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Short communication

Short-latency afferent inhibition as a biomarker of cholinergic degeneration compared to PET imaging in Parkinson’s disease

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ABSTRACT

Introduction: Short-latency afferent inhibition (SAI) is a relatively cheap and non-invasive method that has been proposed as a cholinergic marker in Parkinson’s disease (PD). We aim to verify the clinical feasibility of SAI as a cholinergic marker in PD using positron emission tomography (PET) with the tracer (2R,3R)-5-(2-[18F]fluoroethoxy)benzovesamicol ([18F]FEOBV) as a reference.

Methods: We examined relations between SAI and [18F]FEOBV PET using linear regression analysis, with the primary motor cortex (M1) as primary region of interest. Additionally, we examined relations of both measures with clinical features.

Results: 30 PD patients with varying degrees of cognitive dysfunction and 10 healthy controls (HC) were included in the analysis. SAI was not related to tracer uptake in M1 in the PD group (p = .291) or the HC group (p = .206). We could not replicate the previously published relations between SAI and cholinergic symptoms, such as cognition, psychotic experiences and olfactory function. SAI was not related to [18F]FEOBV imaging parameters, nor to clinical measures of cholinergic dysfunction. Therefore, SAI may not be feasible as a clinically applied cholinergic marker in PD.

1. Introduction

Parkinson’s disease (PD) is a complex neurodegenerative disorder. Besides the well-known dopaminergic deficits, other neurotransmitter systems, especially the cholinergic system, are also affected. Neurodegeneration in the nucleus basalis of Meynert (NBM), the main provider of cholinergic projections to the cortical mantle, occurs early in the disease [1]. Although there is some debate about the pattern of degeneration, the intermediate part of the NBM, projecting to the occipital lobe and laterodorsal frontoparietal areas, seems to be particularly implicated [2,3]. This is reflected by an apparent posterior-anterior gradient in cortical denervation, primarily affecting occipital and parietal areas, as observed with neuroimaging [3]. However, PD patients without dementia show large inter-individual differences in the severity of cholinergic denervation [4]. Moreover, symptoms related to cholinergic deficiency can be multifactorial in their pathogenesis, making it difficult to predict cholinergic deficiency based on the clinical picture [4]. A biological marker reflecting the cholinergic status would be helpful to select patients who could benefit from cholinesterase inhibitors.

The validated PET tracer (2R,3R)-5-(2-[18F]fluoroethoxy)benzovesamicol ([18F]FEOBV) binds to vesicular acetylcholine transporter and provides a valid reflection of cholinergic innervation of the whole brain [5]. However, [18F]FEOBV PET scans are not routinely performed in clinical practice due to its cost, limited availability and radiation burden. A relatively cheap and non-invasive method that has been proposed as a cholinergic marker is short-latency afferent inhibition (SAI). In SAI, stimulation of a peripheral nerve suppresses the excitability of the primary motor cortex in a typical time window of 18–28 ms, which is thought to be mediated by cholinergic neurotransmission [6]. SAI was previously related to cholinergic symptoms in PD, including mild cognitive impairment [7], visual hallucinations (VH) [8], REM sleep behavioral disorder (RBD) [9], anosmia [10], and gait speed [11]. SAI could be a surrogate measure of cholinergic innervation, but this
assumption has never been tested with neuroimaging.

Our objective is to investigate the clinical feasibility of SAI as a biomarker for cortical cholinergic innervation in PD patients, correlating SAI to cholinergic PET imaging and clinical measures of cholinergic deficiency.

2. Material and methods

2.1. Experimental setup

The study was approved by the ethics committee of the University Medical Center Groningen (UMCG). All subjects provided written informed consent in accordance with the Declaration of Helsinki. Subjects came to the UMCG on two occasions. First, they underwent [18F] FEOBV PET imaging and a T1-weighted structural MRI scan. On the second visit SAI was assessed, as well as a number of clinical measures. We aimed for both visits to take place within one week. For 5 participants there was more than one week but less than three weeks between both visits. We do not expect dramatic changes in cognition or cholinergic innervation within this timeframe. Patients were assessed on dopaminergic drugs. Use of anticholinergic drugs or cholinesterase inhibitors were exclusion criteria for this study. Healthy control participants additionally needed to be free of any neurological disorders to participate. Other exclusion criteria were MRI contra-indications (e.g., ferrous objects in the body or claustrophobia), transcranial magnetic stimulation (TMS) contra-indications (e.g., epilepsy) and PET contra-indications (e.g., pregnancy or participation in a scientific study involving radiation in the past year).

A sample size calculation was performed before the start of the study. We expected the correlation coefficient between SAI and cholinergic PET to be greater than 0.5, based on the correlation coefficients reported in studies relating SAI to clinical measures [7,9–11]. With \( \alpha = 0.05 \) and \( \beta = 0.20 \), this resulted in a sample size of 30 evaluable patients, aimed to represent a wide range of cognitive functioning. Ten healthy evaluable controls were added to be able to compare between groups.

2.2. Physiological and imaging data acquisition

The SAI protocol was designed to be clinically feasible, so that the whole protocol including preparations could be performed within 45 min. The target arm (the most affected side in patients and the dominant side in healthy controls) was placed on a pillow in a comfortable position. Electromyographic recordings were made from the first dorsal interosseous muscle (FDI) and the thenar muscles in a belly tendon montage (amplification 200x). Peripheral nerve stimulation was applied with a constant current stimulator (Digitimer DS7A, Welwyn Garden City, UK) and the intensity of median nerve stimulation was set to elicit approximately 10% of the maximum M-wave in the thenar muscles or a visible twitch of the thumb.

TMS was applied with a Magstim 200 stimulator (Magstim Co., Whitland, Dyfed, UK) using a hand-held circular coil (90 mm). The optimal location for FDI stimulation was sought and marked on the subject’s head. For the SAI protocol, TMS intensity was set at approximately 120% of the resting motor threshold and was aimed to evoke at least 5% of the maximum M-wave of the FDI.

The main outcome of the SAI protocol was the reduction in conditioned motor evoked potential (MEP) in the dual stimulus (SAI) condition (% unconditioned MEP, %MEP). The PET and MRI acquisition were performed according to standardized protocols. The main PET outcome was the standardized uptake value ratio (SUVr) of [18F] FEOBV in the primary motor cortex (M1), using supratentorial white matter as a reference. A detailed description of the protocols and processing can be found in the Supplementary material.

2.3. Clinical assessment

Global cognition was assessed using the Montreal cognitive assessment (MoCA) [12]. Patients were subdivided into normal cognition or impaired cognition (MoCA score < 26), based on the level 1 diagnostic criteria of impaired cognition in PD [13]. Presence of visual hallucinations (VH) was assessed using the questionnaire for psychotic experiences (QPE) [14]. We considered VH to be present if they occurred at least once a week in the past month, to exclude incidental VH from the VH group. Presence of RBD was assessed using the RBD screening questionnaire (RBDSQ), with a cut-off score of 5 [15]. Gait speed was assessed using the 10-m walk test (10-MWT), with timing performed over the middle 6 m [16]. Sniffin’ Sticks were used to subdivide patients into hyposmia (score ≤ 10) or anosmia (score ≤ 6) [17]. Normal olfactory function was disregarded since only one patient was assigned to this group. Finally, motor symptoms were assessed using the Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale part 3 (MDS-UPDRS-III) [18].

2.4. Study endpoints and statistical analysis

Our primary endpoint was the relationship between SAI and SUVr in M1 of the stimulated hemisphere. This was assessed separately for both groups, using linear regression models, with SUVr as dependent variable and SAI as independent variable. M1 was chosen as primary volume of interest (VOI) based on the working model of SAI as proposed by Turco et al. [6]. Secondary endpoints were correlations between SAI and SUVr in other VOIs, specifically the primary somatosensory cortex (S1) and thalamus. These VOIs were selected, together with M1, as SAI likely is established through thalamocortical projections to S1 and M1 as well as corticocortical projections from S1 to M1 [6]. Other secondary endpoints were correlations between SAI and cholinergic symptoms that have previously been related with differences in SAI, specifically impaired global cognition, presence of VH, RBD, olfactory dysfunction and impaired gait speed. We performed an additional exploratory voxel-wise analysis correlating tracer uptake to SAI. Details of the statistical analysis can be found in the Supplementary materials.

3. Results

3.1. Subjects

In total, 36 patients and 11 healthy controls underwent all measurements, with the exception of one patient, who had no MRI scan. For this patient, the MRI of a demographically similar participant was used for co-registration with the PET image, which was then manually adjusted for optimal result. It was checked that this participant did not form an outlier in the data distributions of the patient group for all included VOIs and for the SUV of the reference region (all within 10th–90th percentile).

Four patients and one control were excluded because the mean uMEP did not reach the threshold of 0.2 mV (n = 3) or too few trials (<5 for any stimulation state) remained after removal of noisy trials and trimming the highest and lowest 10% MEPs (n = 2). Two more patients were excluded, because they were not able to endure electrical stimulation of the desired intensity (n = 1) or used anticholinergic drugs (n = 1). 30 patients and 10 healthy controls remained for the analysis. Supplemental Table 1 shows the characteristics of all participants included in the analysis. The HC group and the PD group did not differ in age and sex.

3.2. Association between SAI and SUVr of [18F]FEOBV-PET

SAI showed a significant difference between both groups: t(30.91) = -2.44, p = .021 (Fig. 1, top panel). SUVr values in M1 of the stimulated cortex were also significantly different between groups: t(21.79) = 3.74,
3. Linear regression modelling showed that SAI could not predict tracer uptake in M1, in the PD (F(1) = 1.16, R^2_adj = 0.005, p = .291) nor in the HC group (F(1) = 1.89, R^2_adj = 0.090, p = .206) (Fig. 1, main panel). When correcting for LEDD, GABAergic drug use, tremor, age and sex in the PD group, the model did not improve. Inclusion of the mean u-MEP as covariate slightly improved the model in the PD group (F(1) = 4.49, p = .043), resulting in an adjusted R-squared of 0.12. In the HC group, inclusion of age as covariate improved the model and resulted in an adjusted R-squared of 0.58. However, SAI was not of significant added value compared to a model with age as the only independent variable (F(1) = 1.27, p = .297). Similar results were found for the other VOIs (Supplemental Figs. 1 and 2).

### 3.3. Associations with cholinergic symptoms

We were not able to reproduce any of the previously observed relations between SAI and specific cholinergic symptoms of PD, although we found a trend towards a correlation with gait speed (Table 1). SAI (%MEP) and total MDS-UPDRS-III score showed a positive correlation. In contrast, SUVr in M1 showed a significant difference between patients with and without VHs and between patients with and without RBD (Table 1).

<table>
<thead>
<tr>
<th>Modality Subgroup</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Test</th>
<th>Statistic</th>
<th>df</th>
<th>p</th>
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<td>.462</td>
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<td>VH-</td>
<td>25</td>
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<td>36.2</td>
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<td>0.39</td>
<td>26.28</td>
<td>.703</td>
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<td>RBD+</td>
<td>15</td>
<td>70.1</td>
<td>30.8</td>
<td>Welch’s t</td>
<td>−0.22</td>
<td>27.94</td>
<td>.824</td>
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<td>74.1</td>
<td>35.0</td>
<td>Welch’s t</td>
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<td>35.2</td>
<td>Pearson’s r</td>
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<td>.229</td>
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<tr>
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<td>0.27</td>
<td>Welch’s t</td>
<td>1.59-2.03</td>
<td>146</td>
<td>.021</td>
</tr>
<tr>
<td>SUVr VH+</td>
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<td>0.27</td>
<td>Welch’s t</td>
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<td>28</td>
<td>.711</td>
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4. Discussion

In this study, we assessed whether SAI would be a valid biomarker for cholinergic system integrity in Parkinson’s disease, focusing on clinical applicability. Results showed a difference in mean SAI between patients and healthy controls. However, SAI did not correlate with \[ {18}F \] FEOBV-PET in PD patients in M1, S1 and the thalamus. We also could not replicate previously reported correlations of SAI to symptoms related to the cholinergic system. These results imply that SAI cannot be used as a less invasive alternative for \[ {18}F \] FEOBV PET.

SAI was less strong in PD patients versus healthy controls, as was found before [19]. However, linear regression analysis did not show a relationship between SAI and \[ {18}F \] FEOBV PET imaging. Other neurotransmitters besides the cholinergic system affect SAI, as SAI is influenced by the use of dopaminergic as well as GABAergic medication [19, 20]. However, correcting for LEDD or GABAergic drugs did not improve our results. It is possible that SAI and \[ {18}F \] FEOBV PET assess different aspects of cholinergic transmission and are therefore poorly correlated. A selective muscarinic receptor tracer may potentially result in a better correlation. These types of tracers are currently being developed.

We expected the strongest relation between SAI and \[ {18}F \] FEOBV tracer uptake in M1, based on the working model of SAI as proposed by Turco et al. [6]. Although M1 may not be the earliest implicated area in cholinergic degeneration, it was found to be affected in non-demented PD patients [3,21]. In our PET study, degeneration in M1 was associated with presence of VH and RBD, but not with cognitive impairment, olfactory dysfunction or gait disorder. To what extent cholinergic activity in M1 represents global cholinergic functioning or predicts treatment effect has not been investigated.

We found no correlations between SAI and cholinergic symptoms in this study. These negative findings may be explained by limited sample sizes of each clinical subgroups of PD, specifically the VH group analysis \( (n = 5) \). In the study of Turco et al. [22], a change of 10 percentage points in %MEP required a sample size of at least 25. In comparison, Manganeli et al. included 10 patients with VH [8], but the occurrence of VH was assessed differently in their study. Nonetheless, we did find differences in SUVr between VH and RBD patient subgroups, which shows that SAI has an unfavorable sensitivity to cholinergic differences on a group level compared to \[ {18}F \] FEOBV PET imaging.

We found a significant correlation between SAI and MDS-UPDRS-III score. A relation between SAI and motor scores has been published earlier [19]. However, we found no relation between cholinergic imaging and motor score, which shows that a reduced SAI in PD patients with advanced motor symptoms cannot be explained by a co-existing cholinergic deficit at a cortical level, as proposed by Dubbioso et al. [19]. Possibly, SAI was more dependent on dopaminergic activity than to cholinergic activity in our measurements. The relation of SAI to cholinergic imaging did not improve if corrected for MDS-UPDRS-III scores.

4.1. Strengths and limitations

In this study, we specifically focused on the clinical feasibility of SAI as a cholinergic marker. In this light, we made some decisions in the SAI protocol that make it more applicable in clinical practice. For example, we included a relatively heterogeneous patient group in terms of motor and non-motor symptomatology as well as dopaminergic and GABAergic drug use, such as clonazepam, which we believe to be good a representation of the general PD population. However, this may have significantly increased the noise in our data and thus negatively influenced the results.

We fixed our ISIs at 20–28 ms, instead of determining the N20 wave for each subject. It was found that use of the N20 wave results in a stronger SAI, although the measurement error was similar [22]. Thus, we do not expect this method to result in a more variable SAI.

Lastly, we used a circular coil for the assessment of SAI, since it generally is easiest and fastest in its applicability. Most previous SAI studies use a figure-of-eight coil, although a circular coil has been applied before [10,11]. It is unknown how coil shape affects SAI.

Although efforts were made to perform SAI and \[ {18}F \] FEOBV PET with little time in between, for the majority of participants they were performed on separate days, which may have negatively affected the correlation between both measures.

The assessment of gait speed and RBD in the present study was performed less extensively compared to previous literature [9,11], which may play a part in our negative findings. For example, presence of RBD was not confirmed with polysomnography. Additionally, only global cognition was assessed with the MoCA score (in accordance with [7]). Cognitive scores that assess specific domains may have higher sensitivity to cholinergic degeneration [23], which might explain why we did not find differences between normal cognition and cognitive impaired subgroups.

5. Conclusion

In our study, SAI was not related to cholinergic PET imaging results in PD patients, using \[ {18}F \] FEOBV as a presynaptic tracer. Therefore, SAI may not be clinically applicable to predict cholinergic deficiency in individual PD patients.

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CRediT authorship contribution statement

Emile d’Angremont: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Project administration. Iris E.C. Sommer: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. Sygrij van der Zee: Supervision, Writing – review & editing. Teus van Laar: Conceptualization, Supervision, Writing – review & editing. Erik F.J. de Vries: Methodology, Supervision, Writing – review & editing. Inge Zijdevind: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Teus van Laar reports a relationship with AbbVie Inc that includes: consulting or advisory and speaking and lecture fees. Teus van Laar reports a relationship with Britannia Pharmaceuticals Limited that includes: speaking and lecture fees. Teus van Laar reports a relationship with Centrafarm BV that includes: speaking and lecture fees. Teus van Laar reports a relationship with Eurocept that includes: consulting or advisory. Teus van Laar reports a relationship with Genlec that includes: consulting or advisory. Teus van Laar reports a relationship with EVER Neuro Pharma GmbH that includes: consulting or advisory. Erik de Vries reports a relationship with Hoffmann-La Roche Limited that includes: funding grants. Erik de Vries reports a relationship with Eli Lilly that includes: funding grants. Erik de Vries reports a relationship with Bristol-Myers Squibb Co that includes: funding grants. Erik de Vries reports a relationship with Ionis Pharmaceuticals Inc that includes: funding grants. Erik de Vries reports a relationship with Lysonosal Therapeutics Inc that includes: funding grants. Erik de Vries reports a relationship with Manganelli et al. Parkinsonism and Related Disorders 121 (2024) 106032