

RESEARCH ARTICLE

Structural MRI of the basal forebrain as predictor of cognitive response to galantamine in healthy older adults—A randomized controlled double-blinded crossover study

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Abstract

Introduction: Cholinesterase inhibitors can enhance cognitive functions in healthy elderly and delay cognitive decline in patients with Alzheimer's disease (AD). However, not everyone benefits from this treatment (non-responders). Current studies show clinical meaningful improvements only in one third of AD patients treated with cholinesterase inhibitors.

Methods: Here we investigate structural magnetic resonance imaging of the basal forebrain cholinergic system volume (BF_{voI}) as a potential predictor of cognitive response to a single dose of galantamine in healthy adults (n = 18; 59 to 75 years).

Results: We observed that the cognitive response to galantamine, more specifically the attention-dependent filtering performance in a delayed match-to-sample working memory task, correlated with BF_{voI}: Only participants with high BF_{voI} showed a significant positive effect of galantamine on the ability to filter out distracting information during the working memory encoding process.

Discussion: Future studies need to assess whether BF_{voI} may serve as a predictor of the galantamine response in AD patients, too.

KEYWORDS

Alzheimer's disease, basal forebrain, galantamine, magnetic resonance imaging, personalized medicine

1 | INTRODUCTION

Dementia is a major public health problem because of its increasing prevalence, high care costs, and lack of disease-modifying therapies. Alzheimer's disease (AD) is the most common cause of dementia with a share of up to 75%.¹ Among the core clinical symptoms of AD are deficits in working memory and attention.² These cognitive symptoms are related to a loss of cholinergic neurons in the basal forebrain (espe-

cially the nucleus basalis of Meynert).³ This central pathophysiological hallmark of AD is also the target for the symptomatic treatment of the disease with cholinesterase inhibitors, the most often prescribed drugs for the treatment of AD in its early and middle stages. Currently, three cholinesterase inhibitors (rivastigmine, donepezil, galantamine) are Food and Drug Administration–approved for the symptomatic treatment of AD.⁴ Galantamine increases the concentration of acetylcholine in the brain (especially in the synaptic gap) by a twofold

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RESEARCH IN CONTEXT

- 1. Systematic review:** The authors searched for studies for potential predictors of drug response in Alzheimer's disease (AD) using PubMed and Google Scholar. However, so far no predictors, such as genetics, brain structure, and/or cognitive function of drug response could be identified.
- 2. Interpretation:** We observed a significant effect of galantamine on the filter score that depended on basal forebrain cholinergic system volume (BF_{vol}) and a significant correlation between galantamine response and BF_{vol}. Our findings show that only persons with high BF_{vol} benefit from galantamine. These results indicating that the BF_{vol} could be a potential predictor for drug response.
- 3. Future directions:** Additional analyses using larger sample sizes are required to ascertain the potential of BF_{vol} as potential predictor of galantamine response in healthy elderly and patients with mild cognitive impairment and mild to moderate AD.

mechanism of action: On the one hand, galantamine is a selective, competitive, and reversible blocker of the enzyme acetylcholinesterase, which hydrolyzes acetylcholine to acetate and choline; on the other hand, galantamine amplifies the intrinsic activity of acetylcholine at nicotinic receptors.⁵

A current Cochrane review states cholinesterase inhibitors to be safe and to be of moderate efficiency in mild and moderate AD.⁶ However, only one third of patients treated with cholinesterase inhibitors such as galantamine show a clinically meaningful improvement of their cognitive deficits (so-called "responders");^{7,8} namely, an improvement of four or more points on the Alzheimer's Disease Assessment Scale-Cognitive Subscale.⁹

In this context, predictors of a galantamine response are urgently needed to optimize AD treatment. So far, no predictors such as brain structure (hippocampal volume¹⁰), genetics (apolipoprotein E [ApoE ε4]¹¹), or cognitive function of drug response could be identified. Yet, a prediction of individual drug response would enhance patient safety (e.g., avoidance of side effects), and would help optimize patient care and avoid unnecessary costs.

In this study we aimed to investigate the basal forebrain cholinergic system volume (BF_{vol}) as a potential predictor of the galantamine response in healthy, older adults. This structure was chosen for three reasons: First, several *post mortem* and magnetic resonance imaging (MRI)-based *in vivo* studies demonstrated severe basal forebrain volume atrophy in both normal aging and AD.¹²⁻¹⁴ Second, given its interaction with acetylcholine levels, the galantamine response may correlate with this structure in particular. Third, in previous work we have shown that the neurotransmitter acetylcholine plays a crucial role in one specific cognitive process, namely, the filtering out of irrelevant distractors during the encoding of information in working memory.¹⁵

Preclinical data also support that basal forebrain cholinergic projections play an important role in attention.^{16,17} Therefore, we expected BF_{vol} to specifically correlate with this cognitive function. We used a specially designed delayed match-to-sample task paradigm, which allowed us to disentangle two processes crucial for successful working memory performance, namely, storage and filtering, to investigate the drug response in an elderly sample of healthy participants in which some decline of BF could be expected.

2 | METHODS**2.1 | Study design and participants**

The study was designed as a randomized controlled double-blinded crossover study (Figure 1) and approved by the ethics committee at the Otto-von-Guericke University Magdeburg (Germany). All participants signed a written informed consent form prior to participation. Participants were recruited by advertisements in local newspapers and public notices. The data presented here are part of a larger project in which drug effects (galantamine and dopamine) on working memory and attention are examined. Here, only data from galantamine measurements are presented.

Eligibility of 103 elderly participants (age: 66.30 ± .44 standard error of the mean [SEM], range 59–75) was determined in a detailed screening. Only healthy, MRI suitable, right-handed participants without any regular medication and with normal or corrected-to-normal vision were included. These strict inclusion criteria led to the exclusion of a relative large number of participants and only 20 participants were randomized into the trial. In the end, data of 18 elderly (age: 65.2 ± .90 SEM, range 60–75) could be used for analysis. Table 1 provides detailed demographic data for these participants.

2.2 | Treatment

Galantamine: An 8-mg single dose of retarded galantamine (REMINYL R, Janssen-Cilag GmbH) was administered orally as a capsule. The retarded version was chosen for two reasons: (1) the unretarded version is no longer available on the German market, (2) in a pilot study with the unretarded drug imported from France we had seen severe side effects (mainly nausea). Because the retarded form of galantamine reaches maximum release after ≈4 hours (for more details on pharmacokinetics and pharmacodynamics of galantamine, see Huang and Fu¹⁸), the waiting time between drug administration and the experiment was 2 hours. Regarding dosage, our drug treatment (8 mg galantamine) was derived from previous research^{19,20} and clinical recommendations for first-time dosage.²¹ Higher doses would have been associated with numerous side effects (e.g., nausea) and, therefore, were not applicable for ethical reasons.

Placebo: The placebo capsules were provided by the pharmacy of the university hospital Heidelberg and resembled the galantamine capsules. The capsules were composed of magnesium (Abtei Pharma Vertriebs GmbH).

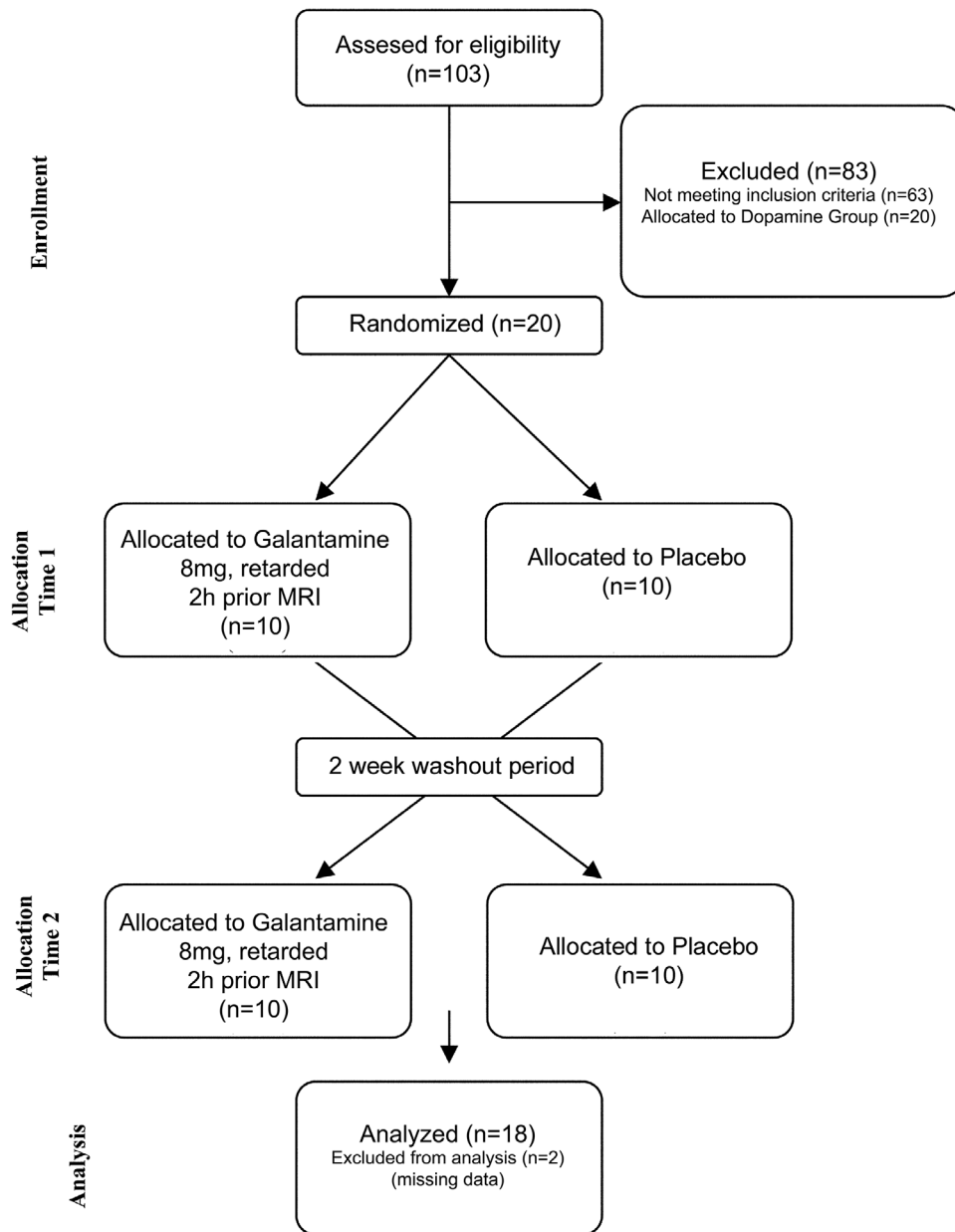


FIGURE 1 Flow chart of study design (all participants received galantamine once and placebo once)

TABLE 1 Demographic information on the participants at baseline (mean \pm SEM)

Measure	Galantamine group
N	18
Age (years)	65.82 (0.90)
Sex (% female)	72
Weight (kg)	70.47 (2.42)
MMSE	29.24 (0.18)

MMSE, Mini-Mental State Examination; SEM, standard error of the mean.

2.3 | Working memory paradigm

We used an adapted delayed-match-to-sample task that allows us to disentangle the contribution of filtering and storage processes to working memory performance²² (Figure 2). In this task, filter and storage demands were manipulated separately, while visual input was kept largely constant (four colored rectangles). The paradigm included three conditions: NFHM (no filtering, high memory), LFLM (low filtering, low memory), and HFLM (high filtering, low memory). In total the participants completed 348 trials (six runs with 58 trials, one run lasting \approx 9 minutes) in one session. Further experimental details can be found in previous work (Vellage et al.²³).

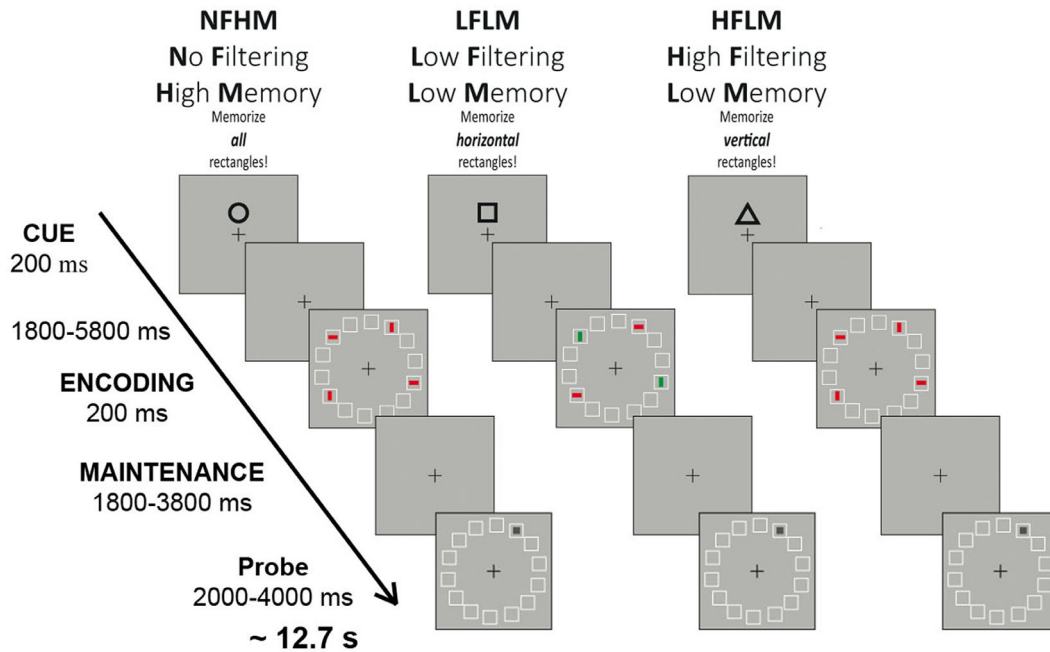


FIGURE 2 Schematic illustration of the delayed match-to-sample task. An instruction cue (200 ms) was followed by a sample display with 14 placeholder squares in a circle (200 ms). Thereby, the squares were filled with four red or two red and two green rectangles. After a phase of maintenance (1900 to 3800 ms) a probe display was shown. The participants had to decide, via button press, whether the probe was in a position that was formerly occupied by a target or not. The experiment included three conditions: (i) baseline condition with low storage and filter demands (baseline; low filtering, high memory [LFLM]; instruction: memorize horizontal rectangles), (ii) high load condition with more to-be-stored items (no filtering, high memory [NFHM]; instruction: memorize all rectangles), and (iii) filter condition with colored distractors (high filtering, low memory [HFLM]; instruction: memorize vertical rectangles). Before the experiment started, participants were familiarized with the paradigm

2.4 | MRI acquisition and data analysis

2.4.1 | Structural MRI

MR images were acquired on a 3 Tesla Siemens MAGNETOM Verio (Syngo MR B17) using a 32-channel head coil. High-resolution T1-weighted MPRAGE sequences were acquired using a 3D magnetization-prepared rapid gradient echo imaging protocol (96 sagittal slices, voxel size = $1 \times 1 \times 2$ mm, TI = 1100 ms; TR = 1660 ms, TE = 5.05 ms).

2.4.2 | Basal forebrain volume (BF_{vol})

BF_{vol} was analyzed using the SPM8 software running on MATLAB R2009b. Thereby, images were first segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF).²³ Based on the resulting GM images, a GM template was generated using DARTEL.²⁴ This GM template was normalized to the MNI (Montreal Neurological Institute) space, modulated to original GM volume, and smoothed with a 4 mm FWHM (full width at half maximum) Gaussian filter. For control of different brain sizes, total brain volume (TBV) was calculated. BF_{vol} was assessed with a basal forebrain cholinergic system mask, based on the histological brain section of a 56-year-old man without neurological or psychiatric symptoms (died from myocardial infarct) as described previously.^{25,26}

2.5 | Behavioral data analysis

Statistical analysis of behavioral data was performed with SPSS (SPSS 22, inc./IBM). To assess filter and storage functions independently of baseline performance, storage (Storage Score = LFLM - NFHM) and filtering (Filtering Score = LFLM - HFLM) scores were calculated from the hit rates. Higher storage scores thereby indicate memory deficits and higher filtering scores indicate filtering deficits. This approach (subtracting different conditions) can reduce baseline differences in cognitive performance.²⁷⁻³⁰ Drug effects were then tested using a repeated measures analysis of variance (rmANOVA) with treatment (galantamine/placebo) as within-subject factors. Additionally, BF_{vol} , age, body weight, and sex were included as covariates.

Furthermore, using a median split, participants were divided into those with low and high basal forebrain volumes to investigate the predictive role of this region on drug response in more detail. Specific differences were identified using Bonferroni adjusted post hoc tests. The statistically significant level was defined at $P < .05$.

3 | RESULTS

Behavioral data after placebo and drug administration are presented in Table 2 and Figure 3A. Administration of a single dose of galantamine had no impact on hit rates, correct rejections, reaction times, filter, or memory scores (all P -values $\geq .05$).

TABLE 2 Effects of galantamine and placebo on cognitive performance in the delayed match-to-sample working paradigm and correlation coefficient between BF_{vol} and performance

Response type	Condition	Placebo (Mean \pm SEM)	Galantamine (Mean \pm SEM)	Main effect drug $F_{1,16}$ (P)	Correlation coefficient between BF_{vol} and performance (P value)		
Hits	%	NFHM	73.80 (3.67)	71.54 (4.24)	2.570 (.231)	.235 (.181)	
		NFLM	90.87 (1.19)	85.03 (2.71)		.317 (.067)	
		HFLM	87.60 (1.27)	81.02 (3.08)		.122 (.493)	
	Ms	NFHM	1191.67 (45.28)	1188.46 (44.10)		1.213 (.289)	-.139 (.435)
		NFLM	1070.98 (46.43)	1077.23 (38.57)			-.169 (.338)
		HFLM	1018.85 (35.89)	1048.51 (45.57)			-.246 (.161)
Correct rejections	%	LFLM	99.44 (.30)	99.03 (.55)	.122 (.732)	-.176 (.318)	
		HFLM	92.09 (1.25)	92.52 (1.38)		-.268 (.125)	
	Ms	LFLM	1040.61 (37.72)	1035.26 (32.54)	.413 (.531)	-.165 (.351)	
		HFLM	1067.83 (34.76)	1037.71 (37.71)		-.152 (.390)	
Filter deficit	Δ %	LFLM-HFLM	4.86 (2.51)	4.00 (1.77)	.083 (.778)	-.181 (.306)	
Memory deficit	Δ %	LFLM-NFHM	8.93 (2.07)	13.50 (2.59)	2.829 (.115)	.040 (.821)	

Abbreviations: BF_{vol} , basal forebrain cholinergic system volume; LFLM, low filtering, low memory; HFLM, high filtering, low memory; NFHM, no filtering, high memory; SEM, standard error of the mean.

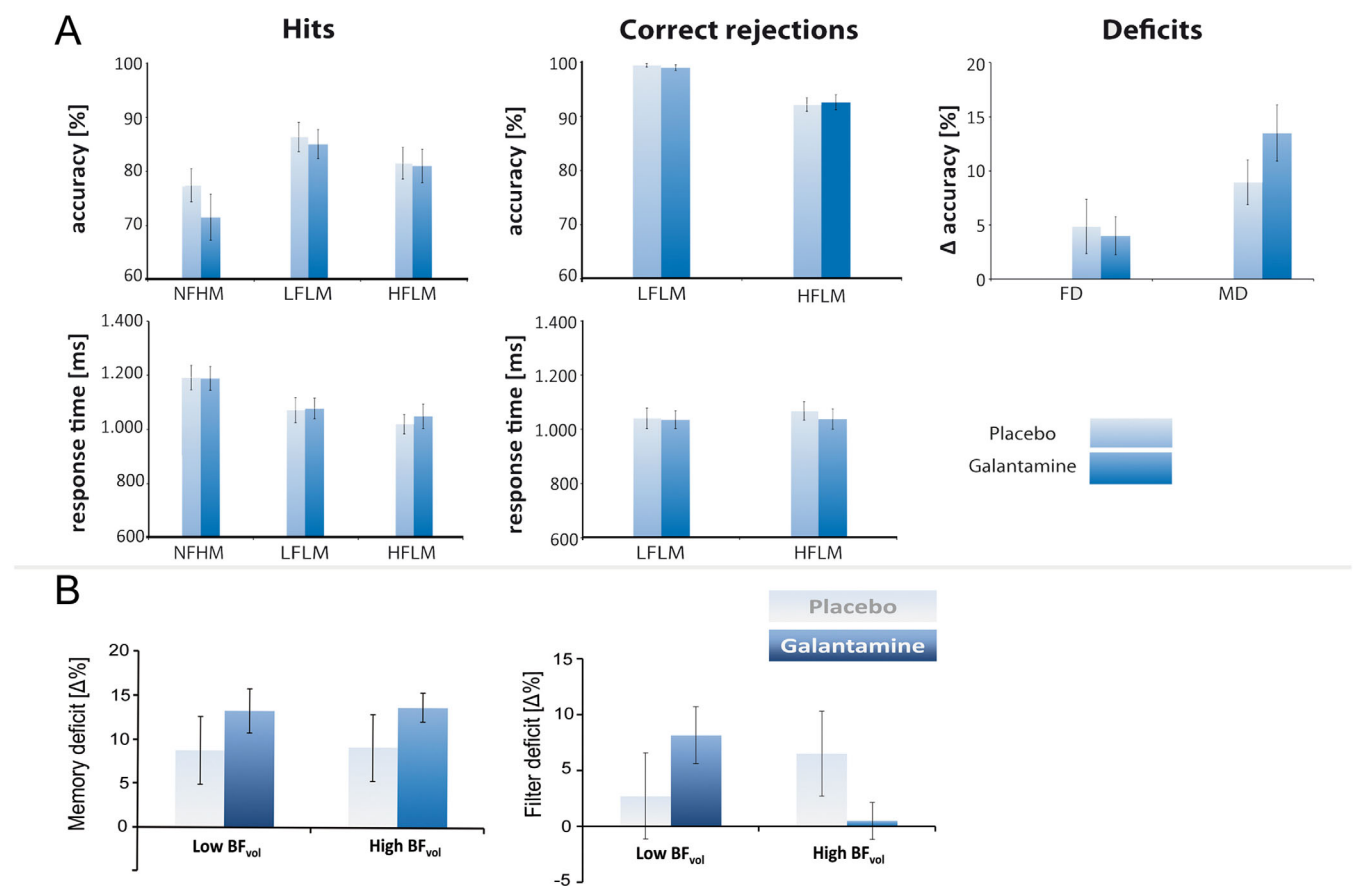


FIGURE 3 A, Means and standard errors for placebo and galantamine condition in the working memory paradigm. Group-averaged hits (%) of all conditions and corresponding response times (ms); middle column: group-averaged correct rejections (%) of low filtering, high memory (LFLM) and high filtering, low memory (HFLM) condition referring to lure trials and corresponding response times (ms); right column: group-averaged filter and memory deficit (Δ %). B, Interaction between basal forebrain cholinergic system volume (BF_{vol}) and galantamine effects on memory and filter deficit (%) in elderly; note that groups were separated by median split based on BF_{vol} for visualization

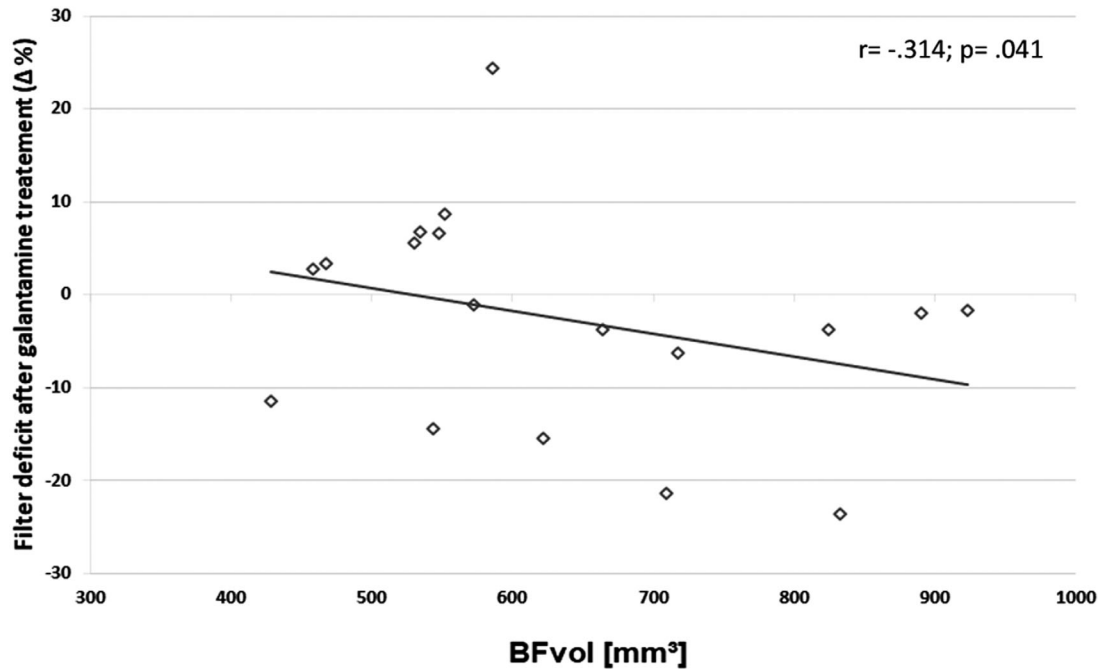


FIGURE 4 Correlation analysis between the galantamine response (filter deficit) and basal forebrain cholinergic system volume (BF_{vol})

3.1 | Impact of BF_{vol} on galantamine response

After splitting participants in high BF_{vol} (mean: 751.7 mm³ ± 12.1) and low BF_{vol} (mean: 514.7 mm³ ± 50.2) groups, the rmANOVA revealed a significant effect of galantamine on the filter score that depended on BF_{vol} (F_{1,15} = 6.063, *P* = .029, η^2 = .274; Figure 3B). Bonferroni post hoc tests revealed a significant negative effect of galantamine compared to placebo on the filter scores in participants with a low BF_{vol} (placebo: 2.72 ± 3.86; galantamine: 8.17 ± 2.52; *P* = .037), while participants with a high BF_{vol} (placebo: 6.50 ± 3.80; galantamine: 0.48 ± 1.66; *P* = .019) demonstrated a significant positive effect. No significant effects of galantamine on memory storage were found. Whereas a correlation analysis between placebo data and BF_{vol} revealed no significant results (Table 2), the correlation analysis of BF_{vol} and the filter score after galantamine application was significant (*r* = -.314; *P* = .041; Figure 4), indicating that participants with lower BF_{vol} showed a larger galantamine-dependent increase in the filtering score.

4 | DISCUSSION

In this study, we observed interindividual differences between behavioral drug responses in relation to BF_{vol}. Only participants with high BF_{vol} revealed a significant positive effect of galantamine on filtering whereas participants with low BF_{vol} revealed negative effects on filtering. Working memory capacity depends strongly on the ability to effectively filter out irrelevant information by attentional selection.³¹ The neurotransmitter acetylcholine seems to modulate such attentional processes via cholinergic receptors in the parietal cortex, which are innervated by the ascending cholinergic system from the basal

forebrain (BF). Furthermore, drugs that inhibit the acetylcholine-degrading enzyme cholinesterase enhance cognitive processes such as attention.³² These findings in humans are corroborated by a number of animal studies showing that basal forebrain cholinergic projections influence performance in a delayed matched-to-sample task^{16,33} and that donepezil and/or galantamine effects rely upon the integrity of the basal forebrain cholinergic system.^{34–36}

During aging, degeneration of cholinergic neurons leads to deficits in neurotransmitter levels and related cognitive abilities, that is, attentional selection. Grothe et al.¹² have shown that the volume of the cholinergic BF system starts to decrease in early adulthood, which is aggravated further in advanced aging. The cholinergic forebrain is also among the structures that are affected early in the course of AD.^{37,38}

4.1 | BF_{vol} as predictor of drug response

The present result, namely that only persons with high BF_{vol} benefit from galantamine, indicates that the BF_{vol} could be a predictor for drug response. Likewise, a recent study stated that BF_{vol} is a predictor of global cognitive decline in AD patients treated with cholinesterase inhibitors.³⁹ In that study, Teipel et al. investigated the potential predictive role of BF_{vol} and hippocampal volume in 124 AD patients and reported that larger BF_{vol} was associated with smaller rates of cognitive decline. More specifically, one standard deviation higher BF_{vol} increased the odds on non-decline by a factor of 2.5 and could be comparable to our results. However, Teipel et al.¹⁰ failed to observe a predictive role of the basal forebrain or the hippocampus for the treatment response in a double-blind, randomized phase 4 trial in patients with amnesic mild cognitive impairment receiving donepezil (10 mg

daily, 12 months). One potential explanation could be that only patients with an intact BF cholinergic system may benefit from galantamine treatment. In patients with mild cognitive impairment (MCI) or AD, the degeneration of the cholinergic neurons could already be too far advanced. This would support the hypothesis that currently the pharmacological treatment of AD starts too late.

Our results also indicate negative outcomes on filtering abilities of a single dose of galantamine in participants with low BF_{vol}. We can only speculate on the reasons for this surprising finding, which needs to be replicated in larger cohorts. The first explanation is that participants with low BF_{vol} might need higher dosages. Indeed, the recommended maintenance dosage of galantamine in the treatment of mild to moderate AD is 16 to 24 mg/d. The second explanation is that galantamine non-specifically increased alertness—including that devoted to distracters—so that the distracters received more attention and were harder to be ignored.

4.2 | Toward personalized medicine in AD

The prediction of response to cholinesterase inhibitors becomes more important in the context of personalized medicine. Here, a priori predictors as well as predictors after initial treatment can be differentiated. Ohnishi et al.⁴⁰ reported that the initial response to galantamine could be a reliable predictor of drug treatment. Thus, patients who show cognitive improvement during the first 4 weeks of galantamine administration may benefit from galantamine treatment later on. The authors hypothesized that drug response is potentially associated with the functional status of the cerebral cholinergic system. Besides neuroimaging, genetic polymorphisms of biomarkers are investigated as potential predictors of drug response. However, studies analyzing the predicted response via genetic polymorphisms of acetylcholinesterase, choline acetyltransferase, butyrylcholinesterase, HHRNA7, and ApoE have yielded inconsistent results.

When examining drug effects on behavior, one should take individual differences in brain structures into account. This approach could produce better responder rates, especially in the early clinical stage, and could also provide substantial benefits to patients suffering from the side effects of common treatments.⁴¹

Because our results indicate that only individuals with high BF_{vol} positively respond to a single dose of galantamine, it can be assumed that only AD patients with little BF damage, that is those in the early (preclinical or prodromal) stage of disease, may benefit from cholinergic drugs such as galantamine and/or that AD patients need higher dosages. These assumptions clearly need to be verified in future studies also investigating clinical cohorts.

4.3 | Limitations

This randomized controlled double-blinded crossover study has several limitations. First, the sample size was small (N = 18) and only nine older adults were included in every BF_{vol} group. Second, we only

investigated the effect of a single dose of galantamine in healthy older adults and the experimental paradigm started before maximal blood levels of the applied drug were achieved. Hence, follow-up studies with AD patients on the usual maintenance dosage are required. For this, the used paradigm needs to be adjusted for task difficulty. Third, it is also known that cholinesterase inhibitors are dose dependent with regard to the individual body weight. To test dose-dependent effects we included body weight as a covariate in our analysis. No significant interactions between body weight and drug administration were found ($P > .05$), so it can be ruled out that drug effects were modulated by body weight in this study. Future studies are needed to replicate our results in larger cohorts and in patients with MCI and AD.

5 | CONCLUSION

Here, we investigated the predictive role of BF_{vol} on the response to a single dose of galantamine in healthy elderly using a delayed matching-to-sample task. Our results show that galantamine effects on filter deficits were related to BF_{vol}. Moreover, the results of our study indicate that galantamine can have detrimental effects on attentional filtering in healthy elderly. In this way, only elderly participants with high BF_{vol} benefitted from a single galantamine dose while participants with low BF_{vol} showed a negative impact of galantamine on attentional filtering. This suggests that only individuals with sufficient acetylcholine production in the BF may benefit from cholinesterase inhibitors. It needs to be investigated in future studies whether BF_{vol} can also serve as a predictor of galantamine response in patients with MCI and mild to moderate AD.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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