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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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 (especially 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...
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 BFvol 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 ± 4.44 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 Fujii18), the waiting time between drug administration and the experiment was 2 hours. Regarding dosage, our drug treatment (8 mg galantamine) was derived from previous research19,20 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 ± 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 performance. 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 ≈9 minutes) in one session. Further experimental details can be found in previous work (Vellage et al.).
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 condition: (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 × 1 × 2 mm, TI = 1100 ms; TR = 1660 ms, TE = 5.05 ms).

2.4.2 | Basal forebrain volume (BFvol)

BFvol was analyzed using the SPM8 software running on MATLAB R2009b. High-resolution T1-weighted MPRAGE sequences were acquired using a 3D magnetization-prepared rapid gradient echo imaging protocol (96 sagittal slices, voxel size = 1 × 1 × 2 mm, TI = 1100 ms; TR = 1660 ms, TE = 5.05 ms).

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, BFvol, 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 ≥ .05).
TABLE 2  Effects of galantamine and placebo on cognitive performance in the delayed match-to-sample working paradigm and correlation coefficient between BFvol and performance

| Response type | Condition | Placebo (Mean ± SEM) | Galantamine (Mean ± SEM) | Main effect drug $F_{1,16}$ ($P$) | Correlation coefficient between BFvol 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        | 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        | 1040.61 (37.72)      | 1035.26 (32.54)          | .413 (.531)                       | −.165 (.351)                                                  |
|               | NFLM      | 1067.83 (34.76)      | 1037.71 (37.71)          |                                   | −.152 (.390)                                                  |
|               | HFLM      | 1018.85 (35.89)      | 1048.51 (45.57)          |                                   |                                                               |
| 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: BFvol, 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 (BFvol) and galantamine effects on memory and filter deficit (%) in elderly; note that groups were separated by median split based on BFvol 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 mm$^3$ ± 12.1) and low BF$_{vol}$ (mean: 514.7 mm$^3$ ± 50.2) groups, the rmANOVA revealed a significant effect of galantamine on the filter score that depended on BF$_{vol}$ (F1,15 = 6.063, P = .029, $\eta^2 = .274$; 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.

During aging, degeneration of cholinergic neurons leads to deficits in neurotransmitter levels and related cognitive abilities, that is, attentional selection. Grothe et al. 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.

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. 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. 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 amnestic 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. 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.

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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