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# Neurocognitive similarities between severe chronic schizophrenia and behavioural variant frontotemporal dementia

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ABSTRACT

This study focuses on a group of patients with chronic schizophrenia who have a more severe form of the disorder, as indicated by socio-functional decline, treatment resistance, and recurrent hospitalisation. Previous research has suggested that the pattern and severity of cognitive deficits in people with severe chronic schizophrenia is similar to that observed in behavioural variant frontotemporal dementia (bvFTD). In the current study, we compared neurocognitive performance in 16 cognitive domains in 7 inpatients with severe chronic schizophrenia, 13 community-dwelling outpatients with chronic schizophrenia, 12 patients with bvFTD, and 18 healthy controls. Our findings revealed more similar cognitive profiles between the schizophrenia inpatient and bvFTD groups compared to the schizophrenia outpatient group, who outperformed the former groups. The current results provide preliminary evidence for a distinct schizophrenia subgroup, distinguishable from other chronic schizophrenia patients by poorer clinical and functional status, who have levels of cognitive impairment comparable to those seen in bvFTD patients.



## 1. Introduction

Schizophrenia was first conceptualised by Emil Kraepelin as "dementia praecox", a group of three disorders of "insanity" with adolescence-to-young-adulthood onset and a progressively deteriorating course culminating in dementia (Kraepelin, 1987; McKenna, 2007). Kraepelin emphasised the involvement of the frontal and temporal lobes, as well as corresponding executive dysfunction, in dementia praecox. The current consensus is that schizophrenia is not a dementia, but Kraepelin's concept of dementia praecox may yet apply to some patients, especially those who are the most severely unwell. These are the patients subjected to recurrent hospitalisation and who are reliant on carers when living in the community. This subtype of schizophrenia has been termed "Kraepelinian schizophrenia" (Keefe et al., 1987) and "poor-outcome schizophrenia" (Mitelman and Buchsbaum, 2007). Some of these patients have cognitive and daily functioning levels similar to that seen in dementia, with a pattern resembling the behavioural variant frontotemporal dementia (bvFTD), including severe executive and memory impairments and fronto-temporal hypoperfusion (de Vries et al., 2001). A key clinical role of our specialist neuropsychiatry unit is to assess patients with chronic schizophrenia who are referred for investigations of possible dementia, due to functional decline over and above that expected in schizophrenia. It is noteworthy that these more severely-unwell schizophrenia patients are often excluded from research studies investigating cognition because of issues with "testability" and compliance.

FTD, a younger-onset dementia, is the most common clinical syndrome associated with frontotemporal lobar degeneration (Neary et al., 2005). This pattern of neurodegeneration may manifest clinically as bvFTD or as one of several variants of language disorders – semantic dementia (SD), progressive non-fluent aphasia (PNFA), and logopenic progressive aphasia (LPA) (Gorno-Tempini et al., 2004; Gorno-Tempini et al., 2011). The current research focused only on the bvFTD population. The characteristic neuropsychiatric disturbances in bvFTD include behaviour and personality change, loss of empathy and insight, emotional blunting, apathy, and executive dysfunction (Gregory et al., 1998; Neary et al., 1998b; McKhann et al., 2001). These features are also seen in people with chronic schizophrenia (Weinberger, 1988; McKenna, 2007), which can result in challenging differential diagnosis between the two disorders (Woolley et al.,

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2011), particularly when age of onset is younger in bvFTD compared to other dementias. The overlap in clinical presentation in bvFTD and schizophrenia mainly pertains to negative symptoms, although behavioural disinhibition is seen in both disorders. Frank psychosis is thought to be rare in bvFTD (Mendez et al., 2008), but the rates of occurrence may differ as a function of age. We have previously reported that younger patients with bvFTD can present initially with a schizophrenia-like psychosis (Velakoulis et al., 2009b). Some patients with late-onset schizophrenia (LOS) have been shown to have FTD-like neuropathological abnormalities (Velakoulis et al., 2009a). While grey and white matter abnormalities are typical of both schizophrenia and FTD (Shenton et al., 2001; Buchsbaum et al., 2006; Schroeter et al., 2008; Looi et al., 2012), the current consensus is that these brain changes are progressive only in FTD. Nevertheless, schizophrenia may also be associated with progression in brain abnormalities (DeLisi, 2008) and there may be an absence of atrophy in a subset of patients with so-called non-progressive FTD (Kipps et al., 2007). Two very recent reviews have investigated the relationship between schizophrenia and FTD from a number of perspectives, including phenotypic or clinical overlaps and shared genetic and pathophysiologic mechanisms (Cooper and Ovsiew, 2013; Harciarek et al., 2013). While a definitive link between the two disorders was not found (Cooper and Ovsiew, 2013), it remains a possibility that the same causal mechanisms are involved early in schizophrenia and late in FTD in some cases (Harciarek et al., 2013).

In the absence of "hard" evidence supporting a relationship between schizophrenia and bvFTD, comparative studies in neuropsychology can provide useful information about the level and profile of impairment in each disorder. Such information has implications for daily functioning and disorder-specific brain-behaviour relationships (Goldberg et al., 2001) and for clinical differentiation between the disorders. Only a few studies have directly contrasted neurocognition in schizophrenia and bvFTD. Zakzanis et al. (2001) identified performance overlap on 34 out of 38 individual test variables between 32 patients with LOS (average age of onset was 48 years) and 12 bvFTD patients. bvFTD patients were significantly more impaired in letter fluency, category fluency, and concept formation/set-shifting, whereas LOS patients were significantly worse on digit span. A second study (Ziauddeen et al., 2011) compared 11 bvFTD patients and 12 patients with negative syndrome chronic schizophrenia patients in executive functioning – bvFTD patients had significantly reduced category fluency and inhibition ability, but the differences were not significant in letter fluency, cognitive estimation, letter-number sequencing, rule attainment, and on a naturalistic multi-tasking test. In a third study, probabilistic association learning, which is thought to rely on intact fronto-striatal function, was found to be equally impaired in nine bvFTD patients and 24 patients with schizophrenia/schizoaffective disorder (Weickert et al., 2013). Lastly, in a Dutch study, bvFTD patients were more impaired on the Mini-Mental State Examination (Folstein et al., 1975) and Frontal Assessment Battery (Dubois and Litvan, 2000) (a measure of executive functioning) than elderly schizophrenia patients (Sanders et al., 2012). Taken together, these studies imply that schizophrenia and bvFTD share many similarities on comprehensive neuropsychological testing, and the lack of a consistent pattern of deficits across studies is likely due to the different subtype of schizophrenia under study.

In summary, there is increasing recognition of possible links between schizophrenia and bvFTD. We postulate that these overlaps may be most apparent in a poorly-functioning Kraepelinian subtype with a dementia-like cognitive and functional status. Kraepelinian patients may differ from those patients with chronic schizophrenia who with treatment eventually stabilise in their clinical picture and are able to maintain some degree of functional and occupational independence (although never quite recovering to pre-morbid levels). Functional and cognitive deficits are thought to be strongly associated in schizophrenia (Mitelman and Buchsbaum, 2007). Consistent with this, previous research has found inpatients with schizophrenia to be more impaired in both global cognition and specific cognitive domains compared to community-dwelling patients with schizophrenia (Irani et al., 2011). A pilot study has reported more impaired executive functioning and fine motor dexterity in Kraepelinian compared to non-Kraepelinian patients (Roy et al., 2003).

In the current study, we aimed to compare the neurocognitive profiles of chronic schizophrenia outpatients (Scz), chronic schizophrenia inpatients conforming to the Kraepelinian schizophrenia subtype (KScz), patients with bvFTD and healthy controls (HC) across major cognitive domains. We hypothesised that (i) the KScz and bvFTD groups would demonstrate very similar performances across cognitive domains, whereas there would be greater difference in the Scz-bvFTD profiles in terms of severity of impairment, and (ii) compared to the control groups, the Scz group would be the least impaired among the patient groups.

## 2. Method

### 2.1. Participants

All potential participants were screened concurrently and recruited into the study if they met the inclusion criteria specific to each group. Exclusion criteria for the patient groups were a significant substance abuse history or a co-morbid condition (e.g., neurological, psychiatric, acquired brain injury) deemed by multidisciplinary consensus to have substantially contributed to a patient's clinical presentation.

#### 2.1.1. Chronic schizophrenia outpatient group (Scz)

Thirteen participants meeting DSM-IV-TR (American Psychiatric Association, 2000) criteria for schizophrenia were recruited. "Chronic schizophrenia" was defined as illness duration of five years or more. Three individuals were recruited via outpatient referrals by consultant neuropsychiatrists based at our clinical unit, the Neuropsychiatry Unit (NPU) of the Royal Melbourne Hospital (RMH), Melbourne. Ten participants were recruited from the volunteer database managed by the Australian Schizophrenia Research Bank (ASRB), an Australia-wide schizophrenia research initiative. All ASRB patient volunteers have a confirmed diagnosis of schizophrenia according to DSM-IV/ICD-10 diagnostic criteria (ASRB, 2013). These 10 individuals had all responded to advertising material from the ASRB and had voluntarily signed up to be involved in research projects.

All 13 participants had been living in the community for a number of years at the time of testing. Ten individuals were engaged in either part-time or full-time employment or voluntary work, two held employment up until the past year, and one was on a pension. Ten participants were on atypical antipsychotic medication (information was unavailable for one individual).

#### 2.1.2. Chronic schizophrenia inpatient group (KScz)

The KScz group comprised six inpatients who met DSM-IV-TR criteria for schizophrenia and one who met DSM-IV-TR criteria for schizoaffective disorder. Two other participants with chronic schizophrenia were excluded from the study due to inability to complete testing. Diagnoses were made by multidisciplinary teams which included neuropsychiatrists, psychiatrists, neurologists, neuropsychologists, and occupational therapists, based on detailed medical/psychiatric file review, information from referring doctors and families/carers, structural and functional imaging, as well as extensive cognitive–behavioural–emotional and occupational therapy assessments. All patients with a schizophrenia/schizoaffective disorder diagnosis at the NPU and the Adult Mental Health Rehabilitation Unit (AMHRU) at Sunshine Hospital, Melbourne, were screened for their suitability for the study. Four participants were recruited from the NPU, which is a highly specialised tertiary/quaternary referral unit for the assessment and treatment of patients with neuropsychiatric conditions. Three participants were recruited from AMHRU, which is a regional service providing rehabilitative care for patients with severe, refractory mental disorders.

All the participants in this group met Keefe et al.'s (1987) criteria for Kraepelinian schizophrenia: (i) none were living independently and all were reliant on carers (family member or healthcare professional) for basic necessities such as food and shelter for the past five years, (ii) most had no gainful employment – five were unemployed, one had intentions to resume part-time study, and another (who was living in a residential care facility) was working part-time as a kitchen hand, and (iii) all had experienced recurrent hospitalisation with an unremitting clinical course. Six patients were on atypical antipsychotic medication (information unavailable for one patient).

#### 2.1.3. bvFTD group

All bvFTD patients admitted to the NPU during the study period were screened for inclusion into the study. Fourteen participants who met clinical, imaging, and

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