EP/W035057/1 - Clinical Trial Readiness for Non-Invasive Therapeutic Neuromodulation in Ataxia Telangiectasia

Background

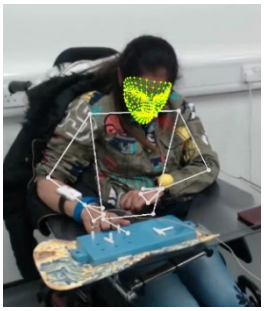
People living with ataxia-telangiectasia (A-T) and oculomotor apraxia type-1 (AOA1) experience involuntary extrapyramidal movements that can dominate cerebellar ataxia, interfere with daily tasks, and reduce the quality of life. The mechanism behind involuntary movements in A-T is not known yet but may involve the basal ganglia. Peripheral median nerve stimulation (MNS) entrains oscillations and increases synchrony of neuronal firing within the sensorimotor cortex, with an observable change in neurometabolites and corresponding entrainment of oscillations in basal ganglia circuits. In a recent trial, MNS reduced severity and frequency of motor tics in Tourette syndrome. MNS may provide a non-invasive, non-pharmacologic treatment option for modulating involuntary movements in A-T and AOA1.

Methodology

MNS - Electrodes over the right median nerve at the distal forearm. Intensity was individually set as the minimal intensity needed to induce visible thenar twitches.

TASKS - Motor and cognitive tasks with MNS on and off, with order randomised per task, mix of validated tests (A-TNEST test, Digital Span forwards and backwards, Grooved Pegboard, etc) and real-world situation (resting, standing, drinking, etc.)

RATING - Paediatric neurologist experienced in A-T, blinded to MNS status, rated on participant' videos at rest and during tasks, presence/absence and severity (i.e. amplitude and frequency) of five types of abnormal movements – Tremor, Dystonia, Athetosis, Bradykinesia, Myoclonus - on five different body parts - Head/Neck, Trunk, Arm, Hand, Face - for both sides – Right and left - for the two conditions tested- MNS on and MNS off.



VIDEO ANALYSES - The videos were processed with MediaPipe's Pose and FaceMesh models. Each frame was analysed to detect and track body joints, facial shapes, and eye positions. The system produced a set of coordinated landmark points that describe the person's movement. These landmarks can then be used in machine learning models to classify movement types, assess movement quality, track progress over time, and identify patterns in motor control.

Results

Participants were five young people (18.6 ±1.9 years), four with A-T and one with AOA1. Before NMS, we **engaged participants** to talk about their movement difficulties. They reported "*frequent muscle spasms and tremors with jerky movements now and again*", leading to "*restricted life*", "*dependence*", and "*some frustration*". Fine and complex movements were particularly affected. Participants would happily try treatments for involuntary movements, but expressed "*scepticism about drugs as mood swings, drowsiness and tiredness*" often accompany them.

MNS was well tolerated by the participants, who said after the neuromodulation that MNS was rated "*not annoying at all*" for 3 participants, "*moderately annoying*" for 2 others. All participants rated MNS as "*not painful at all*". One participant reported that MNS "*tickled*", "*tingled*" or felt "*weird*". No participant withdrew due to MNS discomfort. One participant admitted feeling "*very anxious at the beginning, then much better*". All participants reported they would wear a watch-like device delivering MNS if it helped with their motor difficulties. No participants reported consciously experiencing benefits when the MNS was on.

Video recordings allowed visual rating by paediatric neurologists, experts in A-T, of the presence of extrapyramidal movement abnormalities during tasks and at rest with MNS off. Participants showed broadly similar baseline involuntary movement disorders. Dystonia was the most observed type of involuntary movement, elicited by all tasks except finger tapping, and in all participants. Finger tapping elicited bradykinesia in all tested participants. Choreoathetosis and tremor appeared during more challenging tasks, only for some participants. Myoclonus was rarely observed.

This study was not powered to measure the efficacy of MNS in reducing extrapyramidal movements, but we could compare the prevalence of movement disorder between the MNS on and MNS off conditions. Observed responses varied with subjects: MNS reduced involuntary movements in 3 of 5 participants with dystonia, 2 of 5 participants with choreoathetosis, and 1 of 3 with bradykinesia. Myoclonus was not altered for the 2 affected participants. Tremor seemed worse for 1 of 4 participants. MNS offers a potential non-invasive treatment for involuntary extrapyramidal movements in A-T and AOA1 via oscillatory entrainment of basal ganglia motor circuits. However, efficacy could be reduced by A-T-related peripheral neuropathy, which may limit transmission of MNS to central circuits.

Impact

Our work led to a **successful publication** on the feasibility of MNS in the A-T population (https://doi.org/10.1016/j.nexres.2025.101206).

Our work was based on **collaboration** between neurologists from the UK and Turkey, sharing knowledge and expertise with computer scientists at the University of Nottingham. We aim to develop a **multidisciplinary machine-learning approach** for the analysis of movement disorders in the A-T population. As A-T is a rare disease, we connected with other A-T clinics abroad to enlarge the dataset of video recordings. Unfortunately, the data transfer agreement with Ankara was not able to go ahead with restrictions on their side, despite efforts from the involved clinicians and researchers. We will continue to work towards developing a tool for quantifying movement disorders in videos.

Our work also supported the writing of a full application for a larger grant. This further step, towards **translating our research into a clinical trial**, will deal with the interindividual **variability of MNS effects** due to central or peripheral A-T neurodegeneration and lead to a better **understanding of the brain mechanisms** underlying NMS neuromodulation in the A-T population.