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Title: An application of electronic nose technology for diagnosis of Alzheimer's disease

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Body: Background: Alzheimer's disease (AD) is a chronic neurodegenerative disorder that mainly affects elderly people. Diagnosing AD on clinical grounds is difficult and based on the measurement of amyloid-beta (A β), (phosphorylated)tau-protein in cerebrospinal fluid. The specificity is rather low. Novel diagnostic tools via exhaled breath (EB) have been applied to identify patients with respiratory diseases like electronic nose devices (eNose and ion-mobility spectrometry, (IMS)). In this study, we introduce these techniques to the field of Alzheimer's disease. Methods: AD patients and healthy controls were sampled for EB and EB condensate analysis in two study centers (AD n= 18, 21), (HC n= 19, 16). EB condensate and human lung tissue were analyzed for different A β species, tau-protein using ELISA. EB was analyzed for volatile organic compounds (VOC)s by patterns (Cyrano 320, IMS) and by single VOCs (IMS). Results: By Cyrano 320R we could differentiate with the leave-one-out cross-validation between healthy control and AD patients with a sensitivity of 69.8 % and a specificity of 68.7 %. Based on single identified

substances with IMS a decision tree was calculated to differentiate between AD and HC (sensitivity 81 %, specificity of 95 %). We identified A β species in the lung tissue of healthy controls and within the EB condensate in both groups; however, no significant differences within the groups were detected. Conclusions: These data opens new possibilities in the diagnosis of AD. Interestingly the difference in both groups seems not related to A β species and tau-protein. Further research is required to evaluate the significance of these findings in relation to the pathophysiology of AD.