# PAPER OF THE MONTH 02/2022

TRR 295 ReTune

## A neural network for tics: insights from causal brain lesions and deep brain stimulation.

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Brain. 2022 Jan 13; awac009. doi: 10.1093/brain/awac009. PMID: 35026844

Tic disorders belong to the wide spectrum of hyperkinetic movement disorders, and are characterized by sudden brief movements or sounds that appear repetitive and without appropriate context embedment. Tics are prevalent in the general population, particularly in children, but also persist in adulthood, often compromising quality of life, most commonly due to stigmatization and chronic pain. Despite their nosological classification as a distinct movement disorder already more than a century ago, and perhaps owing to their phenomenological complexity, the pathophysiology of tic behaviors still remains elusive.

Brain lesions are a rare cause of tic disorders that can provide unique insights into tic pathophysiology and also inform on possible neuromodulatory therapeutic targets. Here, we harvest the potential of brain lesions and deep brain stimulation (DBS) cases associated with tics as well as advanced connectomic mapping strategies to provide unique insights into the neural networks that causally contribute to tic occurrence. Specifically, we first performed a systematic literature review to identify 22 rare cases of tics attributed to brain lesions. We then employed 'lesion network mapping' to interrogate whether tic-inducing lesions would be associated with a common network in the average human brain. In order to do so, we mapped the connectivity signature coupled to secondary tic occurrence due to lesions using a 1000-subject normative resting-state functional connectome. Subsequently, we probed the specificity of this network by contrasting tic-lesion connectivity maps to those seeding from 717 lesions associated with a wide array of neurological and/or psychiatric symptoms within the Harvard Lesion Repository. Lastly, we investigated whether connectivity between DBS electrodes implanted to treat patients with Tourette Syndrome – the most common primary tic disorder encountered in clinics – at pallidal (n=15) and thalamic (n=15) targets and the tic-inducing network could predict clinical outcome.

Tic-inducing lesions highlighted a unique network that encompassed an array of brain regions previously involved in tic pathophysiology. These included the striatum, pallidum, thalamus, the insular and cingulate cortices, as well as the cerebellum. Anterior putaminal clusters emerged as key regions that were specific to the tic-inducing network. Deep brain stimulation network mapping showed that connectivity between DBS electrodes and the lesion network map was predictive of tic improvement, regardless of the DBS target. Taken together, these results provide novel insights into tic pathophysiology by highlighting for the first time a common brain network that is causally involved in tic generation. We believe that this network will be crucial to define neuromodulation targets for upcoming prospective DBS trials.

**Dr. Christos Ganos**

Christos Ganos is a consultant neurologist at Charité Berlin with a focus in neuropsychiatric movement disorders. He is a "Freigeist" Fellow of the Volkswagen-Stiftung and a group leader within the Movement Disorders and Neuromodulation Unit. Within the field of tic disorders, his work focuses on tic pathophysiology and mechanisms of tic control. He is the founding chair of the International Movement Disorder Society's Tic Disorders and Tourette Syndrome Study Group.

**Bassam Al-Fatly**

Bassam Al-Fatly is a MD/PhD student in the Movement Disorders and Neuromodulation Unit of Prof. Andrea Kühn at Charité Berlin. His research focuses on mapping the effect of deep brain stimulation in different movement disorders on a distributed brain network scale using state of the art connectomic approaches.

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