

## Right prefrontal hypometabolism predicts delusions in dementia with Lewy bodies

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### Abstract

Delusions (DEL) are frequent in dementia with Lewy bodies (DLB); however, the neural equivalent is poorly understood. The present study therefore aimed to identify the cerebral metabolic pattern of glucose of a DLB group suffering from DEL (DLB + DEL) as compared to a non-delusional group (DLB – DEL) and a control group (NL); and to determine the predictive value of the regional metabolic deficit for DEL symptomatology in comparison to other clinical variables significantly associated with DEL. Voxel-wise comparisons were conducted between the patient and control groups in SPM2. The most significant regional metabolic deficit of the DLB + DEL group was used a predictor for DEL symptomatology in a logistic regression analysis along with other variables significantly associated with DEL, such as visual hallucinations (VH), and overall cognitive impairment. A significant relative hypometabolism of the right prefrontal cortex was found in the DLB + DEL group, which predicted DEL symptomatology in the regression analysis. VH and overall cognitive dysfunction were no significant predictors. These results underline the significance of right prefrontal damage for DEL in DLB.

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### 1. Introduction

In 1990, dementia with Lewy bodies (DLB) was first described as a distinct neuropathological and clinical entity of dementia in the elderly. According to these studies, DLB is the second most common cause of dementia after Alzheimer's disease (AD) (Hansen et al., 1990). Patients with DLB share many clinical features with typical AD, including progressive cognitive decline, age at symptom onset, family history, the duration of the disease, and the severity of brain

atrophy (McKeith et al., 1996). However, there are also symptoms that distinguish DLB from AD without significant Lewy body pathology. Current consensus criteria (Geser et al., 2005) emphasize fluctuations of attention and alertness, spontaneous motor features of Parkinsonism, and recurrent visual hallucinations (VH) as the core features of DLB. Further supportive features include repeated falls, sensitivity to antipsychotic medication, depression, and delusions (DEL). Although psychotic symptoms also occur in AD, they are particularly frequent and distressing in DLB (Ballard et al., 1999). They also have a significant impact on caregiver distress (de Vugt et al., 2006) and early institutionalization (Kim et al., 2002). It has furthermore been reported that patients with psychosis experience faster cognitive decline (Forstl et al., 1993). According to a comprehensive review by Simard et

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al. (2000) on the frequency of different psychotic syndromes in DLB, VH were the most prevalent, followed by DEL. The misidentification syndromes, including the Fregoli (belief that different people are in fact a single person who changes appearance or is in disguise) and the Capgras syndromes (belief that an acquaintance has been replaced by an identical looking impostor) were the most frequent delusional syndromes at any stage of DLB (32.7%). They were followed by paranoid DEL (28.6%), encompassing the Othello syndrome (belief that the spouse or sexual partner is being unfaithful). In spite of the clinical relevance of psychotic symptoms in DLB, little evidence exists on their neurobiological substrate and available treatment options are still unsatisfactory. Although cholinesterase inhibitors showed promising effects (Fischer et al., 2007), hypersensitivity to antipsychotics is frequent. Severe adverse reactions include sedation, delirium, Parkinsonism, accelerated cognitive decline, and even death (Ballard et al., 1998). Identifying factors associated with psychosis in DLB and exploring its pathophysiological substrate is therefore of great relevance for the improvement of therapeutic interventions.

The present study had two main goals. First, we wished to explore the metabolic pattern of delusional patients with DLB using  $^{18}\text{F}$ -fluoro-2-deoxy-glucose positron-emission-tomography ( $^{18}\text{F}$ -FDG PET). Second, we aimed to investigate the predictive value for delusional symptomatology of regional metabolic alterations and clinical variables associated with DEL. Emerging evidence indicates that psychosis and many other psychiatric and behavioral symptoms are a fundamental expression of neurodegenerative disease, in addition to memory deficits and other cognitive problems. However, the specific etiologic factors and pathophysiological mechanisms that are involved remain unclear. It has been previously reported that hypometabolism or hypoperfusion of the right prefrontal cortex was associated with the occurrence of DEL in patients with AD, emphasizing that functional abnormalities are sensitive markers in the pathophysiology of DEL (Staff et al., 2000); nevertheless, there are also reports that stress the level of the general level of cognitive impairment as a risk factor for the occurrence of DEL (Fischer et al., 2006). Furthermore, data from patients with psychosis due to neuropsychiatric disorders other than AD support a role for frontal dysfunction in the expression of delusional thoughts, although other brain regions may also be involved. Most functional magnetic resonance imaging (MRI) studies reported reduced activation of the dorsolateral prefrontal cortex in first episode (MacDonald et al., 2005) and chronic schizophrenic patients (Volz et al., 1997). Other studies suggest that the dysfunction of the dorsolateral prefrontal cortex is even evident prior to the initial onset of psychosis in individuals at high risk for schizophrenia (Fusar-Poli et al., 2007). While a unitary mechanism for DEL across different disorders is intriguing, additional data are needed, and disease-specific factors probably play an important role.

The measurement of the regional cerebral metabolic rate of glucose (rCMRglc) is an established *in vivo* surrogate

marker of synaptic activity. This method has been extensively evaluated and many studies showed that it is a valuable tool for the early and differential diagnosis of neurodegenerative disorders such as AD (Herholz et al., 2002), frontotemporal lobar degenerations (Diehl-Schmid et al., 2007), or DLB (Kono et al., 2007), even in very mild stages (Pernecky et al., 2007b). Most studies in DLB and Parkinson's disease (PD) reported a stronger functional involvement of posterior brain regions than in AD, including the primary visual cortex (Ishii et al., 1998). Boecker et al. (2007) reported a significant rCMRglc reduction in the ventral and dorsal visual streams in patients with PD, who had experienced VH in the past four weeks before their brain scans had been compared with non-hallucinating patients. These significant differences were found although none of the patients had hallucinated during the image acquisition. Higuchi and colleagues (2000) even suggested a correlation between neuropathological findings and reductions of the rCMRglc in patients with DLB. However, the association between structural pathology and DEL symptomatology in DLB has not yet been determined.

## 2. Methods

### 2.1. Study sample

Twenty-one patients with mild to moderate probable DLB, who were consecutively recruited at a university-based neurologic clinic, were included. The dataset had previously been used in a study on cognitive reserve in DLB (Pernecky et al., 2007a). All patients underwent the identical thorough clinical evaluation and the diagnosis of DLB was established by consensus between two experienced neurologists according to current diagnostic guidelines (McKeith et al., 2005). The diagnostic set-up included neuropsychological testing, routine blood sampling, physical examination, and structural (MRI) and functional ( $^{18}\text{F}$ -FDG PET) imaging of the brain. The neuropsychological assessment was based on the German version of the Consortium to establish a registry for Alzheimer's disease neuropsychological assessment battery (CERAD-NAB) (Morris et al., 1988; Thalman and Monsch, 1997), which incorporates the mini-mental-state examination (MMSE) (Folstein et al., 1975). In addition, a total score of the CERAD-NAB was calculated for each patient according to recently published criteria (subtest addition method) (Chandler et al., 2005), because this score allows for a more comprehensive rating of global cognitive function than the MMSE. Briefly, total scores were obtained by summing scores from the individual subtests (excluding the MMSE score) into a total composite score (maximum for verbal fluency set at 24 points, maximum total score 100 points). Neuropsychiatric symptoms, such as frequency and severity of DEL and VH within the past four weeks prior to the examination, were rated on the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). The severity of Parkinsonian symp-

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