers, a number of multidisciplinary neuroimaging research teams have been formed, with the expertise to formulate and test hypotheses of worldwide and local interest in psychiatry. Liaising with radiologists, physicists, radiopharmacists, and computer data analysts, our psychiatric teams have gained access to sophisticated imaging technology, developed the capacity to acquire and analyze quality data from unique, large-sized populations, and established a tradition of collaboration both nationally and internationally with leading institutions. This has allowed our neuroimaging labs to make scientific contributions in several fronts over the past decades, including the reporting of original findings of brain changes in samples of subjects with prevalent psychiatric disorders recruited in our environment before any exposure to treatment[26,79]; original findings of brain changes associated with subtypes of psychiatric disorders rarely or never previously evaluated in other countries[28,207]; the use of cross-sectional and longitudinal epidemiological designs to assess specific populations and address relationships with relevant risk factors for mental disorders[82,176,219]; development of novel intervention studies using imaging markers as outcome measures and predictors of treatment response[220,221]; production of original findings evaluating brain effects of relevant psychopharmacological agents[57,108]; the use of fMRI in studies applying innovative tasks of interest to psychiatry[95-97]; publishing well-cited reviews of neuroimaging issues in top international journals[222,223]; and participation in worldwide consortia organized to analyze neuroimaging data from samples of unprecedented size.[183,184]

Additionally, we have developed awareness of the need to work in close collaboration with experts from other fields of neuroscience to devising studies that integrate neuroimaging indices with other biomarkers of interest to psychiatry. Finally, we now also work hand-in-hand with experts from computer support services in our academic centers to ensure implementation and upgrading of high-performance infrastructure for storing, transferring, and processing hundreds (or even thousands) of individual datasets, as needed to support contemporary research activities of local and interinstitutional neuroimaging consortia.

Working in a resource-limited country facing economic and political turmoil in recent years, Brazilian research groups have been under great strain, even more so in areas that depend on sophisticated technology that demands regular updating. Such a scenario is highly challenging for our neuroimaging research groups, which strive to maintain international relevance and aim to generate quality research data on the unique human populations to which we have access. In the coming years, therefore, it is of critical relevance that government funding agencies maintain their support for the research activities discussed in this paper. Also regarding funding, Brazilian groups should apply for research grants abroad more regularly, as international applications are accepted by institutions such as the National Institutes of Health, in the United States,[224] and private foundations such as the Brain & Behavior Research Foundation.[225] Furthermore, nurturing a culture of private sector funding in Brazil is necessary, following, for instance, the successful example of neuroimaging research sponsored by the IDOR in Rio de Janeiro. Finally, and very importantly, our universities must be able to supply a continued flow of academic career opportunities for young talents working in the field of psychiatric neuroimaging. Under favorable conditions, it may be possible to remain optimistic about our prospects of not only surviving as a relevant psychiatry research subspecialty, but also seizing new opportunities for growth in the future.

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