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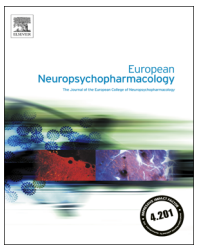

Verbal episodic memory along the course of schizophrenia and bipolar disorder: A new perspective

Letícia S. Czepielewski[a], Raffael Massuda[a], Pedro Goi[a], Miréia Sulzbach-Vianna[a], Ramiro Reckziegel[a], Monise Costanzi[a], Flavio Kapczinski[a], Adriane R. Rosa[a,b], Clarissa S. Gama[a,*]

[a]*Laboratory of Molecular Psychiatry, INCT for Translational Medicine—CNPq, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Post Graduate Program in Medicine, Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos, 2350, Porto Alegre CEP 90035-903, Brazil*

[b]*Department of Pharmacology, Universidade Federal do Rio Grande do Sul Porto Alegre, Brazil; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain*

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Abstract
Impairment on episodic memory (EM) has been strongly correlated with psychiatric disorders, including schizophrenia (SZ) and bipolar disorder (BD). Morevover, the effects of course and progression of the illness on cognitive functioning have not been well established. The aim of the present study is to assess performance of episodic memory in BD and SZ according to their clinical stages.

Subjects who met DSM-IV criteria for bipolar disorder ($n=43$) and schizophrenia (31), on euthymia or clinical remission, were recruited from the outpatients facilities at Hospital de Clínicas de Porto Alegre (Brazil). They were classified into two clinical stages (early or late for BD, and recent onset or chronic for SZ) and compared to 54 healthy controls. Episodic memory performance was assessed by means the Hopkins Verbal Learning Test-Revised (HVLT-R) that measures verbal learning and episodic memory in both disorders. Our results showed that patients in early stage of BD (EBD) performed better performance on the total immediate free recall ($p<0.0001$, $F=12.060$) as well as in delayed free recall ($p<0.0001$, $F=13.914$) compared to late stage (LBD) and SZ groups. In the ability to retain words learned, LBD and chronic (CSZ) were more impaired than other groups. Furthermore, the variation of learning (i.e, learning effects) along the 3 trials of immediate free recall was similar between groups.

In conclusion, we found a cognitive decline alongside with the progression of BD whereas such impairment was evident in the early of SZ. Despite this, both groups (BD and SZ) seem to maintain the ability to learn. It emphasizes the relevance of studying new therapeutic

*Corresponding author. Tel.: +55 5133598845.

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strategies, in particular, cognitive rehabilitation/remediation techniques as promissory treatment for psychiatric patients, even in those with moderate disabilities.

1. Introduction

Cognitive impairment has been consistently associated with severe psychiatric disorders like schizophrenia (SZ) and bipolar disorder (BD) (Vöhringer et al., 2013). SZ and BD present a similar cognitive deficits profile, although their degrees of dysfunction may be different (Vöhringer et al., 2013; Schretlen et al., 2013). Multiple factors such as psychotic symptoms, recurrences, chronicity, drug abuse and medication may contribute to cognitive deficits in both disorders (Au et al., 2013; Meyer et al., In Press). Memory impairment is one of the core features of cognitive and functional decline in psychiatric population (Kuswanto et al., 2013; Schaefer et al., 2013; Yatham et al., 2010).

Episodic memory (EM), an independent declarative memory system, is responsible for storage and conscious recall of past personal experiences that contains details about spatial and temporal context of these occurrences – what/when/where happened (Tulving, 2002). There is an interrelation with memory and other important cognitive domains, such as executive components and language. EM is highly sensitive to aging and to neurodegenerative diseases, and its performance is thought to be predictive of long-term outcome (Pause et al., 2013). Furthermore, in either BD or SZ, EM has been correlated with functioning in everyday life domains (Danion et al., 2007), especially in work performance (Tse et al., 2014; Gilbert and Marwaha, 2013).

A novel approach to understand severe mental disorders is to adopt a clinical staging model (Wood et al., 2011). This model is useful as it differentiates early, milder clinical phenomena from those that accompany illness progression and chronicity (McGorry et al., 2010). Staging models for SZ (Agius et al., 2010; Wood et al., 2011) and BD (Vieta et al., 2011; Kapczinski et al., 2009a,b; Berk et al., 2007) have been proposed in order to personalize and optimize treatments (Berk et al., 2009).

Although cognitive functioning is widely studied in SZ and BD, the performance of EM along the course and progression of both diseases has not yet been studied. Therefore, our goal is to ascertain whether SZ and BD show different patterns of episodic memory performance, according to their clinical stages.

2. Experimental procedures

2.1. Subjects

We included 128 subjects that were recruited throughout outpatient facilities at the Hospital de Clínicas de Porto Alegre, Brazil. The study was approved by the Institutional Review Board, and all individuals signed informed consent after the procedures were fully explained. The participants had ages between 18 and 65 years, and were allocated in six groups: 23 patients with recent-onset schizophrenia (RSZ), 20 patients with chronic schizophrenia (CSZ), 17 patients with early-stage bipolar disorder (EBD), 14 patients with late-stage bipolar disorder (LBD), 28 healthy controls matched with the recent-onset/early-stage patients (EC) and 26 healthy controls matched with chronic/late-stage patients (LC). Patients with BD were in euthymia for at least a month and patients with SZ were in symptomatic remission for at least 6 months. All patients were receiving pharmacological treatment according to previously determined protocols.

The groups of controls (EC and LC) consisted of healthy subjects selected from the pool volunteers at the hospital. They had no current or previous history and no first-degree family history of major psychiatric disorders, including dementia or mental retardation, assessed by the non-patient version of the Structured Clinical Interview for DSM-IV (SCID). They were matched for level of education with the groups of patients, following the early or late distribution.

Patients were diagnosis with BD or SZ according to DSM-IV. Euthymia in BD was defined by the total score on the Young Mania Rating Scale (Young et al., 1978) and Hamilton Depression Rating Scale (Hamilton, 1960) less than 8. Symptomatic remission in SZ was confirmed by Brief Psychiatric Rating Scale (BPRS < 15) (Romano and Elkis, 1996). Early and late classification of BD patients was established in accordance with the staging model described by Kapczinski et al. (2009b). To that end, a semi-structured interview was administered to each patient by two psychiatrists with PhD degrees previously trained in the model. The clinicians collected data on course of illness, presence or absence of psychiatric comorbidities, subjective assessment of work activity and social interactions, and self-care. Patients were stratified into early and late clinical stages by the clinicians considering the self-perception of the patient, regardless of functional status results, as follows: (1) early stage (stage I), individuals who referred the same functioning in the inter-episodic period as they did before the onset of BD; and (2) late stage (stage IV), individuals who referred being unable to maintain personal self-care and to live autonomously. Medical charts were carefully checked and the clinician responsible for each patient consulted in cases of inter-rater disagreement, so that a final decision on clinical staging could be reached. Both clinicians were blind to the results of the clinical evaluation, as well as of cognitive assessment. The same method has been successfully used previously by Rosa et al. (2014).

For SZ patients, recent-onset patients were those within first 5 years of SZ diagnosis while chronic patients had minimum of 20 years after the diagnosis of SZ. This allocation criterion is supported by previous studies (Pedrini et al., 2014).

2.2. Assessment

Subjects underwent a psychiatric evaluation to collect sociodemographic, clinical, and pharmacological data by a structured interview and examining the patients' clinical records. Experienced raters administered the scales of symptoms to assess psychiatric status.

Subsequently, the participants were assessed by trained psychologists with the Hopkins Verbal Learning Test-Revised (HVLT-R), which is a word-list task widely used in psychiatric diseases that measures verbal learning and episodic memory (Benedict et al., 1998). HVLT-R was included in MATRICS Consensus Battery for Schizophrenia (Nuechterlein et al., 2008) and in the proposed