

Supplement 2. Liste of Subprojects BeLOVE STROKE STRATUM

Subprojects BeLOVE STROKE STRATUM	Title/ Subject	Hypothesis
Depression, Cognitive impairment, Epilepsy	Lesion-network mapping of post-stroke symptoms and long-term outcome	We hypothesize that we will be able to identify specific networks that are affected in stroke patients based on our three primary outcome parameters (mRS, CI, and depression) and ultimately be able to predict outcome based on acute lesion location and the associated anatomical and functional connectivity using lesion-network-mapping.
Depression	Common and specific predictors of depressive symptoms three months after an acute cardiovascular event: data from the Berlin Longterm Observation of Vascular Events (BELOVE)	Specific baseline variables are predictive markers of depressive symptoms at 90 days following stroke or myocardial infarction.

stroke-heart syndrome	Cardiac blood biomarkers in acute ischemic stroke	Hypotheses: - elevated MR-proANP levels at day 0-7 are associated with cardioembolic stroke etiology - a higher stroke severity (measured via NIHSS at admission) and larger lesion volume (measured in cMRI at baseline) is associated with higher MR-proANP at day 0-7/3months/2 years -elevated MR-proANP levels (>120 pMol/L, quartiles, continuous) at day 0-7 are associated with: a) a higher rate of unfavorable functional outcome (defined as smRS >1) at day60 and 1year as well as a shift towards higher disability (sMRS as ordinal variable) at day 60 and 1 year b) all-cause mortality at d90/ 1 year -> We state the same hypotheses for the biomarkers nt-proBNP, hs-cTnT, Copeptin and IL-6, respectively. -We furthermore hypothesize that elevated MR-proANP levels at day0-7 are associated with a worse cognitive outcome (measured via MOCA test at V3 months and 2 years). -The discriminatory accuracy of the NIHSS at admission to predict mortality and functional outcome at d90 and d365 respectively is improved when combined with MR-proANP levels at day0-7. -elevated MR-proANP levels (>120 pMol/L, quartiles, continuous) at the timepoint 3 months are associated with: a) a higher rate of unfavorable functional outcome (defined as smRS >1) at 1 year as well as a shift towards higher disability (sMRS as ordinal variable) at 1 year b) all-cause mortality at 1 year -> We state the same hypotheses for the biomarkers nt-proBNP, hs-cTnT, Copeptin and IL-6, respectively. Longitudinal focus: We hypothesize, that patients who develop a rise of cardiac biomarkers in the during the first months after stroke, have a worse functional outcome, higher rate of mortality and worse cognitive outcome: -Patients with a rise of >20% (>50%) of the measured MR-proANP values at 3 months compared to the value at 1 year show a) a higher rate of unfavorable functional outcome (defined as smRS >1) at 1 year as well as a shift towards higher disability (sMRS as ordinal variable) at 1 year b) a higher rate of all-cause mortality at one year -> We state the same hypotheses for the biomarkers nt-proBNP, hs-cTnT, Copeptin and IL-6, respectively. -We hypothesize that an elevated MR-proANP levels (>120 pMol/L) measured at day0-7 is associated with AFDAS at hospital discharge as well as after three and twelve months. Furthermore, we hypothesize that those patients with a rise of MR-proANP >20% between the measurement at day 0-7 and 3 months have a higher AFDAS rate at three month and twelve month after stroke. We expect the same associations for the other cardiac biomarkers of interest. -We furthermore hypothesize that elevated an elevated MR-proANP levels (>120 pMol/L) measured at V1 is associated with the detection of diastolic/systolic cardiac dysfunction (detected in TTE or CMR) at V3 and V6. Also, we expect an association of elevated MR-proANP values at V1 with detection of myocardial fibrosis on CMR (late Gadolinium enhancement [LGE] in CMR) at 3 months and 2 years and with the diagnosis of new myocardial infarction at one year after stroke.
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White matter microstructural (quantitative multiparametric mapping)	Normal appearing white matter microstructural changes assessed by quantitative multiparametric mapping: a BeLOVE- Study.	1. Cardio-/cerebrovascular risk factors play a significant role in progression of CSVD depicted by MRI biomarkers which can already lead to microstructural changes in the NAWM surrounding visible white matter lesions. 2. The changes in NAWM as compared to completely normal white matter will have a significant correlation to cognitive status and cardio-/cerebrovascular risk profile of patients.
cognition (1)	Devising a personalized risk stratification and holistic management for prevention of cognitive decline in patients with different cardiovascular phenotypes: the DORIAN-GRAY project	Through pooling of data with other European databanks and using a state-of-art framework for modelling and simulation (namely: digital twin) we will be able to define classes of risk for mild cognitive impairment in individuals with CVRFs

cognition (2)	Trajectories of cognitive function after stroke and frequency of post stroke cognitive impairment and recovery in the BELOVE COHORT	no specific statistical hypotheses due to an explorative reasearch question. Our reseach aim is to determine the frequency of CI after stroke
quality of life	Quality of Life after Stroke	1) HRQOL in patients with stroke differs compared to the general population and is similar to published stroke cohorts from the US and Netherlands. 2) Patients differ in HRQOL subdomains depending on type of stroke and stroke severity. 3) Despite the same clinician-reported disability (defined by mRS), there are different clinical symptom profiles. 4) Shorter HRQOL questionnaires (here EQ-5D-5L) are easy to use, but there are systematic differences between EQ-5D-5L, SS-QOL and PROMIS-29 questionnaire.
cognition (3)	Exploring Sex Differences and Menopause in Brain Perfusion and Mild Cognitive Impairment in Patients with Vascular Risk	Model 1: Though females demonstrate higher whole brain (and varied regional) perfusion than males prior to menopause, due to the expected age of the Belove participants, we anticipate most will be postmenopausal and thus have similar perfusion compared to males. Model 2: Higher Framingham scores, a measure of CVD risk, will be associated with reduced brain perfusion with significant interaction between sex and Framingham score. Model 3: Higher Framingham score and lower brain perfusion will be associated with lower MoCA score. The association between Framingham risk score and perfusion will be different between males and females.

gait	Investigating brain network interaction across behavioral domains to guide therapeutic stimulation for gait	Our central hypothesis is that we can use the existing clinical and imaging data from the BELOVE cohort with ischemic brain lesions to identify networks involved in multiple domains central to gait function.
pain	STROKE-PAIN: Central Neuropathic Pain Following Stroke: Lesions, Connectivity, and Biomarkers for Pain Prognosis and Treatment Response	• Hypothesis 1a: Brain lesions in specific regions, such as the thalamus or somatosensory cortex, are associated with the development and persistence of central neuropathic pain following stroke. • Hypothesis 1b: Brain lesion location will differ in patient with central neuropathic pain vs. in patients with any pain (without specification of pain aetiology or further pain characterization). • Hypothesis 2: Alterations in brain connectivity, particularly within pain processing networks, will correlate with the severity and chronicity of central neuropathic pain post-stroke. • Hypothesis 3: Biomarkers identified at the onset of stroke, such as inflammatory markers, are associated with the development and severity of central neuropathic pain in stroke survivors • Hypothesis 4: Patients with pain post-stroke will exhibit an increased risk of recurrent strokes compared to those without pain, suggesting a potential bidirectional relationship between pain and stroke recurrence.