Decreased integrity of the monoaminergic tract is associated with a positive response to MPH in patients with vascular cognitive impairment - proof of principle study STREAM-VCI

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ABSTRACT

Background: Patients with vascular cognitive impairment (VCI) are very heterogeneous in both symptoms and type of cerebrovascular pathology. This might be an important reason why there is no symptomatic treatment available for VCI patients. In this study, we investigated in patients with VCI, whether there was an association between a positive response to methylphenidate and galantamine and the type of cerebrovascular disease, structural damage to specific neurotransmitter systems, cerebral perfusion, and presence of co-morbid Alzheimer (AD) pathology.

Methods: We included 27 VCI patients (mean age 67 years ± 8,30% female) from the STREAM-VCI trial who received placebo, methylphenidate(10 mg), and galantamine(16 mg) in a single challenge, cross-over design. In this study, we classified patients improving on a task for executive functioning after methylphenidate compared to placebo as methylphenidate responders (MPH+; resp. non-responders, MPH−) and patients improving on a task for memory after galantamine compared to placebo as galantamine responders (GAL+; resp. non-responders, GAL−). On baseline MRI, we visually assessed measures of cerebrovascular disease, automatically segmented white matter hyperintensities, used diffusion tensor imaging to visualize the integrity of mono-aminergic and cholinergic neurotransmitter systems with mean diffusivity (MD) and fractional anisotropy (FA). Comorbid AD pathology was assessed using CSF or amyloid-PET. We tested differences between responders and non-responders using ANOVA, adjusting for age and sex.

Results: Nine patients were MPH+ vs 18 MPH−. MPH+ had higher MD (1.22 ± 0.07 vs 0.94 ± 0.05); $p = .001$) and lower FA ($0.38 \pm .01$ vs $0.43 \pm .01$); $p = .04$) in the monoaminergic tract compared to MPH−. Eight patients were GAL+ and 18 GAL−. We found no differences between GAL+ and GAL− in any of the MRI measures. Information on co-morbid AD pathology was present in 17 patients. AD pathology tended to be more frequent in GAL+ vs GAL− (5(71%) vs 2(20%); $p = .06$).

Conclusions: In patients with VCI, we found that decreased integrity of the monoaminergic tract is associated with a positive response to MPH. Responsiveness to galantamine may be related to co-morbid AD pathology.

Introduction

Vascular cognitive impairment (VCI) is a common cause of cognitive impairment and dementia, with executive dysfunction and memory impairment as its most frequent cognitive symptoms [1].

In VCI, executive dysfunction is thought to be caused by damage to the monoaminergic system. An important tract of the monoaminergic system is the noradrenergic tract. This tract projects mainly from the locus coeruleus to the frontal lobe [2]. Methylphenidate may improve executive functioning by increasing the concentrations of dopamine and norepinephrine in the synaptic cleft of this tract [3].

Memory impairment in VCI is thought to be related to a defect of the cholinergic system. An important part of the tract for memory is thought to project from the cholinergic basal forebrain to the hippocampus [4–6]. Galantamine increases the availability of acetylcholine in the synaptic cleft of the cholinergic neurotransmitter system, leading to better memory performance [7].

We previously reported that methylphenidate improved executive functioning in VCI patients, but that galantamine did not improve memory function on a group level [8]. This is in line with results from other studies [3,9,10]. However, patients with VCI constitute a heterogeneous group, both with regard to symptomatology and to underlying pathology. Thus far, interindividual differences between VCI patients in their response to particular drugs are not well understood. Omitting to take this heterogeneity into account may be one of the reasons why drug intervention studies failed to demonstrate any cognitive improvement in VCI. It might be possible that specific patients respond to a particular pharmacological challenge, even though on group level no effects on cognition are seen.

Here, we hypothesize that a response to methylphenidate and galantamine is most likely in case of damage to the monoaminergic (methylphenidate) and cholinergic (galantamine) neurotransmitter systems. This hypothesis provides a window of opportunity for personalized therapy, administering specific symptomatic drugs based on the specific vascular injury reported in the patient affecting one or more neurotransmitter systems. Diffusion tension imaging (DTI) can be used to visualize white matter tracts that are part of the monoaminergic and cholinergic neurotransmitter system. DTI can provide an indication of microstructural damage to white matter pathways by measuring water diffusivity, resulting in measures of fractional anisotropy (FA) and mean diffusivity (MD). Vascular brain injury leading to damage to these specific white matter tracts may thus result in the aforementioned cognitive deficits.

In addition to structural vascular markers, we measured cerebral blood flow (CBF) as a functional marker of total cerebrovascular function and disease severity [11,12]. We measured CBF with arterial spin labeling (ASL) in our patients to see whether a difference exists between responders and non-responders. In a subset of patients, we assessed the presence of comorbid AD pathology in CSF or on amyloid-PET.

In the current study, we investigated whether structural brain changes and cerebral perfusion at baseline (so not in response to therapy) are associated with a response to methylphenidate on executive functioning and with a response to galantamine on memory. Furthermore, we assessed whether these associations are modified by comorbid AD pathology.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design

We included patients from the STREAM-VCI [13,14]. This is a single center, double-blind, three-way, cross-over study, in 30 VCI patients investigating the immediate effect of a single dose methylphenidate and galantamine on central nervous system functions. In short, patients diagnosed with VCI according to the definitions of the American Heart Association/American Stroke Association were recruited from outpatient memory clinic [15]. The most important inclusion criteria were: a clinical diagnosis of vascular mild cognitive impairment (MCI) or vascular dementia, with imaging evidence of vascular brain injury (white matter hyperintensities (WMH; Fazekas score ≥2), (lacunar) infarcts, and or (micro)hemorrhages), an MMSE score ≥16 and a Clinical Dementia Rating score of 0.5–1.0. Patients received in random order a single dose of methylphenidate 10 mg, galantamine 16mg, and placebo on three separate visits with a washout period of one week between visits. Presence of comorbid Alzheimer's disease (AD) pathology/a clinical diagnosis of both VCI and AD were not an exclusion criterion. The study design and main results have been published previously [8,14].

Due to side effects after administration of galantamine, or personal circumstances, some patients did not complete all study visits and thus did not receive both study drugs and/or placebo. All patients provided written informed consent. The protocol of this study was approved by the Medical Ethics Committee of Amsterdam UMC and the competent authority (CCMO). The study was conducted according to the Dutch Act on Medical Research involving Human Subjects (WMO) and in compliance with good clinical practice (ICH-GCP). The trial is registered at the European Union Clinical Trials Register (2013-003396-35).

Patients

Patients were included in the present study, when test results on the placebo visit, and on either the methylphenidate visit or galantamine visit, or both, were available. Twenty-seven patients had available data for methylphenidate and 26 for galantamine.

Response to methylphenidate

Response on methyphenidate was defined based on the primary outcome measure for this intervention, namely the adapative tracker. The adaptive tracker is a pursuit-tracking task that measures executive functioning [16]. The duration of the task is 3 min, preceded by a 30 s run-in period in which the data are not recorded. The measurement unit for the adaptive tracker is the average velocity as percentage of the maximum velocity possible. In the current study, patients had a range of 3.2 to 29.6% of the maximum speed possible. The adaptive tracker was performed 1, 5 h and one hour before drug administration and three times after (approximately 1, 2, 5 and 3, 5 h after). We defined response on the adaptive tracker as a mean change on the three measurements after methylphenidate administration of 2%-units (1 SD) relative to the mean change after placebo [14,17]. The cut-off value was predefined, and a difference of 2% on the adaptive tracker after methylphenidate is a difference of about 1 standard deviation.

There were 9 methylphenidate responders (MPH+) and 18 methylphenidate non-responders (MPH−).

Response to galantamine

Response on galantamine was defined based on the primary outcome measure for this intervention, namely the Visual Verbal Learning Task-15(VVLT-15). The VVLT-15 is a verbal memory task that measures episodic memory and was chosen as the primary task for the quantification of galantamine effects in this study. We defined response on the VVLT-15 as remembering an additional 2 or more words after 3 trials on the immediate recall of the VVLT-15 after galantamine relative to placebo based on an previous study [14,18]. The cut-off value was pre-defined and a difference of 2 words is also a difference of about 1 standard deviation. The VVLT-immediate was performed approximately 2 h after drug administration. There were eight galantamine responders (GAL+) and 18 galantamine non-responders (GAL−).

Magnetic resonance imaging

Protocol

All patients were scanned on a single 3T whole body MRI scanner (MR750; GE Medical Systems Milwaukee, WI, USA) at baseline, using an eight-channel *in vivo* head coil. Patients were only scanned at baseline, prior to any pharmacological challenge. The scanning protocol lasted approximately 50 min. All scans were inspected for incidental findings and visually rated for quality control and scoring. See supplementary methods for a detailed description of the scanning protocol and quantification methods of the WMH, gray matter volume and brain perfusion.

Visual scoring

We used a previously described protocol for markers of cerebral small vessel disease (SVD) including WMH, cerebral microbleeds and lacunes [14]. In short, WMH were rated using the Fazekas scale (ranging from 0–3) on the FLAIR images [19]. Microbleeds were defined as small (maximum diameter of 10 mm) round hypointense foci on T2*-weighted images. Lacunes were defined as deep lesions (3–15 mm) with cerebral spinal fluid-like signal on all sequences. Number of microbleeds and lacunes were counted. Cortical infarcts were assessed visually. Medial temporal lobe atrophy was rated on the coronal reconstructions of the T1-weighted images with scores ranging from 0–4 [20].

White matter hyperintensities

WMH were automatically segmented with a previously described algorithm using T1-weighted and FLAIR images [21]. All WMH segmentations were visually checked by an experienced rater. One patient was excluded because of motion artefacts.

Gray matter volumes and brain perfusion

Total brain and gray matter volumes and perfusion were calculated using ExploreASL(pre-release version 0.9.9) [22] toolbox based on Statistical Parametric Mapping (SPM) 12 [23,24]. CBF quantification could not be performed in 4 patients due to low ASL image quality.

The GM spatial coefficient of variance (CoV) was defined as the standard deviation of GM CBF divided by the mean GM CBF [25].

Neurotransmitter systems

DTI were preprocessed to correct for motion, EPI distortion and eddy currents. The HARDI atlas was used to identify the tracts of interest using MRTrix for their reconstruction since the tracts of interest did not exist already in an atlas. For the monoaminergic tract, tractography was performed from the locus coeruleus defined from a probabilistic atlas [26] and the frontal cortex including the anterior cingulate gyrus, (anterior, medial, posterior and lateral) orbital gyrus, central and frontal operculum, frontal pole, gyrus rectus, medial frontal cortex, superior and middle frontal gyrus, subcallosal area, triangular, orbital and opercular part of the inferior frontal gyrus (Fig. 1a). For the cholinergic tract, the tract of interest was defined between the hippocampus and the basal forebrain cholinergic nuclei using a statistical atlas described elsewhere (Fig. 1b)[27].

We used the regions of interest in a population DTI atlas to create a mask of the tract between the two regions of interest. The weighted density masks of tracts created in template space were propagated to subject space using NiftyReg. These were used to determine the values of FA and MD within individual tracts [28]. Tract lesion occupancy was defined as the ratio between the tract volume occupied by a lesion and the total tract volume.

Comorbid Alzheimer pathology

For a subgroup of patients ($N = 17$), information on AD biomarkers was known at inclusion. Presence of comorbid AD pathology was based on amyloid-β and tau levels in CSF ($N = 16$) or on an amyloid-PET scan ($N = 1$)[29]. Patients were diagnosed with comorbid AD pathology when their CSF amyloid-β42 ≤ 640 pg/ml, their tau levels were >375
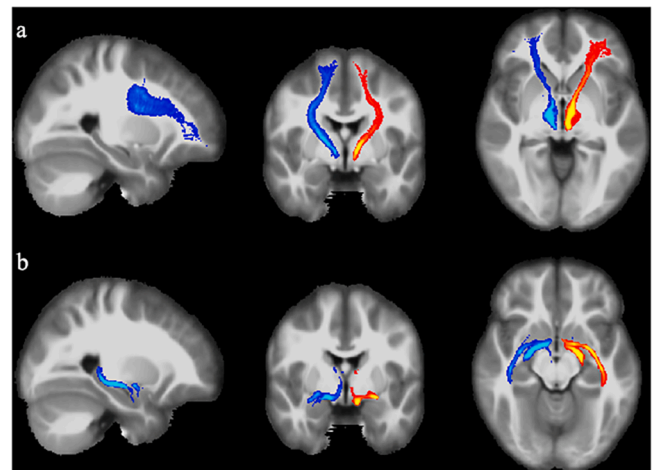

Fig. 1. (a) Monoaminergic tract from the locus coeruleus to the prefrontal cortex. (b) Cholinergic tract from the cholinergic forebrain to the hippocampus, overlaid on the population-average T1-weighted image. The left tract is red, the right tract blue.

and ptau levels >52. The amyloid PET (^{18}F-Florbetaben) scan was labeled as amyloid positive or negative based on visual reading by an experienced nuclear medicine physician. Nine of the 17 (53%) patients could be diagnosed with co-morbid AD pathology based on their CSF or the amyloid PET.

Outcome

Our primary outcome was the microstructural integrity of the specific neurotransmitter tracts, expressed as DTI measurements of FA and MD in the full tract. We only investigated differences in the monoaminergic tract between responders and non-responders to methylphenidate and differences in the cholinergic between responders and non-responders to galantamine in accordance with our research question.

Secondary outcome measures were WMH lesion volume, gray matter volume, cortical CBF and spatial CoV, and comorbid AD pathology.

Data analysis

Analyzes were performed in SPSS (version 22, IBM, Chicago IL, USA). Differences in demographic characteristics and visual scoring for markers of cerebral SVD were assessed using ANOVA for continuous variables and χ^2 - or Mann-Whitney U-tests for dichotomous or categorical variables.

We investigated differences between responders and non-responders with exploratory data analysis for all quantitative MRI measures using ANOVA, adjusted for age and sex. WMH was expressed as fraction of the total intracranial volume.

Normality of data was judged by using visual inspection in combination with values of skewness and kurtosis. We applied log-transformation for skewed distributions. Analyzes were done separately for methylphenidate and galantamine. Because of the small sample size, we did not perform correction for multiple testing.

Results

Twenty-seven patients (67 ± 8 years, 8 (30%) were female) had information available for methylphenidate analyzes. Nine (33%) patients were MPH+ and 18 (67%) MPH−. See Supplementary Fig. 1 for the histogram showing the differences in change from baseline on the adaptive tracker between methylphenidate and placebo. Twenty-six VCI patients had data available for galantamine analyzes with a mean age of 67 ± 8 years, 7 (27%) were female. Eight (31%) patients were GAL+ and

18 GAL−. Supplementary Fig. 1 shows the histogram on the difference in remembered words on the VVLT between galantamine and placebo. More information on total group characteristics and on patients who responded to both galantamine and methylphenidate can be found in the Supplementary Results. Results on the adaptive tracker after methylphenidate compared to placebo and on the VVLT after galantamine on group level have been published previously [8].

Methylphenidate

All patients had cerebral SVD on MRI and 7 (26%) patients also presented with one or more cortical infarcts. MPH+ did not differ from the MPH− on baseline characteristics including Fazekas score for WMH, microbleeds, lacunes or cortical infarcts. No differences in presence of AD pathology was seen between responders and non-responders (Table 1).

In MPH+ patients, we found higher MD and lower FA values in the full monoaminergic tract, compared to MPH− (Table 2). We also found larger GM volumes in MPH+ compared to MPH−. We did not observe any differences in WMH volumes, lesion tract occupancy, whole brain perfusion or spatial CoV.

Galantamine

GAL+ patients were more often female compared to GAL− patients. There were no differences in vascular risk factors or MRI markers of vascular brain injury between GAL+ and GAL−. We found that responders to galantamine tended to more often also have AD pathology compared to non-responders ($p = 0.06$ Table 1;).

No differences in WMH or gray matter volumes, cholinergic tract lesion occupancy, MD or FA values of the full cholinergic tract, or total brain perfusion were found (Table 2).

Table 1
Clinical features, vascular risk factors, and MRI characteristics for methylphenidate and galantamine analyzes.

Clinical and MRI features	MPH+ N = 9	MPH− N = 18	GAL+ N = 8	GAL− N = 18
Clinical features				
Age	69 ± 3	66 ± 2	64 (3)	68 (2)
Females	3 (33)	5 (28)	5 (63)	2 (11)[†]
MMSE score	26 ± 1	26 ± 1	25 (1)	27 (1)
CDR	.5 (.5–1)	0.5 (.5–1)	.75 (.5–1)	.5 (.5–1)
Diagnosis MCI	5 (56)	8 (44)	4 (50)	9 (50)
Clinical VCI + AD	4 (44)	7 (39)	5 (63)	5 (28)
Amyloid pathology present*	3 (75)	4 (31)	5 (71)	2 (20)[‡]
Vascular risk factors				
Hypertension	5 (56)	12 (68)	5 (63)	12 (67)
Hypercholesterolemia	3 (33)	9 (50)	3 (38)	9 (50)
Diabetes mellitus	0 (0)	3 (17)	1 (13)	2 (11)
Smoking	2 (22)	2 (11)	3 (38)	1 (6)
MRI characteristics				
WMH (Fazekas)	3 (2–3)	2 (2–3)	2 (2–2.75)	3 (2–3)
≥1 microbleed	7 (78)	13 (72)	6 (75)	13 (72)
≥1 lacune	4 (44)	9 (50)	4 (50)	9 (50)
≥1 cortical infarct	2 (22)	5 (28)	2 (25)	5 (28)
MTA	1 (1–2.25)	1.75 (1–2.5)	1 (1–2.25)	1.75 (1–2.5)

Numbers are mean ± SE, median (IQR) or n (%).
Abbreviations: CDR = clinical dementia rate, GCA = global cortical atrophy, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, MTA = medial temporal lobe atrophy, PCA = posterior cortical atrophy, WMH = white matter hyperintensities.
  * Total N = 17 patients.
  † $p < 0.05$.
  ‡ $p = 0.06$.

Table 2
Differences in quantitative MRI characteristics between methylphenidate responders and non-responders.

Qualitative MRI Markers	MPH+ N = 9	MPH− N = 17	GAL+ N = 8	GAL− N = 17
Monoaminergic tract				
Lesion occupancy (%)	8.54 (1.86)	5.43 (1.36)	NA	NA
MD Full tract*	1.22 (0.07)	0.94 (0.05)[‡]	NA	NA
FA Full tract	0.38 (0.01)	0.43 (0.01)[§]	NA	NA
Cholinergic tract				
Lesion occupancy (%)*	NA	NA	1.25 (0.40)	1.37 (0.27)
MD Full tract	NA	NA	1.61 (0.09)	1.70 (0.06)
FA Full tract	NA	NA	0.33 (0.02)	0.33 (0.01)
WMH (%TIV)*				
Total	3.01 (0.57)	2.52 (0.42)	1.60 (0.54)	3.06 (0.37)
Frontal	1.72 (0.34)	1.36 (0.24)	0.83 (0.33)	1.72 (0.22)
Parietal	0.79 (0.15)	0.66 (0.11)	0.43 (0.14)	0.78 (0.10)
Temporal	0.23 (0.05)	0.22 (0.04)	0.14 (0.05)	0.24 (0.04)
Occipital	0.22 (0.05)	0.25 (0.04)	0.15 (0.05)	0.27 (0.04)
BGIT	0.05 (0.01)	0.04 (0.01)	0.04 (0.01)	0.05 (0.01)
Gray matter volume				
Total gray matter volume	0.60 (0.02)	0.57 (0.01)	0.54 (0.02)	0.60 (0.01)
Cortical perfusion				
Gray matter[†]	24.70 (1.89)	28.07 (1.43)	28.3 (1.9)	26.0 (1.5)
Spatial CoV	0.28 (0.02)	0.28 (0.02)	0.26 (0.01)	0.29 (0.01)

Numbers are means ± SE,. Analyzes were performed with log transformed values and adjusted for age and sex.
WMH volumes were divided by TIV.
MD numbers are x10^{-3}.
Abbreviations: BGIT = basal ganglia and infratentorial, CoV = coefficient of variance, FA = fractional anisotropy, MD = mean diffusivity, TIV = total intracranial volume, WMH = white matter hyperintensities.
  * Analyzes were performed with log transformed values.
  † Total N = 22 patients; 8 MPH+, 14 MPH−; 8 GAL+, 14 GAL.
  ‡ $p < 0.005$.
  § $p < 0.05$.

Discussion

In the proof-of-principle STREAM-VCI trial, we found that a positive response to methylphenidate or galantamine was associated with different pathology; VCI patients who responded to methylphenidate had reduced microstructural integrity of the monaminergic tract as identified using DTI compared to the non-responders. No differences were found between patients who responded to galantamine and those who did not, although a trend for more AD pathology was seen.

Previously, we reported that on group level a single dose of methylphenidate 10 mg can lead to acute improvement of executive functioning in VCI patients [8]. In order to move towards personalized medicine, it is important to identify VCI patients who respond to a pharmacological challenge on an individual level. Here, we show that a pharmacological response to methylphenidate 10 mg is more likely when damage of the monoaminergic neurotransmitter system is present between the locus coeruleus and the frontal cortex. The monoaminergic system, especially the noradrenergic tracts, is important for several cognitive functions, such as executive functioning [2]. When noradrenergic transmission in the prefrontal cortex is decreased, executive function becomes impaired [30]. Vascular lesions are known to cause

structural damage to white matter tracts and earlier studies have shown that microstructural damage measured with DTI in specific tracts in VCI patients can explain variance in cognitive impairment, over and above the presence of visible MRI damage, such as WMH and lacunes [31–33]. We found no differences in total vascular brain injury or total brain perfusion.

These results provide support that damage to a monoaminergic tract is more important than total burden of vascular brain injury for a positive response to methylphenidate on executive functioning and DTI-based quatification of such damage might be useful to select these patients.

So far, acetylcholinesterase-inhibitors are only registered for AD patients [34]. In line with other studies, we previously reported that in VCI patients galantamine did not improve cognition [8,10]. The application of acetylcholinesterase inhibitors is based on the cholinergic hypothesis of AD, according to which the number of basal forebrain cholinergic neurons that project to the cortex and hippocampus are decreased [35]. In VCI, it is thought that not the nucleus itself is damaged, but the subcortical cholinergic tracts that project from the nucleus [36]. Therefore, we hypothesized that responders to galantamine would have more damaged cholinergic tracts. However, we did not find any differences between responders and non-responders to galantamine in the microstructure or the load of vascular lesions in the cholinergic tract between the basal forebrain cholinergic neurons and the hippocampus.

An alternative hypothesis is that the response to galantamine in VCI patients can be explained by comorbid AD pathology. Comorbid AD pathology is a frequent finding in VCI [37]. Here, responders to galantamine tended to have more associated AD pathology than non-responders. These results must be taken with caution, since sample size was small, and hence results reached only trend significance. However, these results are consistent with a previous trial showing a beneficial effect of galantamine in VCI patients with comorbid AD [38]. Furthermore, loss of cholinergic function has been shown to be greater in VCI patients with concurrent Alzheimer pathology than in patients with pure VCI [5]. It is possible that VCI patients with co-morbid AD pathology may benefit from cholinesterase inhibitors.

In addition to relations between effects of a monoaminergic or cholinergic challenge with abnormalities of established neurotransmitter tracts, we also explored relationships with other functional structural and MRI-parameters i.e. ASL-derived measures of CBF and spatial CoV. Quantifying CBF in VCI patients poses some challenges, as this measure depends on the correct estimation of label arrival time in the cortex. In patients with a compromised cerebral vasculature, such as in VCI, this condition may not always be met. Despite our relatively long post-labeling delay of 2025ms - which is recommended for the elderly and vascularly compromised [39], four of our patients were excluded from the CBF analysis because the label had incompletely reached the cerebral cortex at the time of scanning. Apparently, this population requires a longer post-labeling delay, or a different ASL technique for accurately quantifying cortical perfusion in all patients. By using the spatial CoV as a marker of the amount of label arriving in the proximal vessels and/or distal brain tissue, we still managed to generate an estimate of the cerebrovascular sufficiency of the VCI patients [25].

A general difficulty with tractography in patients with vascular brain injury is that tracts may not be identified correctly when FA is too low in regions with WMH. We used a DTI-specific atlas to identify the neurotransmitter tracts and then propagated the tracts to the individual subjects. By using this method, the tracts could be identified for all patients, despite the extensive amount of WMH.

For the study we operationalized the monoaminergic tract as one projection arising from the locus coeruleus to frontal cortex [2]. This is however only a section of the entire monoaminergic system and belongs to the noradrenergic tract of the monoaminergic system. The entire monoaminergic system encompasses much more, such as for example the dopaminergic tract arising from the substantia nigra, and the

ventrotegmental area and the serotonergic tract, arising from the nucleus raphe [40]. This is also true for the cholinergic tract. We operationalized the identification of the cholinergic system through tractography-based tract identification connecting the basal forebrain nuclei to the hippocampus. Nonetheless, it should be noted that the cholinergic system has other projections to the brain [6]. As this was a proof-of-principle study, we investigated only these parts of the neurotransmitter systems, as these tracts are thought to be important in executive functioning and memory. This rationale, however, can be extended to other neurotransmitter tracts and other symptoms, such as neuropsychiatric symptoms which are also frequently seen in VCI [37]. Perhaps differences between methylphenidate or galantamine responders/non-responders exist in other parts of these neurotransmitter systems or in different tracts, than the ones that we primarily identified for this study, which are also important for cognitive and/or neuropsychiatric symptoms.

A strength of this trial is the case cross-over design. Using such a within-subject design has relatively high statistical power allowing a relatively low sample size. Moreover, the quantification of MRI outcomes on multiple modalities allowed us to assess different aspects on brain pathology using continuous measures.

There are some limitations of the study that need to be addressed. In this proof-of-principle study, patients received a single dose of methylphenidate 10 mg and galantamine 16mg. This is a potent pharmacological challenge capable of stimulating responsive neurotransmitter systems, but this response is not necessarily indicative of therapeutic effects in every individual patient. The results of this study give direction that methylphenidate and galantamine may be effective in specific patients with VCI and should be confirmed by further research. Future studies are needed to investigate the clinical effect on cognition when administered for a longer period of time in a larger group of patients, after prior selection of predominant neurotransmitter system abnormalities. Furthermore, future studies should extend the results of this study by investigating different drugs able to boost neurotransmitter systems and other (parts of these) neurotransmitter tracts and vascular brain injury.

In conclusion, we found that decreased integrity of the monoaminergic neurotransmitter system is associated with a positive response to MPH in VCI patients, whereas responsiveness to cholinergic treatment may be related to presence of comorbid amyloid pathology. These findings may contribute to personalized treatment of VCI in the future.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2022.100128.

References

[1] J.V. Bowler, Vascular cognitive impairment, J. Neurol. Neurosurg. Psychiatry 76 (5) (2005) v35–v44. Suppl.

[2] T.W. Robbins, AF. Arnsten, The neuropsychopharmacology of fronto-executive function: monoaminergic modulation, Annu. Rev. Neurosci. 32 (2009) 267–287.

[3] I. Galynker, C. Ieronimo, C. Miner, J. Rosenblum, N. Vilkas, R. Rosenthal, Methylphenidate treatment of negative symptoms in patients with dementia, J. Neuropsychiatry Clin. Neurosci. 9 (2) (1997) 231–239.

[4] N.I. Bohnen, M.L. Muller, H. Kuwabara, G.M. Constantine, SA. Studenski, Age-associated leukoaraiosis and cortical cholinergic deafferentation, Neurology 72 (16) (2009) 1411–1416.

[5] G.C. Roman, RN. Kalaria, Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia, Neurobiol. Aging 27 (12) (2006) 1769–1785.

[6] N.R. Selden, D.R. Gitelman, N. Salamon-Murayama, T.B. Parrish, Mesulam MM. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain, Brain 121 (12) (1998) 2249–2257. Pt.

[7] E.X. Albuquerque, M.D. Santos, M. Alkondon, E.F. Pereira, A. Maelicke, Modulation of nicotinic receptor activity in the central nervous system: a novel approach to the treatment of Alzheimer disease, Alzheimer Dis. Assoc. Disord. 15 (1) (2001) S19–S25. Suppl.

[8] J.F. Leijenaar, G.J. Groeneveld, E.S. Klaassen, A.E. Leeuwis, P. Scheltens, H. C. Weinstein, J.M.A. van Gerven, F. Barkhof, W.M. van der Flier, Prins ND. Methylphenidate and galantamine in patients with vascular cognitive impairment-the proof-of-principle study STREAM-VCI, Alzheimers Res. Ther. 12 (1) (2020) 10.

[9] N. Herrmann, L.S. Rothenburg, S.E. Black, M. Ryan, B.A. Liu, U.E. Busto, KL. Lanctot, Methylphenidate for the treatment of apathy in Alzheimer disease: prediction of response using dextroamphetamine challenge, J. Clin. Psychopharmacol. 28 (3) (2008) 296–301.

[10] M.U. Farooq, J. Min, C. Goshgarian, P.B. Gorelick, Pharmacotherapy for vascular cognitive impairment, CNS Drugs 31 (9) (2017) 759–776.

[11] E. Farkas, PG. Luiten, Cerebral microvascular pathology in aging and Alzheimer's disease, Prog. Neurobiol. 64 (6) (2001) 575–611.

[12] M.R. Benedictus, A.E. Leeuwis, M.A. Binnewijzend, J.P. Kuijer, P. Scheltens, F. Barkhof, W.M. van der Flier, ND. Prins, Lower cerebral blood flow is associated with faster cognitive decline in Alzheimer's disease, Eur. Radiol. 27 (3) (2017) 1169–1175.

[13] J.F. Leijenaar, C. Groot, C.H. Sudre, D. Bergeron, A.E. Leeuwis, M.J. Cardoso, F. P. Carrasco, R. Laforce, F. Barkhof, W.M. van der Flier, et al., Comorbid amyloid-beta pathology affects clinical and imaging features in VCD, Alzheimers Dement. 16 (2) (2020) 354–364.

[14] J.F. Leijenaar, G.J. Groeneveld, W.M. van der Flier, P. Scheltens, E.S. Klaassen, H. C. Weinstein, G.J. Biessels, F. Barkhof, ND. Prins, Symptomatic treatment of vascular cognitive impairment (STREAM-VCI): protocol for a cross-over trial, JMIR Res. Protoc. 7 (3) (2018) e80.

[15] P.B. Gorelick, A. Scuteri, S.E. Black, C. Decarli, S.M. Greenberg, C. Iadecola, L. J. Launer, S. Laurent, O.L. Lopez, D. Nyenhuis, et al., Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association, Stroke 42 (9) (2011) 2672–2713.

[16] J. van Gerven, G. Nomikos, D. Douglas Feltner, Chapter 4. Functional measurements of central nervous system drug effects in early human drug development, editors. Translational Medicine in CNS Drug Development, Elsevier Academic Press, 2019, p. 29.

[17] A. Busse, A. Hensel, U. Guhne, M.C. Angermeyer, SG. Riedel-Heller, Mild cognitive impairment: long-term course of four clinical subtypes, Neurology 67 (12) (2006) 2176–2185.

[18] A.C. Baakman, C. Gavan, L. Van Doeselaar, O.A. Bajenaru, L. Camps, E.L.N. Swart, A.W. Lemstra, P. Scheltens, A.F. Cohen, J.M. Van Gerven, et al., Acute response to cholinergic challenge predicts long-term response to galantamine treatment in patients with Alzheimer's disease, Br J. Clin. Pharmacol. (2021), https://doi.org/10.1111/bcp.15206. Epub ahead of print.

[19] F. Fazekas, J.B. Chawluk, A. Alavi, H.I. Hurtig, R.A. Zimmerman, MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJR Am. J. Roentgenol. 149 (2) (1987) 351–356.

[20] P. Scheltens, L.J. Launer, F. Barkhof, H.C. Weinstein, WA. van Gool, Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability, J. Neurol. 242 (9) (1995) 557–560.

[21] C.H. Sudre, M.J. Cardoso, W.H. Bouvy, G.J. Biessels, J. Barnes, S. Ourselin, Bayesian model selection for pathological neuroimaging data applied to white matter lesion segmentation, IEEE Trans. Med. Imaging 34 (10) (2015) 2079–2102.

[22] H. Mutsaerts, J. Petr, P. Groot, P. Vandemaele, S. Ingala, A.D. Robertson, L. Václavů, I. Groote, H. Kuijf, F. Zelaya, et al. ExploreASL: an image processing pipeline for multi-center ASL perfusion MRI studies. bioRxiv. 2019:845842.

[23] H. Mutsaerts, J. Petr, D.L. Thomas, E. De Vita, D.M. Cash, M.J.P. van Osch, X. Golay, P.F.C. Groot, S. Ourselin, J. van Swieten, et al., Comparison of arterial spin labeling registration strategies in the multi-center GENetic frontotemporal dementia initiative (GENFI), J. Magn. Reson. Imaging 47 (1) (2018) 131–140.

[24] J. Ashburner, SPM: a history, Neuroimage 62 (2) (2012) 791–800.

[25] H.J. Mutsaerts, J. Petr, L. Vaclavu, J.W. van Dalen, A.D. Robertson, M.W. Caan, M. Masellis, A.J. Nederveen, E. Richard, B.J. MacIntosh, The spatial coefficient of variation in arterial spin labeling cerebral blood flow images, J. Cereb. Blood Flow Metab. 37 (9) (2017) 3184–3192.

[26] K.D. Tona, M.C. Keuken, M. de Rover, E. Lakke, B.U. Forstmann, S. Nieuwenhuis, M.J.P. van Osch, *In vivo* visualization of the locus coeruleus in humans: quantifying the test-retest reliability, Brain Struct. Funct. 222 (9) (2017) 4203–4217.

[27] S.J. Teipel, W.H. Flatz, H. Heinsen, A.L. Bokde, S.O. Schoenberg, S. Stockel, O. Dietrich, M.F. Reiser, H.J. Moller, H. Hampel, Measurement of basal forebrain atrophy in Alzheimer's disease using MRI, Brain 128 (11) (2005) 2626–2644. Pt.

[28] M. Modat, G.R. Ridgway, Z.A. Taylor, M. Lehmann, J. Barnes, D.J. Hawkes, N. C. Fox, S. Ourselin, Fast free-form deformation using graphics processing units, Comput. Methods Progr. Biomed. 98 (3) (2010) 278–284.

[29] M. Zwan, A. van Harten, R. Ossenkoppele, F. Bouwman, C. Teunissen, S. Adriaanse, A. Lammertsma, P. Scheltens, B. van Berckel, W. van der Flier, Concordance between cerebrospinal fluid biomarkers and [11C]PIB PET in a memory clinic cohort, J. Alzheimers Dis. 41 (3) (2014) 801–807.

[30] DJ. Chandler, Evidence for a specialized role of the locus coeruleus noradrenergic system in cortical circuitries and behavioral operations, Brain Res. 1641 (B) (2016) 197–206. Pt.

[31] J.M. Biesbroek, H.J. Kuijf, Y. van der Graaf, K.L. Vincken, A. Postma, W.P. Mali, G. J. Biessels, M.I. Geerlings, SS. Group, Association between subcortical vascular lesion location and cognition: a voxel-based and tract-based lesion-symptom mapping study. The SMART-MR study, PLoS One 8 (4) (2013) e60541.

[32] J.M. Biesbroek, N.A. Weaver, GJ. Biessels, Lesion location and cognitive impact of cerebral small vessel disease, Clin. Sci. 131 (8) (2017) 715–728 (Lond.).

[33] J.M. Biesbroek, A. Leemans, H. den Bakker, M. Duering, B. Gesierich, H.L. Koek, E. van den Berg, A. Postma, GJ. Biessels, Microstructure of strategic white matter tracts and cognition in memory clinic patients with vascular brain injury, Dement. Geriatr. Cogn. Disord. 44 (5-6) (2017) 268–282.

[34] J. Grutzendler, JC. Morris, Cholinesterase inhibitors for Alzheimer's disease, Drugs 61 (1) (2001) 41–52.

[35] W. Lojkowska, D. Ryglewicz, T. Jedrzejczak, S. Minc, T. Jakubowska, H. Jarosz, A. Bochynska, The effect of cholinesterase inhibitors on the regional blood flow in patients with Alzheimer's disease and vascular dementia, J. Neurol. Sci. 216 (1) (2003) 119–126.

[36] H.J. Kim, W.J. Moon, SH. Han, Differential cholinergic pathway involvement in Alzheimer's disease and subcortical ischemic vascular dementia, J. Alzheimers Dis. 35 (1) (2013) 129–136.

[37] W.M. van der Flier, I. Skoog, J.A. Schneider, L. Pantoni, V. Mok, C.L.H. Chen, P. Scheltens, Vascular cognitive impairment, Nat. Rev. Dis. Primers 4 (2018) 18003.

[38] T. Erkinjuntti, A. Kurz, G.W. Small, S. Bullock, C.V. Damaraju, Group G-I-S. An open-label extension trial of galantamine in patients with probable vascular dementia and mixed dementia, Clin. Ther. 25 (6) (2003) 1765–1782.

[39] D.C. Alsop, J.A. Detre, X. Golay, M. Gunther, J. Hendrikse, L. Hernandez-Garcia, H. Lu, B.J. MacIntosh, L.M. Parkes, M. Smits, et al., Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia, Magn. Reson. Med. 73 (1) (2015) 102–116.

[40] L. Trillo, D. Das, W. Hsieh, B. Medina, S. Moghadam, B. Lin, V. Dang, M. M. Sanchez, Z. De Miguel, J.W. Ashford, et al., Ascending monoaminergic systems alterations in Alzheimer's disease. translating basic science into clinical care, Neurosci. Biobehav. Rev. 37 (8) (2013) 1363–1379.