**IMAGING IS A PROMISING BIOMARKER FOR ALS: NO**

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The need for biomarkers in ALS has recently been enforced by the successful staging effort by the group of Heiko Braak (Brettschneider et al., 2013). It has been shown that the spreading of the molecular marker TDP-43 follows a stereotyped pattern which involves the association fibres of the cerebral cortex and also the corticofugal, monosynaptic tracts (Braak et al., 2013). We have recently shown in a cross-sectional effort in more than 80 patients that these alterations of fiber tracts are mirrored by DTI changes of the corticofugal tracts which permit definition of patient groups *in vivo* (Kassubek et al, in press).

However, even if this effort results in the demonstration of longitudinally defined clinical stages of ALS, this has only a limited value for the definition of the clinical picture and the prognosis of the patient since major prognostic factors are not represented by defining the tract disease alone:

1. Anterior horn cell loss determines the advent and severity of respiratory deficits of ALS patients which are the major cause of death. Tract disease does not reliably predict the severity of anterior horn cell disease, as exemplified by the ALS variant primary lateral sclerosis.
2. The prognosis of the patient is not only determined by the tract disease, but also by the involvement of the frontal cortex. We know that patients suffering from severe behavioral and cognitive deficits have a worse prognosis than those having minor deficits.
3. The prognosis of the patient is also largely defined by metabolic deficits, such as BMI, triglycerides and cholesterol levels. We have evidence that the loss of appetite and the resulting weight loss may be largely dependent from an impairment of central, potentially hypothalamic, metabolic regulation. A potential relation of hypothalamic deficits to motor deficits has not been demonstrated yet and seems clinically unlikely.

A definition of ALS stages by DTI imaging of corticofugal tracts is a major step into the direction of the development of relevant biomarkers for ALS by potentially reducing the noise of future studies. It is, however, likely that current approaches are not sufficient to define the most relevant clinical aspects of ALS, in particular prognosis.