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Nanoparticle axonal transport assessment in neurodegeneration susceptible mice strain

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Abstract: Neurodegenerative diseases have no treatment yet, due to their stealthy nature: to the moment when pathology can be diagnosed, the brain damage is already unrecoverable. The tight link between neuronal transport impairments and various forms of neurodegeneration has long been established. Noninvasive assessment of axonal transport can be valuable in studying and diagnosing such diseases. Paramagnetic nanoparticles are a new promising group of magnetic resonance contrasts, which may be a solution to this problem.

Motivation and Aim: It was proposed that neurodegenerative diseases, such as Parkinsons, are often caused by axonal transport disruption. Such disruption occurs long before the neurodegeneration starts [1, 2]. Therefore a noninvasive method to assess axonal transport rate could potentially allow for early diagnosis of such diseases. Earlier it was shown that Mn3O4 nanoparticles (Mn3O4-NP) can act as an magnetic resonance imaging (MRI) contrast, that upon intranasal injection can be engulfed by olfactory neurons, and subsequently get transported into the deeper brain areas [3]. In this study we have assessed Mn3O4-NP spreading in brain of two congenic mice strains: *C57Bl* and *B6.Cg-Tg(Prnp-SNCA*A53T)23Mkle* (with high α-synucleinopathy risk, motor impairments become evident at the age of 12 months [4]).

Methods and Algorithms: 4 groups of 2 mice strains (*C57Bl* and *B6.Cg-Tg*), and 2 ages (8 and 12 week old) were used. Each group consisted of 6 males. Mn3O4-NP were prepared as previously described [3]. They were suspended in saline and intranasally instilled. Then 3, 6, 9, 12, 24, 48, 96 hours post injection mice head was MRI-scanned using Rapid Acquisition Relaxation Enhancement (RARE) pulse-sequence to obtain T1 weighted images. Acquired images were automatically parcellated based on manually marked keypoints. For each parcel maximum T1 signal value and maximum T1 signal change rate were calculated. Comparison between the groups was carried out using analysis of variance (ANOVA) with Fisher least significant difference (LSD) post-hoc analysis.

Results: Elevated T1 signal (proportional to Mn3O4-NP concentration) spreads primarily into olfaction-related brain structures: main olfactory bulbs (MOB), lateral olfactory tract, anterior olfactory nuclei, olfactory tubercle, piriform and piriform-amygdalar (AmPir) cortex, cortical-amygdalar area, entorhinal cortex. T1 signal peaks in these structures coincide with the structure position along the olfactory tract.

ANOVA with Fisher LSD showed significant differences for T1 maximum signal was found in AmPir: 12 week old *B6.Cg-Tg* mice had elevated T1 signal compared to other groups. T1 maximum change rate was significantly elevated in the MOB of 12 week old *C57Bl* mice compared to other groups.

Conclusion: It was shown that intranasally instilled Mn3O4-NP have a characteristic spreading pattern in mice brain, as they accumulate primarily in the olfactory structures. Differences observed in between 12 week old mice groups may be related to the α-synuclein accumulation [4], that is believed to upregulate axonal transport in normal physiological quantities and impair transport in pathologically high quantities [5].

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