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Brazilian psychiatric brain bank: a new contribution tool to network studies

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Abstract There is an urgent need for expanding the number of brain banks serving psychiatric research. We describe here the Psychiatric Disorders arm of the Brain Bank of the Brazilian Aging Brain Study Group (Psy-BBBABSG), which is focused in bipolar disorder (BD) and obsessive compulsive disorder (OCD). Our protocol was designed to minimize limitations faced by previous initiatives, and to enable design-based neurostereological analyses. The Psy-BBBABSG first milestone is the collection of 10 brains each of BD and OCD patients, and matched controls. The brains are sourced from a population-based autopsy service. The clinical and psychiatric assessments were done by an expert team including psychiatrists, through an informant. One hemisphere was perfused-fixed to render an optimal fixation for conducting neurostereological studies. The other hemisphere was comprehensively dissected and frozen for molecular studies. In 20 months, we collected

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36 brains. A final report was completed for 14 cases: 3 BDs, 4 major depressive disorders, 1 substance use disorder, 1 mood disorder NOS, 3 obsessive compulsive spectrum symptoms, 1 OCD and 1 schizophrenia. The majority were male (64%), and the average age at death was 67.2 ± 9.0 years. The average postmortem interval was 16 h. Three matched controls were collected. The pilot stage confirmed that the protocols are well fitted to reach our goals. Our unique autopsy source makes possible to collect a fairly number of high quality cases in a short time. Such a collection offers an additional to the international research community to advance the understanding on neuropsychiatric diseases.

Keywords Brain banking · Psychiatry · Bipolar disorder · Postmortem · Autopsy · Obsessive compulsive disorder · Stereology, neuropathology

Introduction

Bipolar disorder (BD) type I is a serious and devastating psychiatric illness, the lifetime prevalence of which in the general population is approximately 1.6% (Regier et al. 1993; Andrade et al. 2002). Frequent re-hospitalizations, associated or not with suicide attempts, occupational disability, and destabilization of family and personal life make BD one of the most debilitating diseases worldwide (Regier et al. 1993; Murray and Lopez 1996; Andrade et al. 2002; Merikangas et al. 2007). The pathophysiology of BD is unknown, but several neuroimaging studies published in the last two decades consistently indicate that subregions of the prefrontal cortex, medial temporal lobe, basal ganglia, and cerebellum are involved, suggesting that the affective, cognitive, and behavioral symptoms arise from malfunctions involving two inter-correlated brain circuits, namely the limbic-thalamo-cortical and the limbic-striato-thalamo-pallidal circuits (Soares 2003; Gigante et al. 2010).

Obsessive-compulsive disorder (OCD) is also a chronic psychiatric disorder, with lifetime prevalence ranges from 1.0 to 2.5% (Schmitt et al. 2008). It is the fourth most common psychiatric illness in the general population and tends to be associated with other mood disorders such as major depression in about 67% of cases and Tourette syndrome (TS) in about 7% of cases (Rasmussen and Eisen 1992). OCD is considered a heterogeneous syndrome of multiple etiologies involving different brain circuits (Miguel et al. 2005; Mathis et al. 2006), specially the corticostriatal-thalamo-pallido-cortical pathway (Saxena et al. 1998; Saxena and Rauch 2000; Rotge et al. 2008).

Over the last two decades several neuroimaging findings brought new understanding of the pathophysiology of BD and OCD. However, the validation of these findings at the cellular and molecular levels is contradictory (Bielau et al. 2005). Unlike Alzheimer's, Parkinson's, and Huntington's disease, no histopathological hallmark characteristic of BD and OCD has been recognized to date. Therefore, among the neuropathological methods, neurostereology is the gold standard for morphological analysis of area, volume, number of cells, cell density, and nuclear volume (Schmitz and Hof 2005). Therefore, neurostereological methods are considered the methods of choice for studying neurobiological changes in psychiatric diseases. These methods, in combination with appropriate statistical tests, identify brain structural changes that can be distinguished in diseased versus control brains. However, neurostereology requires the use of good quality *postmortem* tissue and controlling of several parameters. Due to the worldwide lack of autopsies, tissue shortage constitutes one of the major constraints for validation studies in neuropsychiatric diseases (Waldvogel et al. 2006). A recent review pointed out that the majority (69%) of *postmortem* studies about BD in the last 30 years had used material from a single source, the Stanley Foundation collection, which harbors fifty cases (Torrey et al. 2000). If the second most widely used collection—the tissue bank of Harvard, with twenty-two cases—is considered, 80% of studies were conducted with the same seventy-two cases (Deep-Soboslay et al. 2008). In addition, as far as we know, there is no structured brain bank dedicated to collecting brains of OCD patients. This shows how difficult it is to collect well-characterized brains of BD and OCD patients.

Aiming to expand the collection of *postmortem* psychiatric well-characterized cases for the use of the scientific community, a group of multidisciplinary researchers belonging to the Bipolar Disorder Research Program (PROMAN) and the Obsessive

Compulsive Disorder Research Program (PROTOC) both from the Institute of Psychiatry at the University of São Paulo Medical School, the Brain Bank of the Brazilian Aging Brain Study Group (BBBABSG) and the Laboratory for Research on Cerebral Morphology of Clinical Psychiatry at the University of Wurzburg, Germany launched a joint initiative to create a human brain collection focusing on psychiatric disorders: the Psychiatric Disorders arm of the brain bank of the BBBABSG, or Psy-BBBABSG. The standard operative protocols (SOPs) were adapted from the BBBABSG protocol (Grinberg et al. 2007a) for meeting the needs of a psychiatric disease collection.

The present paper aims (1) to describe the procedures used by Psy-BBBABSG to collect brains of psychiatric donors; (2) to justify the choice of the SOPs used in our protocol; and (3) to discuss the differences between our protocols and those adopted by other similar brain banks in the world.

Methods

The psychiatric disorders arm of the brain bank of the brazilian aging brain study group (Psy-BBBABSG)

The Psy-BBBABSG was established in 2008. Its SOPs are based on the experience of a local successful brain bank focused in aging and neurodegenerative diseases, the Brain Bank of the Brazilian Aging Brain Study Group (BBBABSG) and other brain banks focused on psychiatric disorders (Schmitt et al. 2008; Ferrer et al. 2008; Deep-Soboslay et al. 2005). The Psy-BBBABSG focuses its collection on brains of BD and OCD patients, but also collects cases of major depressive disorder (MDD), schizophrenia, and substance use disorders (SUD), since such cases are sometimes identified after the final assessment of cases previously screened as possible BD or OCD.

The first year was dedicated to developing the protocols for screening, reception, collection, and storage of cases. The collection effectively started in 2009. All the protocols are approved by the local internal review board.

The Psy-BBBABSG has two cores: (1) clinical—in charge of screening and clinical assessment, and (2) pathological—in charge of tissue procurement, handling, and storage. The clinical core is composed of a team of gerontology nurses and psychiatrists extensively trained in psychiatric research and overseen by a seasoned psychiatrist specializing in mood disorders, and the pathological core is composed by a multidisciplinary team of health-related graduates and undergraduate students, overseen by an experienced neuropathologist.

Structure and recruitment of cases

The brains are sourced from the Autopsy Service of the São Paulo Medical School. The Autopsy Service is responsible for performing autopsies of individuals who died from a natural death within the São Paulo City metropolitan region, and performs around 13,000 autopsies per year. All autopsies are complete and carried out by board-certified pathologists.

We collect brains of individuals who presented with OCD or BP and died aged 50 years and older. The cases are selected according with BBBABSG criteria (Grinberg et al. 2007a) with some modification (Table 1).

Screening and clinical assessment

a. Initial screening and *postmortem* psychiatric interview

All deceased subjects over 50 years arriving at the Autopsy Service are candidates to participate in the Psy-BBBABSG. A team of nurses and gerontologists on duty explain the project to the next of kin of eligible subjects, before the autopsy procedure, and invite them to participate. Once the written informed consent is granted, a reliable informant is submitted to a semi-structured clinical, functional and psychiatric assessment. This assessment includes medical and demographics data, family history, and several questionnaires and scales covering multiple cognitive domains and activities of daily living. In addition, possible psychiatric symptoms are screened using the SCID (Spitzer et al. 1992; Ferretti et al. 2010).

The scales and questionnaires are widely accepted and validated as instruments of assessment via informant (Table 2). In those cases in which the psychiatric symptoms screen positive, we request authorization to access external medical records and for performing a confirmation interview with a

Table 1 Selection criteria of the Psy-BBBABSG

Criteria for inclusion and exclusion
Inclusion criteria
I. Age higher than 50 years old
II. Having a informant who lived close to the patient and can provide relevant information
III. Diagnosis of bipolar disorder I according to *Diagnostic and Statistical Manual* (*DSM-IV*), or
IV. Diagnosis of OCD according to DSM IV
V. *Postmortem* Interval up to 24 h
VI. Cerebrospinal fluid pH higher than 6.5
Exclusion criteria
I. Individuals who died of brain primary causes (eg, acute stroke, head trauma, meningitis, tumors, etc.)
II. Individuals who have had situations with the potential to cause ischemic brain damage
III. Individual with comorbidities that may impair cognitive function, such as dementia or mental retardation
IV. Lack of primary caregiver or guardian able to provide the information

Source: Adapted from Grinberg et al. 2007a

Table 2 Instruments used in the clinical interview

	Assessment instrument
Obsessive compulsive disorder	Screening adapted by structured clinical interview for DSM-IV Axis I disorders—SCID-I/P 2.0 (First et al. 1996) and Yale-Brown obsessive-compulsive scale—YBOCS (Goodman et al. 1989)
Bipolar disorder	DSM IV—Structured clinical interview (SCID) for depression and manic disorders (Del-Ben et al. 1996; Spitzer et al. 1992)
Cognitive domain	Clinical dementia rating scale—CDR (Morris 1993)
	Informant quest. cognitive decline in the elderly—IQCODE (Jorm 1996)
BPSD	Neuropsychiatric inventory—NPI (Cummings et al. 1994)
Functional assessment	The Katz index
	Instrumental activities of daily living (Lawton and Brody 1969)
Parkinson's disease	The brief screening questionnaire for parkinsonism (Tanner et al. 1990)
Social information	ABIPEME—a Brazilian scale used to determine social-economic condition (Almeida and Wickerhauser 1991)

Psy-BBBABSG. Sao Paulo, 2009

BPSD behavioral and psychological symptoms of dementia

psychiatrist, at a later time (between 1 and 3 months after the death).

The confirmation interview has two parts: (1) assessment of personal psychiatric history during the lifespan, and (2) a structured instrument composed of scales for psychiatric evaluation. Table 3 describes the instruments used in the confirmation interview. The results of both interviews and the data of the medical records are analyzed together by a group of three psychiatrists specializing in BD and OCD research from PROMAN and PROTOC groups. The

Table 3 Instruments used in the complementary diagnostic interview. Sao Paulo, 2009

Disorder	Scales or instruments
OCD	Cut version of DYBOCS e SCID-I
TS	YGTSS
BD	SCID—I
Another psychiatric disorders (Eixo I)	SCID—I (Del-Ben et al. 1996; Spitzer et al. 1992)

BD bipolar disorder, *OCD*, obsessive-compulsive disorder, *TS* Tourrette syndrome

final diagnosis is reached after consensus and follows the principle of "best estimate diagnosis" (Deep-Soboslay et al. 2005).

Pathological procedures

Cases screened following the flow chart, briefly described in Fig. 1.

Step 1-collection of samples

At autopsy, the brain is removed, put immediately on ice, transported to the BBBABSG laboratory (one floor above) and immediately processed. During the autopsy, before removing the brain, the cerebrospinal fluid (CSF) is collected from the ventricles and its pH is measured to assess the quality of the tissue. The CSF sample is centrifuged and stored in 1.5 mL samples at 80°C, for further studies. Likewise, blood samples are collected, with DNA extraction. The brain is removed with the circle of Willis intact.

Step 2-processing of brains

Brain weight and volume are measured and the hemispheres are sectioned sagittally. Because it is not clear if there is a hemispheric dominance in BDD and OCD, alternately, one hemisphere is fixed by perfusion and the other one is dissected and snap frozen at −80°C. For the perfusion, the vascular system is washed with 250 mL of mannitol and 10 mL of warm heparin (Grinberg et al. 2008), followed by 5 L of 20% formalin. The post-fixation is made in 20% formalin for 3 weeks. Because half of the brain is severed before the infusion, the arteries supplying the hemisphere to be frozen are dissected and blocked with a string to prevent the leakage of solutions. Perfusion fixation renders fewer volume changes and allows excellent preservation of neurons and glia (Grinberg et al. 2008).

The hemisphere chosen to be dissected is cooled to −20°C for about 20 min to allow better visualization and demarcation of 43 regions of interest. These regions of interest have been chosen based on neuro-imaging and previous *postmortem* studies on BD and OCD, (Table 4). The dissected areas are stored in double identified, 4.5 mL cryotubes. A previous study shows that this method of collection is ideal for molecular studies in our material (Silva et al. 2007).

Step 3-processing of the fixed hemisphere for stereological studies

The fixed hemisphere is sent to the University of Würzbrug, in accordance with all legal and ethical regulations.

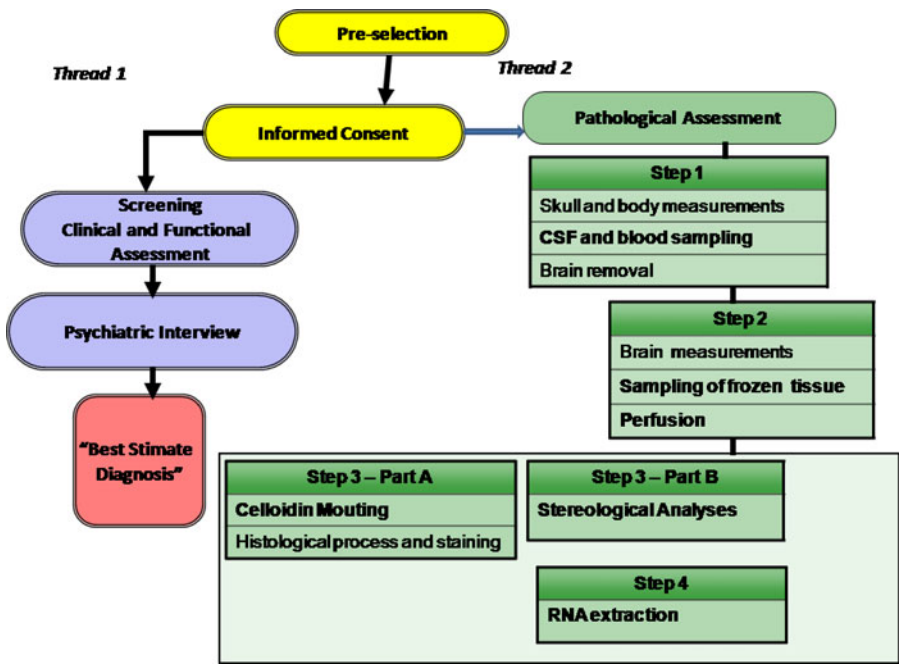

Fig. 1 Flow chart of Psy-BBBABSG procedures. Sao Paulo, 2009

Table 4 Areas represented for storage at −80°C

Cortical	*Subcortical structures*
Dorsal cingulate cortex (32)	Amygdala (lateral and medial subnuclei)
Dorsolateral frontal cortex (9, 46)	Caudate nucleus (head, body and tail)
Entorhinal cortex (28)	Globus pallidus (external and internal)
Frontopolar cortex (10)	Hipothalamus
Inferior frontal gyrus (45)	Hippocampus (anterior and posterior)
Middle prefrontal cortex (25)	Internal capsule
Orbitofrontal cortex (47, 11)	Mamillary body
Premotor area (6)	Nucleus basalis of Meynert
Primary visual cortex (17)	Putamen
Subgenual cingulate cortex (24)	Thalamus (pulvinar, ventral, anterior and mediodorsal nuclei)
Superior and inferior parietal cortices (7, 49)	
Superior and inferior temporal cortices (22, 21)	
Supragenual cingulate cortex (24)	
	Brainstem and cerebellum
	Cerebellar hemisphere
	Cerebellar vermis (anterior, medio, posterior)
	Dentate nucleus
	Midbrain
	Pons

Psy-BBBABSG, 2009

Brodmann areas in parenthesis

At the University of Würzburg, hemispheres are subjected to an improved and fast process of celloidin embedding, suitable for neurostereological and cit-oarchitectonic studies (Heinsen et al. 2000; Grinberg et al. 2008). This same method has previously been used successfully in several studies focused on psychiatric disorders (Kreczmanski et al. 2007; Casanova et al. 2008; van Kooten et al. 2008; Teipel et al. 2005).

Heinsen's method for celloidin embedding

The modified celloidin embedding method is fast and economical (Heinsen et al. 2000). The method allows sectioning of a cerebral hemisphere in thick histological sections (440 μm), which has the advantage of suffering less distortion than other traditional methods, and renders excellent delineation of regions of interest in the brain. These features are prerequisites for the stereological analysis and 3D reconstruction of the cerebral hemispheres. In addition, this method makes the process cheaper, because the entire hemisphere is sectioned in 300–400 slices. With the help of the software Amira 5 (Visage Imaging Inc.), the brain is reconstructed in 3D for assessing the volumes of the region of interest. For further details, see Schmitz and Hof. (2005), Heinsen et al. (2000), Grinberg and Heinsen (2007b) and Grinberg et al. (2008). Finally, routine histological methods, stereological techniques, immunohistochemistry, and quantitative studies can be applied in the same areas, which allows the correlation of the findings of cellular and molecular pathology and deeper understanding of the regional pathophysiology (Grinberg et al. 2008, 2009a).

Preliminary results

Between February 2009 and December 2010, of all 747 brains collected, 77 screened positive for psychiatric disorder. Forty-four of these cases were donated to the Psy-BBBABSG. Another 33 did not meet the Psy-BBBABSG criteria due to concomitant cerebrovascular accident, dementia, trauma, low pH, postmortem interval higher than 24 h, and lack of reliable informant.

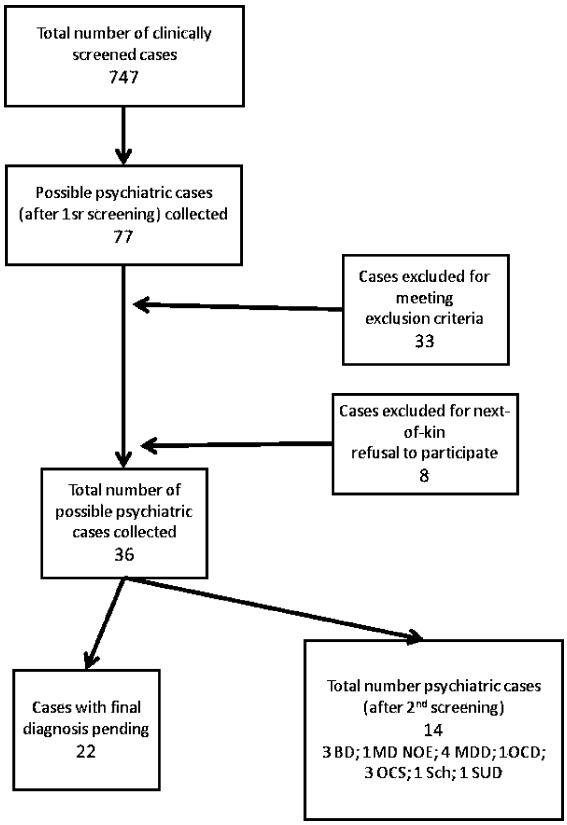

Fig. 2 Characteristics and outcome of the collected cases. Psy-BBBABSG. 2011. *SUD* substance use disorders, *OCS* obsessive compulsive spectrum disorders, *BD* bipolar disorder, *MMD* major depressive disorder, *MD-NOS* mood disorder not otherwise specified, *Sch* Schizophrenia

Out of the 44 donated cases, eight were excluded after the confirmation interview, due to informant refusal to return, and 22 have the second interview and the "best estimate diagnosis" pending. The remaining fourteen cases were included in the collection with the following diagnoses: BD (3), major depressive disorder (4), obsessive compulsive spectrum (OCS) (3), OCD (1), substance use disorders (1), mood disorder not otherwise specified (1) and schizophrenia (1), (Fig. 2). The majority were male (64%), and the average age at death was 67.2 ± 9.0 years (Table 5). The average postmortem interval was 15.5 ± 4.9 h and the mean CSF pH was 7.3. About 43% of the subjects included had no psychiatric diagnosis in life. We collected three controls; 65% were female, and the average age was 74.6 ± 8.3 years. The average postmortem interval was 17 h, and the mean CSF pH was 8.

The fixation by perfusion is shown in Fig. 3.

The standardization of the dissection of 43 areas is shown in Fig. 4 and Table 4. The average time to dissect all the areas is 2 h.

Discussion

Well-conducted clinicopathological studies have proved to significantly contribute to the understanding of a disease pathogenesis. Neuropsychiatric diseases represent one-third of the chronic diseases affecting the population (Kretzschmar 2009) and their biological bases are not clarified. Structured brain banks are designed to provide high-quality material and comprehensive clinical information (Blumberg et al. 2003; Beyer et al. 2004; Rosso et al. 2007; Doty et al. 2008). Therefore, structured brain banks specialized in psychiatry disorders are important to foster clinicopathological studies aiming to clarify the basis of these disorders. Several factors limited the creation of a bigger number of psychiatric disorder-orientes brain banks, including the decrease of autopsy rates worldwide. As a result, the majority of the postmortem studies on BD are based on the same collections with the same few subjects, which obviously limits the representativeness, reproducibility, and generalization of findings (Benes et al. 2001; Cotter et al. 2002; Uylings et al. 2005).

The São Paulo Autopsy Service performs all the natural-death autopsies of São Paulo, an 18 million-person metropolitan region. It performs more than 13,000 autopsies a year. Given the fact that prevalence of BD type I in the Brazilian general population ranges from 1 to 1.6% (Regier et al. 1993; Andrade et al. 2002; Merikangas et al. 2007), we could possibly recruit 130 cases of BD per year.

We consider the strengths of the present collection to be: a short PMI a large number of potential control cases, older subjects, less severe cases, and no treated cases. A long *postmortem* interval is a major limiting factor in brain banking (Atz et al. 2007; Schmitt et al. 2008). The autopsy service structure combined with a permanent shift of our team resulted in a collection with shorter PMI. The average *postmortem* interval of our pilot study was lower than the lowest average *postmortem* interval described in the literature for bipolar disorders. The Stanley Foundation collection has a PMI over than 30 h and the and Harvard Brain

Table 5 Characteristics of patients

Patient	Gender	Age	CDR	PMI (h)	Cause of death	Years of schooling	Psychiatric disease
1	F	66	0	13	Chronic obstructive pulmonary disease	3	BD
2	F	65	0	6	Myocardial infarction	5	BD
3	M	74	0	22	Bronchopneumonia	4	BD
4	M	77	0	17	Neoplasm	0	OCD
5	M	66	0	9	Myocardial infarction	0	OCS
6	M	73	0	23	Pulmonary oedema	2	OCS
7	M	74	0	19	Pulmonary oedema	8	OCS
8	F	66	0	13	Pulmonary oedema	2	MDD
9	F	61	0	22	Acute peritonitis	3	MDD
10	M	81	0	14	Bronchopneumonia	1	MDD
11	M	58	0	13	Bronchopneumonia	7	MDD
12	M	53	0	18	Chronic renal failure	3	MD-NOS
13	M	60	0	16	Pulmonary oedema	6	SUD
14	F	64	0.5	13	Thromboembolism	4	Sch

CDR Clinical dementia rating, *PMI postmortem* interval, *SUD* substance use disorders, *OCS* obsessive compulsive spectrum disorders, *BD* bipolar disorder, *MMD* major depressive disorder, *MD-NOS* mood disorder not otherwise specified, *Sch* Schizophrenia

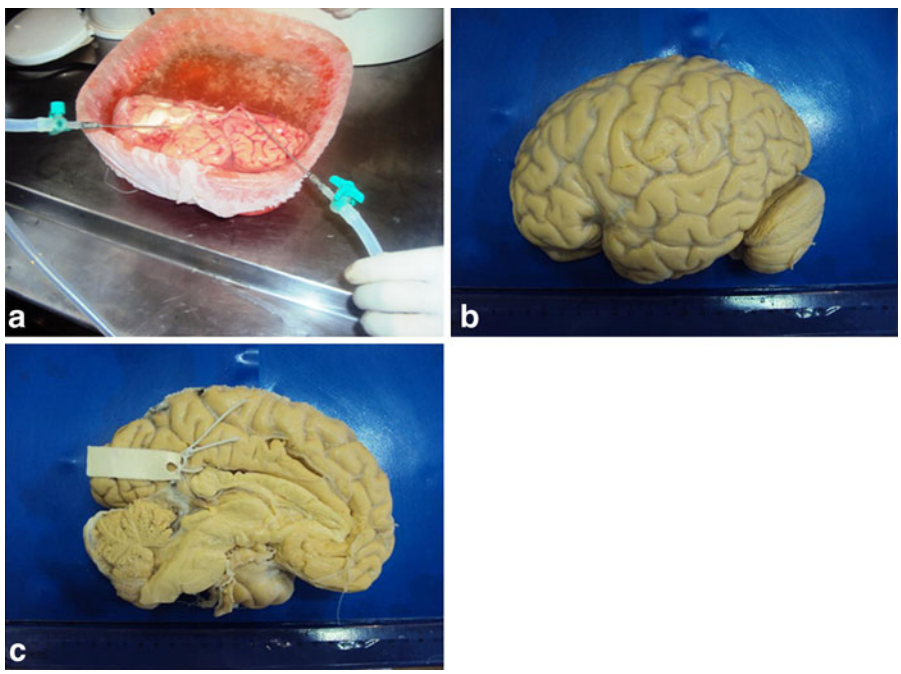

Fig. 3 Perfusion fixation of a brain hemisphere. **a** The hemisphere during fixation. **b**, **c** Final results (lateral and medial surface, respectively). *Note*: that the brain shape is very well preserved

Tissue Repository center has a PMI over than 20 h (Torrey et al. 2000; Harvard Tissue Repository Center 2010). In addition, none of our cases has a PMI over than 24 h. Moreover, we apply some quality control measures such as the elimination of cases with low CSF pH. This minimize the collection

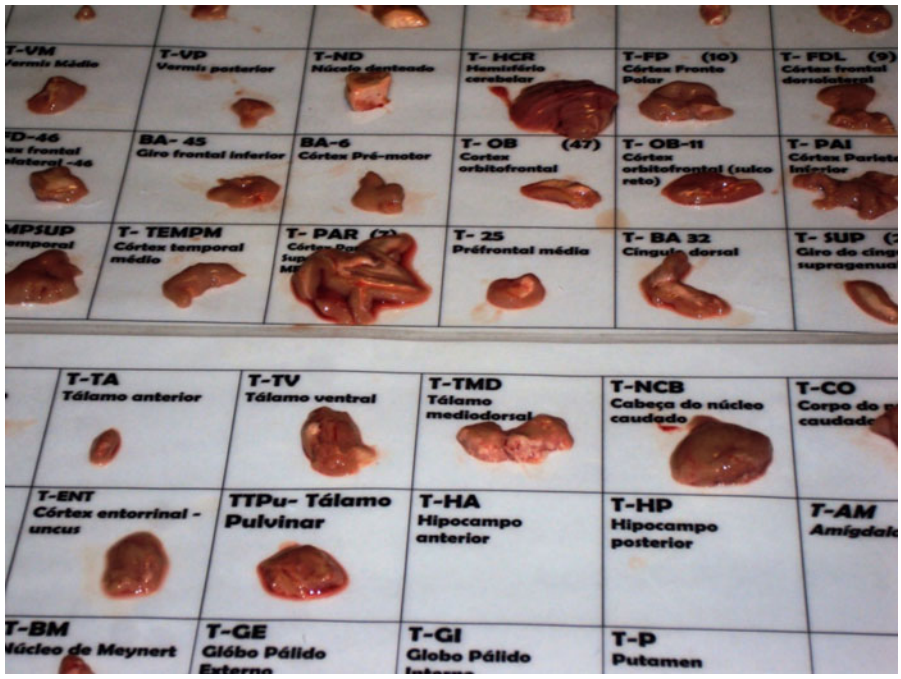

Fig. 4 Example of some of the 43 areas dissected from the fresh tissue for further molecular analyses. A cold plate helps to keep the tissue form for dissection. Psy-BBBABSG. 2011

of tissue of good quality and, thus, useless for biochemical and molecular studies (Kingsbury et al. 1995).

Due to its characteristics, our collection complements the other cohorts. Most of the cases belonging to the other collections belonged patients who committed suicide at a young age. Therefore neurobiological abnormalities specifically associated with suicide and disproportional number of severe cases may be a confounding factor in these studies (Torrey et al. 2000). Meanwhile, the Psy-BBBABG hosts cases belonging to subjects older than 50 years who died by a natural causes., many of them unmedicated or only slightly exposed to psychiatric medications, maybe more closely reflecting the majority of BD patients. Indirectly, by systematically detecting untreated cases, we believe that our results will raise attention for the need of improving detection and treatment of patients with psychiatric conditions in our country. Finally, given the cases are screened from a general autopsy service, a great number of control cases are available to match the disease cases.

Another additional strength is that our protocol is especially suitable to allowing further molecular and stereological studies.

Stereologic methods have been successfully applied in studies of schizophrenia and autism (Heinsen et al. 2000; Kreczmanski et al. 2007; Casanova et al. 2008; van Kooten et al. 2008). Neurostereological investigation is the gold standard for morphological analysis of area, volume, number of cells, volume density, and nuclear volume in areas of interest in neuropsychiatric disorders (Schmitz and Hof 2005). The results obtained with design-based stereology methods are unaffected by size, shape, spatial orientation, and spatial distribution of the cells to be investigated. Moreover, the systematic error is believed to be minimal.

However, we also face limitations.

Our study design is retrospective, cross-sectional and the clinical information is informant-based, rather than longitudinal, prospective and based on a direct assessment of the subject. Our protocol was designed to minimize potential diagnostic biases associated to our conditions. We employ a comprehensive diagnostic interview, carefully search medical records, and the diagnosis is based on a consensus involving several specialists. Diagnosis of BD and major depressive disorder can be reliably obtained with an informant (Torrey et al. 2000; Bielau et al. 2005). However, we acknowledge that OCD diagnosis via informant faces more constrains, due to the fact that the obsessive symptoms (and some of the compulsive rituals) may not be observed

in some cases by an external informant. Therefore, we grant at a maximum diagnosis of *possible* OCD or *definite* OCS in our cohort.

The potential contribution of Psy-BBBABSG and conclusion remarks

The BBBABSG model, including structured protocol and a multidisciplinary team, is proving to be successful and is generating several relevant findings in aging and neurodegenerative disease (Azevedo et al. 2009; Grinberg et al. 2009a, b; Teipel et al. 2010). The significant number of potential psychiatric cases screened in the last years, and taking advantage of a long lasting collaboration with the Department of Psychiatry at the University of São Paulo and University of Würzburg, permitted the creation of the Psy-BBBABSG, the first Brazilian bank brain of patients with BD and OCS. Based on the preliminary results, we believe that this collection may contribute for untangling the pathophysiology of these diseases. We hope that the present collection, derived from a sample that reflects the environmental and genetic effects of a heterogeneous population, will be able to provide high-quality tissue to the international research community engaged in filling this gap.

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