Dear Editor,

In their recent paper entitled *A review of psychiatric genetics research in the Brazilian population*, Cordeiro et al. conducted an interesting review by describing the most important research groups now at work and their main findings on the Brazilian population. The authors briefly discussed relevant findings on drug addiction, alcohol dependence, pathological gambling, schizophrenia, bipolar disorder, obsessive compulsive disorder, suicidal behaviors and attention deficit hyperactivity disorder. Additionally, they argued their point of view with respect to the obstacles and challenges faced by psychiatric genetic studies considering Brazil’s heterogeneous ethnicity.

Although the paper is very interesting, its authors failed to describe the methodology employed for conducting the research and, apparently, their failure in performing a systematic review resulted in they neglecting publications already available in the field. Our group has been studying anxiety and its endophenotypes, like personality traits as neuroticism, harm avoidance and behavioral inhibition, as well as suicidal behavior in depressed patients. In brief, with respect to anxiety disorders and endophenotypes, we found no association between the serotonin transporter promoter polymorphism (5-HTTLPR) and personality traits in asymptomatic patients with panic disorder. We have also described preliminary evidence of the association between EFHC2 (a gene implicated in fear recognition) and harm avoidance. In this study, an intronic single nucleotide polymorphism (SNP), rs1562875, was associated with harm avoidance, accounting, alone, for over 3% of variance in this trait. This same SNP was nominally but not empirically associated with behavior inhibition and panic disorder with an odds ratio of 2.64.

The main results of our studies in suicidal behavior include a replication of an association between suicidal behavior and a polymorphism in the serotonin transporter gene (5-HTTLPR), demonstrating a higher risk for suicide behavior among depressed patients bearing SS or LS genotypes. We also performed a re-analysis of a novel 5-HTTLPR functional variant identified within the L allele which alters its messenger RNA production. Even though our results did not replicate the association between functional 5-HTTLPR suicidal behavior in depressed patients who have attempted suicide, this was the first study to ever perform this kind of this analysis in a Brazilian population.

As properly emphasized by Cordeiro et al, the Brazilian population is composed of the admixture between European, African and Native American populations, a fact which raises a number of problems when performing genetic studies. In order to avoid stratification, in our studies we use more homogenous samples like the Caucasians that live in the southern state of Rio Grande do Sul, which is an area that has recently received an important inflow of European migrants, and has suffered less African and Native American genetic influence as described in the same study.

Psychiatric genetic studies in the Brazilian population are still very much needed and, in the field of anxiety disorders and suicidal behavior, this need is even more evident. Along with the well established groups new research enterprises emerged and added relevant information to the understanding of these complex traits and behaviors. As much as ours other groups might not have their research acknowledged reinforcing the use of systematic reviews for searching manuscripts as an indispensable tool in reviewing medical literature.

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**Carta aos editores**

**Emerging research groups studying Brazilian psychiatric genetics**

**Grupos de pesquisa emergentes em estudos de genética psiquiátrica brasileira**

Dear Editor,

In their recent paper entitled *A review of psychiatric genetics research in the Brazilian population*, Cordeiro et al. conducted an interesting review by describing the most important research groups now at work and their main findings on the Brazilian population. The authors briefly discussed relevant findings on drug addiction, alcohol dependence, pathological gambling, schizophrenia, bipolar disorder, obsessive compulsive disorder, suicidal behaviors and attention deficit hyperactivity disorder. Additionally, they argued their point of view with respect to the obstacles and challenges faced by psychiatric genetic studies considering Brazil’s heterogeneous ethnicity.

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Dear Editors,

It is really very exciting to know that another Brazilian group is working with molecular investigation in the field of psychiatric genetics. When we decided to write a paper about the particularities, advantages and difficulties of conducting psychiatric genetic studies in the Brazilian population, we were aware of the possible biases of a narrative review. However, that kind of approach seemed to be a more appropriate method in terms of our proposal because we believe that, by describing the history, development, and management of psychiatric genetic investigations in Brazil, we would be contemplating several contextual, cultural and political aspects and integrating different and independent fields of research in order to acquire a wider and multidisciplinary view of the subject at hand.

There is also another important point raised by Salum et al. that needs to be addressed. Differently from what they claim, the use of “more homogenous samples like the Caucasians” does not "avoid stratification" in association studies on complex disorders such as neuropsychiatric disorders.

Nowadays, it is well known that even when studying samples from a specific continental population such as the European, ethnic stratification can produce false associations at markers whose frequency differs across subpopulations. For example, in a recent whole genome association study of rheumatoid arthritis in European Americans, markers in the LCT and IRF4 genes could have been falsely implicated as being associated with the disease had no control method been applied to for the population's

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Note: HCPA = Hospital de Clínicas de Porto Alegre; FIPE/HCPA = Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre; UFRGS = Universidade Federal do Rio Grande do Sul; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

For more information, see Instructions for authors.

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**References**


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**Population stratification in European South-American subjects and its importance to psychiatric genetics research in Brazil**

**Estratificação populacional em sul-americanos de origem européia e sua importância para a pesquisa genética psiquiátrica no Brasil**

Dear Editors,

It is really very exciting to know that another Brazilian group is working with molecular investigation in the field of psychiatric genetics. When we decided to write a paper about the particularities, advantages and difficulties of conducting psychiatric genetic studies in the Brazilian population, we were aware of the possible biases of a narrative review. However, that kind of approach seemed to be a more appropriate method in terms of our proposal because we believe that, by describing the history, development, and management of psychiatric genetic investigations in Brazil, we would be contemplating several contextual, cultural and political aspects and integrating different and independent fields of research in order to acquire a wider and multidisciplinary view of the subject at hand.

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92 • Revista Brasileira de Psiquiatria • vol 32 • nº 1 • mar2010
Certain studies have suggested that angiotensin I converting enzyme (ACE) gene polymorphism is associated with an increased risk of late onset Alzheimer’s disease. However, when studying this, Panza et al. have found inconsistent findings within European studies. Interestingly, there is a statistically significant decreasing trend of the ACE*I/*D genotype frequency from northern to southern regions of Europe, which may contribute to explain the different patterns of associations found between such polymorphism and Alzheimer’s disease across Europe. Recent investigations have suggested that genetic association studies in European Americans should use ancestry informative markers for examining north-south, Ashkenazi Jewish, and Irish ancestry.

Several statistical methods have been developed to control for population stratification. Some studies have proposed that, considering that a small number of candidate markers may not be sufficiently informative and that genotyping a large number of markers can be expensive, the use of microarrays for ancestry estimation and correction has to be considered as a valuable tool when attempting to identify genes for complex traits through association studies involving European and European American populations. However, while studying subjects from European ancestry in Rio Grande do Sul, which is also Mr. Salum and his colleagues ’ home state, a group of Brazilian researchers found a hidden ethnic admixture and proposed an interesting and cheap genomic control that can be used at the individual level, thus correcting for stratification by removing certain individuals from the sample without losing any statistical power due to statistical corrections.

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For more information, see Instructions for authors.
Treatment of apathy in Alzheimer’s disease with transdermal rivastigmine: report of three cases

Dear Editor,

Apathy in Alzheimer’s disease is one of the most difficult behavioral and psychological symptoms to treat. Anticholinesterasic drugs, dopaminergic agonists, and psychostimulants are treatment alternatives based on studies with contradictory results. The use of transdermal rivastigmine has not been sufficiently studied in clinical trials, especially regarding the treatment of apathy. We report below 3 cases of dementia and apathy treated with transdermal rivastigmine, with behavioral symptoms analysis, cognitive testing and outcome measurement in the first, second, third and sixth months.

Case reports: Three female patients were evaluated – MO (81 years old), ECN (74 years old) and DM (84 years old) – all of them meeting the criteria for Alzheimer’s Disease (based on DSM-IV) and for apathy (based on the following criteria proposed by Robert P, 2009: 1) the core feature of apathy, diminished motivation, must be present for at least four weeks; 2) two of the three dimensions of apathy (reduced goal-directed behaviour, goal-directed cognitive activity, and emotions) must also be present; 3) there should be identifiable functional impairments attributable to apathy; 4) exclusion criteria are specified to exclude symptoms and states that mimic apathy. After the diagnosis of Alzheimer’s disease, the patients were treated with transdermal rivastigmine (4.6mg in the first month and 9.5mg after the second month). The improvement of apathy was observed after the introductions of anticholinesterasic treatment. The three cases are presented below:

1) DM presented at first meeting with: Mini Mental State Examination (MMSE) of 15/30, poor verbal contact, walking impairment, loss of manual abilities, and social isolation. After two months of treatment, the patient started to interact during the examination, returned to her manual and social activities, improved her walking balance and presented a MMSE of 21/30. After six months, the improvements were maintained.

2) ECN presented at first meeting with: MMSE of 20/30, difficulties in verbal contact, loss of instrumental activities of daily living (iADL), and social isolation. After two months of treatment, the patient returned with great improvement in verbal contact, returned to her iADL and presented a MMSE of 22/30. After six months, the improvements were maintained.

3) MO presented at first meeting with: MMSE of 13/30, poor verbal contact, loss of iADL and interruption of her morning exercise (walking). After two months of treatment, the patient was more collaborative, showed iADL improvement, returned to her physical activity and presented an MMSE of 10/30. The improvements were maintained after 6 months.

Discussion: Apathy is the most common neuropsychiatric syndrome in Alzheimer’s disease, affecting 30 to 60% of patients. Its pharmacologic therapy is based on three strategies: psychostimulants, dopaminergic agonists and anticholinesterasic drugs. Despite being first tested and developed for the improvement of cognition in Alzheimer’s disease, anticholinesterasic drugs showed many benefits in the treatment of behavioral and psychological symptoms related to dementia, including apathy. Although systematic reviews point to a lack of well-designed studies concerning this issue, anticholinesterasic drugs remain as an appropriate therapy for apathy. The new presentation of transdermal rivastigmine has been studied as an option with fewer adverse effects (nausea and vomiting) when compared to other oral anticholinesterasic drugs, but no studies concerning their use in behavioral symptoms have been conducted. In the cases reported above, there was a surprising improvement in the apathy of all patients, regardless of the changes in cognitive function. This finding brings new perspectives for the conduction of future randomized and double-blind studies evaluating the use of transdermal rivastigmine.
Use of lithium during pregnancy: a case report using clinical decision analysis

Utilização de lítio durante a gravidez: uma análise de decisão clínica usando um processo relatório

Dear Editor,

There is great potential for the application of decision-making analysis in Psychiatry; especially in situations where the risk of continuing treatment is considerable. While the implementation of decision analysis can be time consuming, once in place, it can be a useful tool in difficult clinical situations.1,2

Case: A 32-year-old Hispanic female with a 9-year-history of bipolar disorder type I, presenting 4 severe manic episodes, requiring prolonged hospitalizations. The patient was stabilized with 1500mg of lithium carbonate per day with a normal serum level. The patient wanted to become pregnant. She had questions whether to continue lithium and having the risk of having a child with Ebstien’s or another anomaly, or to discontinue the treatment and face the risk of relapse. The patient and the psychiatrist decided to use a decision tree for the potential outcomes, which are measured from 0, being the least desirable condition, “patient relapses and has an abnormal child”, to 10, being the best option “patient does not relapse, and has a normal child”. The patient and the psychiatrist came to a mutual decision to assign utilities based on their therapeutic relationship and the patient knowing that 10 is having a normal child and 0 having a child with a heart abnormality. Numbers in between were based on outcomes subjectively assigned by the patient with the help of her psychiatrist. Figure 1 illustrates the construction of the decision tree. The probabilities are assigned to each event taken from reports from literature. The sum of the probabilities of the events represented in each chance node must equal 1. Based on what the literature has described, approximately 21% of women who are pregnant decide to continue lithium treatment.3 The risk of Ebstien’s anomaly has been described to be approximately 0.05%. Studies have reported that in patients taking lithium, the risk for developing abnormalities is approximately 11%; for presenting a cardiac abnormality it is close to 8%, and for Ebstien’s anomaly it is approximately 2%.4,5 Pregnant women with bipolar disorder have a 52% probability of experiencing recurrence of their illness during their pregnancy if lithium is discontinued. Additionally, a patient receiving lithium treatment will have a 37% likelihood of relapsing.6 Patients who stopped lithium may have a 55% risk of relapse within 3 months of discontinuation of treatment.5 Based on these probabilities, the calculations were made from far right to left and where placed in each chance node. The patient decided that she would continue lithium treatment during her pregnancy and she expected to have a normal child. She gave a utility

References
of 10. For the decision tree, the calculations were as follows:

\[ 1A: (\text{Assigned Utility} \times \text{Probability of having Normal Child}) + (\text{Assigned Utility} \times \text{Probability of Having a Child with an anomaly}) = (10 \times 0.89) + (4 \times 0.11) = 9.34 \]

Same procedure is used for the other assigned utilities.

Our decision tree shows a final expected value of 7.10. This value compared with 6.99 favors the use of lithium during pregnancy. Using different probabilities and assigned utilities, our results show that lithium is a viable option to use in pregnant women who have a history of bipolar disorder. The outcomes tend to favor the use of lithium, even though there were high values assigned to undesirable outcomes. In our case, the baby was delivered without any complications and the mother continued lithium during pregnancy without any exacerbation of her bipolar disorder.

This methodology could be applied to different scenarios. We considered this specific case because of the frequency of this situation in clinical practice. The outcomes could vary according to the subjective input of the patient and her family. Also there are different probabilities that could be changed according to the clinician’s judgment, his or her experience, and new reports in the literature. Nevertheless, it offers a valuable example of how to provide some objective information to patients in complex clinical situations.

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Figure 1 - Lithium tree decision analysis
Disclosures

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