

## SCAIFIELD Scientific Abstract:

The spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of autosomal dominantly inherited disorders that are clinically characterized by progressive loss of balance and coordination. Brain pathology of SCAs centers around the cerebellum and brainstem. The most common SCAs (SCA1, SCA2, SCA3, and SCA6) are caused by instable expansions of polyglutamine encoding CAG repeats which led to the designation of these diseases as polyglutamine SCAs. Based on a greatly increased understanding of the pathobiology of polyglutamine SCAs, new treatments that aim at silencing the disease genes are close to clinical trials. These approaches are particularly promising, if applied as preventive therapies in presymptomatic mutation carriers. For any trial, whether therapeutic or preventive, meaningful and sensitive biomarkers that reflect disease state and severity are of critical importance. Cerebellar and brainstem regional volumes derived from 3T MRI studies are useful tools to assess SCA-related alterations, but are in no way sufficient in view of the challenges to the required specificity and sensitivity of clinical biomarkers in upcoming clinical trials. Ultra-high field MRI (UHF-MRI) has an enormous potential to detect and monitor structural and chemical brain changes at an unprecedented level of detail that cannot be achieved with 3T. However, technical shortcomings caused by field inhomogeneities at 7T that degrade image quality of the cerebellum and brainstem have so far prevented the exploitation of UHF-MRI to study SCAs. Overcoming these technical challenges by utilizing novel parallel transmission (pTx) MRI technology, the application of quantitative MRI at 7T in SCAs will mark a breakthrough with direct translational impact for SCAs.

Our goal is to establish quantitative UHF-MRI biomarkers for polyglutamine SCAs with high potential for detecting early disease manifestation and monitoring progression. We will explore high-resolution multi parametric mapping (MPM) of brain structure, which provides estimates of MR relaxation times ( $T_1$  &  $T_2^*$ ), proton density (PD) and magnetization transfer saturation (MTsat). Additionally, we will utilize diffusion weighted imaging (DWI) to quantify brain connectivity and tissue microstructure, quantitative susceptibility mapping (QSM) to estimate tissue iron load, and arterial spin labeling (ASL) to quantify brain perfusion. Finally, brain metabolism will be explored with molecular imaging, namely MR spectroscopic imaging (MRSI) and chemical exchange saturation transfer (CEST) imaging. All sequences will be tailored for imaging the cerebellum and brainstem and for convenient application in patients. Firstly, UHF-specific transmit field inhomogeneities, which are specifically challenging in the cerebellum and brainstem, will be mastered with novel pTx technology. Secondly, fast sequences will be implemented to acquire all contrasts in short, patient-friendly acquisition times.

The project partners contribute complementary expertise: the MR Physics group at DZNE (Bonn) will implement fast quantitative UHF-MRI sequences, which utilize the pTx technology developed by NTNU (Trondheim), while data analysis and parameter mapping will be developed by GIGA-CRC (Liege). Finally, a multicenter study involving all participating sites that applies the new UHF-MRI sequences will be coordinated by DZNE Clinical Research (Bonn).