GR.4

EEG biomarkers for Alzheimer's Disease: a novel automated pipeline for detecting and monitoring disease progression

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Background: Electroencephalography (EEG) has emerged as a minimally invasive technique to quantify functional changes in neural activity associated with neurodegenerative disorders such as Alzheimer's Disease (AD). Given its non-invasive approach, EEG has the potential to fill the pressing gap forearly, accurate, and accessible methods to detect and characterize disease progression in AD. Methods: To address these challenges, we conducted a pilot analysis of a custom machine learning-based automated preprocessing and feature extraction pipeline to identify indicators of AD and correlates of disease progression. Results: Our pipeline successfully detected several new and previously established EEG-based measures indicative of AD status and progression. Key findings included alterations in delta and theta band power, network connectivity disruptions, and increased slowing of brain rhythms. Additionally, we observed strong correlations between EEG-derived metrics and clinical measures such as Mini-Mental State Examination (MMSE) scores, supporting the external validity of our approach. These findings highlight the sensitivity of EEG biomarkers in differentiating between early and late stages of AD. Conclusions: Our findings suggest that this automated approach provides a promising initial framework for implementing EEG biomarkers in the AD patient population, paving the way for improved diagnostic and monitoring strategies.

GR.5

Identification of molecular biomarkers of response to combinatorial PARP inhibition and immune checkpoint blockade in IDH-Mutant Gliomas

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Background: The combination of PARP inhibitor and immune checkpoint inhibitors have been proposed as a potentially synergistic combinatorial treatment in IDH mutant glioma, targeting dysregulated homologous recombination repair pathways. This study analyzed the cell-free DNA methylome of patients in a phase 2 trial using the PARP inhibitor Olaparib and the PD-1 inhibitor Durvalumab. Methods: Patients with recurrent high-grade IDH-mutant gliomas were enrolled in a phase II open-label study (NCT03991832). Serum was collected at baseline and monthly and cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) was performed. Binomial GLMnet models were developed and model performance was assessed using validation set data. Results: 29 patients were enrolled between 2020–2023. Patients received olaparib 300mg twice daily and durvalumab 1500mg IV every 4 weeks. The overall response rate was 10% via RANO criteria. 144 plasma samples were profiled with cfMeDIP-seq along with 30 healthy controls. The enriched circulating tumour DNA methylome during response periods exhibited a highly specific signature, accurately discriminating response versus failure (AUC 0.98 ± 0.03). Additionally, samples that were taken while on treatment were able to be discriminated from samples off therapy (AUC 0.74 ± 0.11). Conclusions: The cell-free plasma DNA methylome exhibits highly specific signatures that enable accurate prediction of response to therapy.

GR.6

Deep brain stimulation of the nucleus accumbens for severe self-injurious behaviour in children: a phase I pilot trial

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Background: Self-injurious behaviours (SIB) are repetitive, non-accidental movements that result in physical damage inflicted upon oneself, without suicidal intent. SIB are prevalent among children with autism spectrum disorder and can lead to permanent disability or death. Neuromodulation at a locus of neural circuitry implicated in SIB, the nucleus accumbens (NAc), may directly influence these behaviours. Methods: We completed a phase I, open-label clinical trial of deep brain stimulation (DBS) of the NAc in children with severe, treatment-refractory SIB (ClinicalTrials.gov NCT03982888). Participants were monitored for 12 months following NAc-DBS to assess the primary outcomes of safety and feasibility. Secondary outcomes included serial assessments of SIB, ambulatory actigraphy, and changes in brain glucose metabolism induced by DBS. Results: Six children underwent NAc-DBS without any serious adverse events. NAc-DBS resulted in significant reductions in SIB and SIB-associated behaviours across multiple standardized scales, concurrent with clinically meaningful improvements in quality-of-life. Ambulatory actigraphy showed reductions in high-amplitude limb movements and positron emission tomography revealed treatment-induced reductions in metabolic activity within the thalamus, striatum, and temporoinsular cortex. Conclusions: This first-in-children phase 1 clinical trial demonstrates the safety and feasibility of NAc-DBS in children with severe, refractory SIB at high risk of physical injury and death and supports further investigations.

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