Progress in Neuropsychopharmacology & Biological Psychiatry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

A double dissociation between two psychotic phenotypes: Periodic catatonia and cataphasia

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ARTICLE INFO

Keywords:
Schizophrenia
Endogenous psychosis
Periodic catatonia
Cataphasia
Regional cerebral blood flow
Functional brain imaging

ABSTRACT

Schizophrenia as a single liability model was confronted to the multiple psychotic phenotypes model proposed by the Wernicke-Kleist-Leonhard school, focusing on two: periodic catatonia (PC) and cataphasia (C). Both are stable and heritable psychotic phenotypes with no crossed liability and are coming with the buildup of specific residual symptoms: impairment of psychomotricity for PC and a specific disorganization of thought and language in C. Regional cerebral blood flow (rCBF) was used as a biomarker. We attempted to refute the single phenotype model by looking at relevant and specific rCBF anomalies for PC and C, that would exceed anomalies in common relative to controls (CTR), i.e. looking for a double dissociation. Twenty subjects with PC, 9 subjects with C and 27 matched controls had two MRI QUIPSS-II arterial spin labeling sequences converted in rCBF. One SPM analysis was performed for each rCBF measurement and the results were given as the conjunction of both analysis. There was a clear double dissociation of rCBF correlates between PC and C, both being meaningful relative to their residual symptomatology. In PC: rCBF was increased in the left motor and premotor areas. In C: rCBF was decreased bilaterally in the temporo-parietal junctions. Conversely, in both (schizophrenia): rCBF was increased in the left striatum which is known to be an anti-psychotics' effect. This evidence refutes the single schizophrenia model and suggests better natural foundations for PC and C phenotypes. This pleads for further research on them and further research on naturally founded psychotic phenotypes.

Clinical trial: Name of the registry: ClinicalTrials.gov
Identification: NCT02868879

1. Introduction

The field of endogenous psychoses (Foucher and Stöber, in press) is the one for which “cerebral diseases hypotheses” are the most likely in psychiatry. But the failure to validate schizophrenia as a model has generated a great skepticism against the traditional naturalist paradigm of scientific medicine which supposes the existence of “natural morbid entities”, i.e. diseases (Boorse, 1977). According to this framework, a disease is a biological model of the “pathological dysfunction” able to account for a specific phenotype, i.e. clinical manifestations. The validation process of a disease model generally starts with the “correlation method” (de Saint-Maur, 2012), looking for a robust and specific association of the putative phenotype with a biomarker. We questioned the “single” schizophrenia model and confronted it to the “multiple” psychotic phenotypes model proposed by the Wernicke-Kleist-Leonhard (WKL) school focusing on two of them: periodic catatonia (PC) and cataphasia (C).

As the other ICD/DSM diagnoses, schizophrenia and schizo-affective disorders were constructed by consensus, a procedure that only favors minimal common views. Following Carl Hempel, Rober Spitzer only focused on the strengthening of their reliability (Hempel, 1961), not questioning their natural foundations as proposed by Eli Robin and Samuel Guze (Robins and Guze, 1970). Definitions of natural phenotypes are generally constructed by an optimization process consisting in a back and forth between observation and description, which could not go on if the definition remained fixed (Foucher and Bennouna Greene,

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https://doi.org/10.1016/j.pnpbp.2018.03.008
Received 8 December 2017; Received in revised form 5 March 2018; Accepted 9 March 2018
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2010). To our knowledge, only the Wernicke-Kleist-Leonhard (WKL) school sustained this optimization effort over three generations, guided by three specifications of the principle of parsimony (Foucher and Stöber, in press) (see S1). This ended up with the distinction of 35 major phenotypes which span from affective to psychotic disorders, with 22 of them being able to fulfill the DSM-5's schizophrenia diagnosis (Leonhard, 1999). All have a good reliability (Pfuhlmann et al., 1997), but also excellent predictive validity (Pethő et al., 2008) and differential validity on age of onset, inheritance, fetal event and treatment response (Foucher and Stöber, in press).

Previous attempt to select among the best categorical model used heritability as an external validator. The WKL framework outperformed the DSM-III in a twin study (Franzek and Beckmann, 1998) and more recently the DSM-IV, ICD-10 and an exploratory latent class analysis in a multiplex family study for predicting heritability (Peralta et al., 2016). We wanted to push the same question a little bit further in looking at brain correlates of these phenotypes.

For the purpose of this study, both schizophrenia and schizo-affective disorders, as operationalized in the DSM-5, were considered together as being part of the “single” schizophrenia model, which was confronted to the WKL “multiple” phenotypes model. Only two of the phenotypes that are regularly taken for schizophrenia were used because of their frequency: C and PC. Both have an estimated prevalence between 0.1 and 0.2% of the West-European population (Jabs, 2005). Depending on the episode, both phenotypes generally fall within the schizoaffective and schizophrenic disorders according to ICD/DSM criteria although other diagnosis such as depressive, bipolar, or non-otherwise specified bipolar or psychotic disorders might be determined for an episode (Neumärker et al., 1995). Both typically have a bipolar relapsing-progressive course. This means that both excited and inhibited phases can be observed and that their respective specific residual symptoms will progressively increase especially after each relapse. Both phenotypes are among the most hereditable WKL “psychotic” phenotypes, with affected first degree relatives' percentage, ranging between 15 and 26% depending on the study (Jabs, 2005; Stöber, 2001; Stöber et al., 2000). PC has a major susceptibility locus on chromosome 15q15 (MIM 605419) (Stöber et al., 2000). Importantly, C and PC appear to be independent phenotypes as there is no crossed inheritance (Jabs, 2005; Stöber, 2001). The core residual symptoms of the cataphasic phenotype consist in a disordered logic or incoherence and a specific language disorder, affecting both syntax and semantic (Leonhard, 1999). This is especially present during the episode, variably associated with unspecific affective or psychotic features, but it is also more and more apparent between the episodes while the phenotype progresses. Conversely, the core residual symptoms of PC consist in a quantitative and qualitative disorder of psychomotricity (Leonhard, 1999).

This study intends to confront the single schizophrenia model to the PC and C independence model, using a comprehensive biological marker, the whole brain regional cerebral blood flow (rCBF). We anticipated two main issues. 1) PC and C show the same rCBF changes in the same brain regions relative to controls (CTR), without any phenotype-specific changes. This would validate schizophrenia as a single liability model, especially if the changes had some relevance for psychosis proneness. 2) PC and C have specific anomalies, and these anomalies are relevant with their core symptoms. This would refute, in the Popperian sense, the single schizophrenia model and provide some validation to PC and C as independent phenotypes. Specificity was operationalized as a double dissociation between PC and C (Dunn and Kirsner, 2003), which means that PC had to differ from CTR in the same regions than it differed from C and vice versa.

2. Material and methods

2.1. Participants

Thirty-one patients were recruited by WKL-trained psychiatrists (MR, OM, SW, FB, JF) from the non-invasive neuromodulation center, the schizophrenia expert center (Schürhoff et al., 2015) and the university psychiatric ward of Strasbourg, by convenience sampling method. They had to be right-handed, aged between 18 and 65 years, in outpatient setting, stabilized for more than a month and fulfill the double diagnoses of DSM-5's schizophrenia or schizo-affective disorder (American Psychiatric Association, 2013) and WKL's periodic catatonia (PC) or cataphasia (C). Although the screening was based on the original description of these phenotypes (Leonhard, 1999), for replicability, patients also had to fulfill operationalized criteria for these phenotypes designed to favor specificity over sensitivity (see S1). Exclusion criteria included MRI contraindication, neurological history, current drug abuse except nicotine and past electroconvulsive therapy. Twenty-eight controls subjects were included, matched by age, sex and year of education with the patients' group. Exclusion criteria were the same but adding any significant personal or family psychiatric history using both the screening level 1 instrument proposed in the DSM-5 (American Psychiatric Association, 2013) and medical interview. The study protocol complies to the declaration of Helsinki (World Medical Association, 2013) and was approved by the local ethic committee. Each participant signed informed consent and received compensation for their participation.

All subjects were appraised for handedness by the Edinburgh inventory (Oldfield, 1971), IQ was estimated using the French National Adult Reading Test or fNART (Mackinnon and Mulligan, 2005) and the Mill Hill Vocabulary Scale synonym section (part B) as a rating of conceptual ability (Raven, 1998). Patients' general psychopathology was evaluated using the positive and negative syndrome scale (PANSS) (Kay et al., 1987), with a special attention to depressive symptoms using the Calgary Depression Scale (CDSS) (Addington et al., 1992) and according to the eight dimensions of the Clinician-Rated Dimension of Psychosis Symptom Severity (CRDPSS) (American Psychiatric Association, 2013). Specific catatonic symptoms were evaluated using the Bush and Francis Catatonia Rating Scale (BFCRS) (Bush et al., 1996) whereas specific cataphasic symptoms were evaluated using the French version of the psychic experimental test operationalized for Cataphasia (TePEO-C) (Mainberger, 2015), an operationalized version of the test used by the WKL school for thought and language disorders. Antipsychotics doses were converted to olanzapine equivalent (OLZ) (Leucht et al., 2016), and benzodiazepines doses were converted to diazepam equivalent (DZP) (Brett and Murnion, 2015).

2.2. Imaging protocol

The scanner was a 3 Tesla VERIO with a 32-channel head receiver antenna (Siemens, Erlangen, Germany). All scanning session took place in the morning, and participants were instructed to have a good night before, not taking more than one cup of coffee and not more than the nicotine equivalent of two cigarettes before the scanning session. After the acquisition of a 3D T1-weighted (MP-RAGE), a FLAIR 3D anatomical volume and a field map, participants passed two sets of arterial spins labeling images covering the whole brain using an EPI based QUIPSS-II sequence (Wong et al., 1998) both acquired while subjects were in different cognitive sets (see below). The first was a “pure ASL” sequence, thanks to a short TE of 9.7 ms, while the second was an “ASL-BOLD” sequence by using a long TE of 21 ms (Foucher et al., 2011a). Except for the number of volumes and acquisition time (101 vol in 5 min for pure ASL, 405 vol in about 20 min for ASL-BOLD), all imaging parameters were kept the same: TR = 3000 ms, TI1 = 600 ms, TI2 = 1325 ms, flip angle = 90°, resolution = 4 × 4 × 4 mm. The ASL signal was computed after rigid registration of the EPI series and

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