TRACTOGRAPHY IMAGING DETECTS THE LOSS OF CHOLINERGIC BASAL FOREBRAIN NEURONS IN A MOUSE MODEL OF ALZHEIMER’S DISEASE

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Loss of basal forebrain cholinergic neurons (BFCNs) is an early and key feature of Alzheimer’s disease. Early detection of this neurodegeneration will be critical for the timely treatment of this disease including improving efficacy of the currently prescribed acetylcholine esterase inhibitors. The aim of this study is to determine if loss of BFCNs can be detected using diffusion magnetic resonance imaging tractography in a mouse model. C57Bl6 mice were infused intracerebroventricularly with the toxin saporin conjugated to a p75 neurotrophin receptor antibody (mu-p75-SAP) to induce BFCN death and then underwent MRI scanning with subsequent histological analysis to determine the extent and specificity of the lesion.

Tractography of the septo-hippocampal tracts connecting basal forebrain and hippocampus showed a significant reduction of connectivity in mice injected with mu-p75-SAP. Streamline number and volume were significantly decreased in comparison to controls indicating a degeneration of BFCN axons. In contrast, corpus callosum streamlines in both groups were unaffected. Our findings were validated histologically, with mu-p75-SAP producing a specific lesion of BFCNs in the basal forebrain and significant loss of terminal projections in the hippocampus. Furthermore, linear regression analysis showed a strong correlation of normalised streamline number with the number of ChAT positive neurons.

This study shows that loss of BFCNs can be detected by measuring streamlines of septo-hippocampal tracts, even though they represent only ~25% of all septo-hippocampal axons. Given cholinergic basal forebrain degeneration is an early feature of Alzheimer’s disease, our work demonstrates the potential feasibility of tractography as a non-invasive diagnostic tool.