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Review article

Neurobiological underpinnings and modulating factors in schizophrenia spectrum disorders with a comorbid substance use disorder: A systematic review

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ABSTRACT

Recently there is a growing interest in the interaction of schizophrenia spectrum disorders (SSD) and substance use disorders (SUD), a condition named dual schizophrenia spectrum disorders (SSD+). While previous research has focused on clinical and cognitive aspects, little is known about the impact of comorbidity in the brain structure and functions. Evidence suggests that dual diagnosis patients, including SSD+, show a better neurocognitive functioning during the first years of illness, followed by a serious long-term decline. The initial search retrieved 94 articles, 12 were excluded for being redundant and 49 for not fulfilling the selection criteria. Thirty-three structural and functional neuroimaging studies that compare SSD and SSD+ patients were included. Both groups exhibited more brain alterations, in comparison to only SUD patients and healthy controls. SSD+ patients are less cognitively and emotionally impaired than non-dual SSD, but worse than healthy controls. The neurobiological alterations are prominent in SSD+ after five years of illness or longer. Moreover, SUD characteristics are important modulating factors, contrary to clinical severity or specific SSD diagnosis.

Contents

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1. Introduction

In traditional terms, dual diagnosis has been defined as the comorbidity between a severe mental illness and a substance use disorder (SUD) (Di Lorenzo et al., 2014). Within this group, schizophrenia spectrum disorders (SSD) have been the most studied, because these patients have a high lifetime SUD prevalence, which has been estimated around 50% with variations depending on the substance (Bourque et al., 2013; Schiffer et al., 2010; Mancini-Marie et al., 2006; Wobrock et al., 2009). It is common that studies exclude patients with comorbidity when studying SSD or SUD, but due to its high prevalence and its clinical implications, nowadays a growing interest has emerged towards a dual diagnosis research. For this work's purpose, we will refer to this type of comorbidity as dual schizophrenia spectrum disorders (SSD+).

Both SSD and SUD are associated to brain changes and cognitive impairment. The study of brain structural and functional alterations in SSD deserves greater consideration because it appears to be a neurobiological vulnerability to psychosis, which is considered as an endophenotype in SSD (Kumra et al., 2012). In this regard, it has been found that changes in grey matter (GM) could be considered biomarkers for the illness, since deficits in temporal and frontal cortices are linked to cognitive impairments in SSD (James et al., 2011), including chronic patients, first-episode patients, prodromal stages, and even in high risk mental state individuals. Nonetheless, structural brain alterations in the concrete diagnosis of schizophrenia (SZ) have been also linked with environmental factors such as substance use, which may affect neurodevelopmental processes are known to be impaired in SZ (Bangalore et al., 2008).

Drug abuse has been discussed as an important risk factor for developing SZ (Wobrock et al., 2009), with a prevalence about 4.6 times higher than in normal population (Malchow et al., 2013a,b). SUD are associated by themselves to structural and morphological brain changes that may aggravate SSD, such as GM volume decreases (Sullivan et al., 2003) and subcortical shape abnormalities (Smith et al., 2011). For example, it has been found that cannabis has an effect on the development of psychosis in a structurally preserved brain, and after the illness onset, the drug effects can be associated to GM deficits (Cunha et al., 2013). Indeed, SUD usually have an adverse impact on the clinical course of SZ, including a greater symptom severity (Bennett et al., 2009) and suicide risk (Mathalon et al., 2003; Mancini-Marie et al., 2006; Suokas et al., 2010) and it is also related with a worse prognosis (Schmidt et al., 2011). While it is well known that both SSD and SUD have detrimental effects on cognition, patients with both conditions do not necessarily show an additional alteration or a severe cognitive deficit (Benaiges et al., 2013a,b).

The compounding implications of SSD+ in brain functions and structure have not been analyzed in enough detail and the data are heterogeneous. Some reviews have analyzed MRI data in SZ vulnerability (Seidman et al., 2003), data regarding brain morphology in cannabis abuse in SZ (Malchow et al., 2013a,b), in early SZ (Cookey et al., 2014) and in psychosis (Rapp et al., 2012). To our knowledge, there is one recent review that analyzes comorbid substance use in SZ (SZ+) and it focuses mainly on epidemiological aspects, psychosocial determinants of substance use, comorbidity theories and cognitive effects of specific substances in individuals with SZ (Thoma and Daum, 2013). Regarding structural and functional brain changes in SZ+, the authors concluded that there is not enough empirical evidence for describing a specific profile in SZ+. In our review, we encompassed key SSD+ aspects, in addition to analyzing several of its neurobiological underpinnings. Thus, structural and functional MRI studies have reported discordant results about brain shape and volume, finding from similarities to notable differences. Whilst some studies found a severe cognitive impairment (Ho et al., 2011; Epstein and Kumra, 2014) or structural deficits in SSD+ (Rais et al., 2010; Szeszko et al., 2007), one did not show significant differences between comorbid patients and those with only one disorder SSD− or SUD (Wobrock et al., 2009) whereas others even found a better cognitive performance (Mancini-Marie et al., 2006) or structural preservation (Cunha et al., 2013) in SSD+ compared to SSD−. Despite the discrepant findings, there has been observed an important pattern related to time's/temporal course being that brain differences between groups may become apparent over time. From all the variables, the phase and/or duration of illness seem to be an important modulator in brain changes, suggesting the existence of a long-term decline. In addition, there are some particular features that may alter or be linked to the outcomes, such as SUD characteristics, including type of substance and consumption severity, pharmacological treatment and patient's clinical features.

The main purpose of the present systematic review is to assess the brain structural and functional differences among persons with SSD only and persons with SSD and SUD comorbidity providing a better understanding of the neurobiological underpinnings of SSD+. With this aim, we analyzed and organized the modulating factors to find a structured explanation using the existing data, reviewing MRI structural and functional results comparing SSD+ and SSD− patients. Likewise, for analyzing the impact of course of illness, those studies taking into account the duration of illness and made a comparison between two groups were reviewed: Up to five years and over five years of illness.

2. Methods

The search, selection and critical assessment of relevant studies related to our topic was performed and reported according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Liberati et al., 2009; Urrútia and Bonfill, 2010).

2.1. Search strategy and data sources

The data search was conducted through computerized databases MEDLINE, Web of Science and Cochrane Library. The following keywords were used for the search: "Substance-Related Disorders" and "Schizophrenia", and "Magnetic Resonance Imaging" or "Image Processing, Computer-Assisted", and "Comorbidity" or "Brain/pathology". In addition, we searched for further studies by reviewing the references of relevant articles identified through the search.

2.2. Study selection criteria

The inclusion criteria comprehended articles: (a) published since January 1999 to July 2016, (b) written in English language, (c) published on-line and full text available, d) comparison between