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The contribution of acetylcholine and dopamine to subprocesses of visual working memory – What patients with amnestic mild cognitive impairment and Parkinson's disease can tell us

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ABSTRACT

Attentional selection, i.e. filtering out of irrelevant sensory input and information storage are two crucial components of working memory (WM). It has been proposed that the two processes are mediated by different neurotransmitters, namely acetylcholine for attentional selection and dopamine for memory storage. However, this hypothesis has been challenged by others, who for example linked a lack in dopamine levels in the brain to filtering deficits.

Here we tested the above mentioned hypothesis in two patient cohorts which either served as a proxy for a cholinergic or a dopaminergic deficit. The first group comprised 18 patients with amnestic mild cognitive impairment (aMCI), the second 22 patients with Parkinson's disease (PD). The two groups did not differ regarding their overall cognitive abilities. Both patient groups as well as a control group without neurological deficits ($n=25$) performed a visuo-spatial working memory task in which both the necessity to filter out irrelevant information and memory load, i.e. the number of items to be held in memory, were manipulated.

In accordance with the primary hypothesis, aMCI patients displayed problems with filtering, i.e., were especially impaired when the task required ignoring distracting stimuli. PD patients on the other hand showed difficulties when memory load was increased suggesting that they mainly suffered from a storage deficit. In sum, this study underlines how the investigation of neurologic patients with a presumed neurotransmitter deficit can aid to clarify these neurotransmitters' contribution to specific cognitive functions.

1. Introduction

Working memory (WM) is a multicomponent model that – amongst others – involves filtering out of irrelevant and storage of relevant information in short-term memory. Indeed, it has been shown that there is a strong correlation between the ability to filter out irrelevant stimuli and WM capacity, so that subjects with good filtering abilities have higher WM capacities (Knudsen, 2007; Lavie, Hirst, Fockert , & de Viding, 2004). It has also been stated that memory storage in WM and attentional selection are sustained by two different neurotransmitter systems, namely dopamine and acetylcholine, respectively. For example, a study on genetic polymorphisms of an acetylcholine binding receptor (CHRNA4) and a dopamine metabolizing enzyme (DBH) in humans found a correlation between performance in a visuo-spatial attention task for the first and for a working memory task, a delayed match-to-sample task, for the latter (Parasuraman, Greenwood, Kumar, & Fossella, 2005). Regarding the dependency of attentional processes on acetylcholine and memory storage on dopamine, these findings were reinforced by genetic and pharmacological studies with healthy subjects (Muller, von Cramon, & Pollmann, 1998; Knecht et al., 2004; Flöel et al., 2008; Furey, Pietrini, Haxby, & Drevets, 2008; Stormer, Passow, Biesenack, & Li, 2012). However, whilst there is consensus that acetylcholine mainly sustains attentional processes, the role of dopamine within WM remains less clear. In fact, whereas some studies confirm the hypothesis put forward in the genetic study by Parasuraman et al. (2005) namely that dopamine is related to memory storage but not to attentional selection, others do find attentional deficits associated with a lack in dopamine (Robbins & Roberts, 2007).

In Alzheimer's disease (AD) and Parkinson's disease (PD), patients have imbalanced neurotransmitter levels. Therefore, both

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degenerative diseases can serve as clinical models for neurotransmitter deficits, with a cholinergic deficit due to a degeneration of the nucleus basalis Meynert in AD and a dopaminergic deficit due to a degeneration of the substantia nigra in PD. Of course this clinical approach cannot be assumed to provide as a pure model of a neurotransmitter deficit as a dedicated animal model. On the other hand, making inferences from animal to human behavior is also problematic as even if the same task is used in an animal model it has to remain unclear whether humans would display the same behavior. Hence, the major advantage of testing patients is that this approach allows to directly assess how neurotransmitters affect *human* behavior. In this respect, it is known that attention is the first non-memory domain to be affected in AD even before deficits in language and visuo-spatial functions become relevant (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Nestor, Parasuraman, Haxby, & Grady, 1991; Parasuraman, Greenwood, Haxby, & Grady, 1992; Foster, 2001; McGuinness, Barrett, Craig, Lawson, & Passmore, 2010; Redel et al., 2012). However, patients diagnosed with AD, per definition, suffer from deficits in several (at least two) cognitive domains that are severe enough to compromise daily life activities. Consequently, patients' failure in performing a task might be misinterpreted as a deficit specific to the cognitive function the task was designed to challenge whereas in reality it may be related to general difficulties in, for example, comprehending and remembering task instructions over the course of the experiment. Indeed when piloting the present paradigm, we observed that even mildly affected AD patients tended to forget the fact that they should ignore the distractor stimuli. Hence, their seeming filtering deficit would in reality have reflected a problem in keeping the task instructions in episodic memory. For this reason, in the present study we refrained from recruiting AD patients and relied on amnestic mild cognitive impairment (aMCI) subjects instead.

There is evidence that even in preclinic stages, aMCI patients have a cholinergic deficit as well (Herholz, Weisenbach, Kalbe, Diederich, & Heiss, 2005; Haense et al., 2012). MCI represents a condition with an increased risk of developing dementia with yearly conversion rates estimated at 10–15% (Petersen, 2004; Petersen & Bennett, 2005; Gauthier et al., 2006). Of the four subtypes, patients with aMCI are assumed to have the highest risk of conversion to AD and, therefore, are more probable to suffer from a cholinergic deficit than other MCI subtypes (Winblad et al., 2004).

In this regard, the hypothesis that a loss of cholinergic neurons affects selective attention has been confirmed by studies on patients with AD and by the fact that this cognitive component, more than any other, can be improved by drugs of the cholinesterase inhibitor type that increase acetylcholine levels in the brain (Parasuraman & Nestor, 1991; Parasuraman & Martin, 1994; Maruff, Malone, & Currie, 1995; Parasuraman, Greenwood, & Alexander, 1995; Foster, Behrmann, & Stuss, 1999; Perry & Hodges, 1999; Rizzo, Anderson, Dawson, Myers, & Ball, 2000; Gainotti, Marra, & Villa, 2001; Solfrizzi et al., 2002; Levinoff, Li, Murtha, & Chertkow, 2004; Pignatti et al., 2005; Gorus, Raedt, de Lambert, Lemper, & Mets, 2006).

Here we tested in which cognitive domains of WM aMCI and PD patients are impaired. To this end, a WM paradigm was applied that had been designed to disentangle WM filtering and storage processes. In this respect it is noteworthy that in every WM task both processes are present and interact as for example even in a mere 'storage task' it is necessary to filter out ambient noise and visual distraction by things beyond the test screen. Hence, it is only possible to create tasks that emphasize the one process or the other. With this in mind our primary hypothesis was that aMCI subjects would show lower filtering abilities because of their assumed cholinergic deficit whereas the PD patients with their primary dopaminergic deficit would be more challenged by increasing memory load indicating a storage problem. In other words, we expected an interaction cognitive function (filtering vs. storage) with patient group (aMCI vs. PD). Taking into account the conflicting findings of earlier studies, alternative expectations regarding the PD patients were conceivable; for example that they would be impaired in both WM subprocesses (Lee et al., 2010).

2. Methods

2.1. Participants

Written informed consent was obtained from all subjects prior to participation. Ethics review criteria conformed to the Helsinki declaration.

PD patients and aMCI subjects were recruited from the outpatient clinic of the Department of Neurology at the University Clinic Magdeburg. The diagnoses were based on current clinic criteria for aMCI (Winblad et al., 2004) and PD (UK brain bank criteria, see Reichmann (2010)) and were established by experienced neurologists. Exclusion criteria were the presence of dementia, acute major depression or psychotic syndromes, history of stroke or other known brain lesions and uncorrectable visual deficits. Subjects for a control group (CG) were recruited in a medical practice for otorhinolaryngology, so they were likewise patients but were not suffering from any neurodegenerative condition.

All participants performed the Minimental Status Examination (MMSE, see Folstein, Folstein, and McHugh (1975)) as a screening test of cognitive function to assess overall cognitive abilities and to further rule out the presence of dementia. Moreover, an olfactory screening test (Sniffin sticks, Burghart Medizintechnik, Germany) was applied to corroborate the neurodegenerative processes in both patient groups (Huttenbrink, Hummel, Berg, Gasser, & Hahner, 2013). In addition, the aMCI patients received a more extensive neuropsychological assessment to test whether they fulfilled the criteria for the amnestic subtype, i.e. memory performance below 1.5 standard deviations with respect to their age, gender and education matched control cohort (Petersen, 2004). To this end the verbal learning test and delayed recall from the CERAD test battery were analyzed (CERAD plus test battery, http://www.memoryclinic.ch/ceradnew/).

Regarding medication, one aMCI patient had been prescribed rivastigmine, and all PD patients were on dopaminergic medication (L-dopa and/or dopamine agonists). Four aMCI and three PD patients were taking anti-depressants (SSRI, SNRI, NaSSA) but had no acute depressive symptoms. Among all subjects, regularly taken medications comprised anti-hypertensive drugs, anti-platelet-aggregating drugs or anticoagulants, oral antidiabetics or insulin, CSE inhibitors (statins), L-thyroxine, and bronchodilators. Some of these medications may have overall effects on performance of the working memory task used in the present study. However, there is no a priori reason for supposing that they would have differential effects on components of performance, e.g., filtering vs. storage.

In the aMCI group, of nine patients on whom a lumbar puncture had been performed during a clinic stay, five subjects showed a cortico-spinal fluid protein pattern (increased protein-tau, decreased ß-amyloid) consistent with Alzheimer's disease. Data of this subgroup with positive biomarkers will be presented although the small number of patients requires the statistical analysis of this subgroup to be considered with care.

2.2. Experimental design

The visuo-spatial WM task we used was adapted from McNab and Klingberg (2008) and Baier et al. (2010). The adaptation was performed in order to increase filtering demands which were found to be rather low in the earlier studies. To this end target and distractors were rendered less distinguishable and differed by orientation instead of color. Stimuli were red (RGB 250, 0, 0) bars shown within quadratic white frames with targets being vertical bars and distractors being horizontal bars. Probe stimulus was a white question mark. The 12 placeholder squares were arranged in an imaginary circle with a visual angle of 15°; the angle between squares was 3.6° from center to center. Background color was gray (RGB 130, 130, 130). Subjects were asked to fixate a cross presented in the middle of the circle throughout the test.

Subjects had to remember the location of the vertical bars and ignore the horizontal bars. The task involved three different conditions (see Fig. 1): in the low load condition (LL), two vertical bars were presented without distractors; in the high load condition (HL) four vertical bars without distractors were on display. The distractor condition (LLDIS) comprised two vertical bars as targets and two horizontal bars that were to be ignored.

There were 60 trials in each condition with the probe appearing on a former target position or in a former empty square, adjacent to the target field, with equal probability in the low and high load condition. In the distractor condition, the probe would appear on a former target position in 50% and on a former non-target position in 50% of trials.

Timing of the paradigm can be depicted from Fig. 2. After the sample stimulus, a mask was presented for 100 ms to prevent any after-image effects. The delay period was kept constant at 2.1 s as varying the lengths of delay periods in order to assess delay-dependent effects would have unacceptably increased the number of

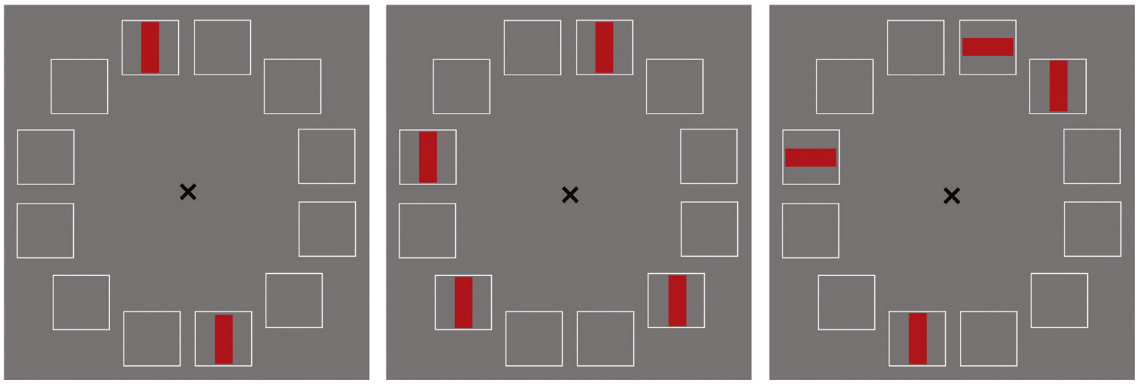

Fig. 1. Examples for the three different conditions (from left to right): LL (low load), HL (high load) and LLDIS (low load plus distracter). (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

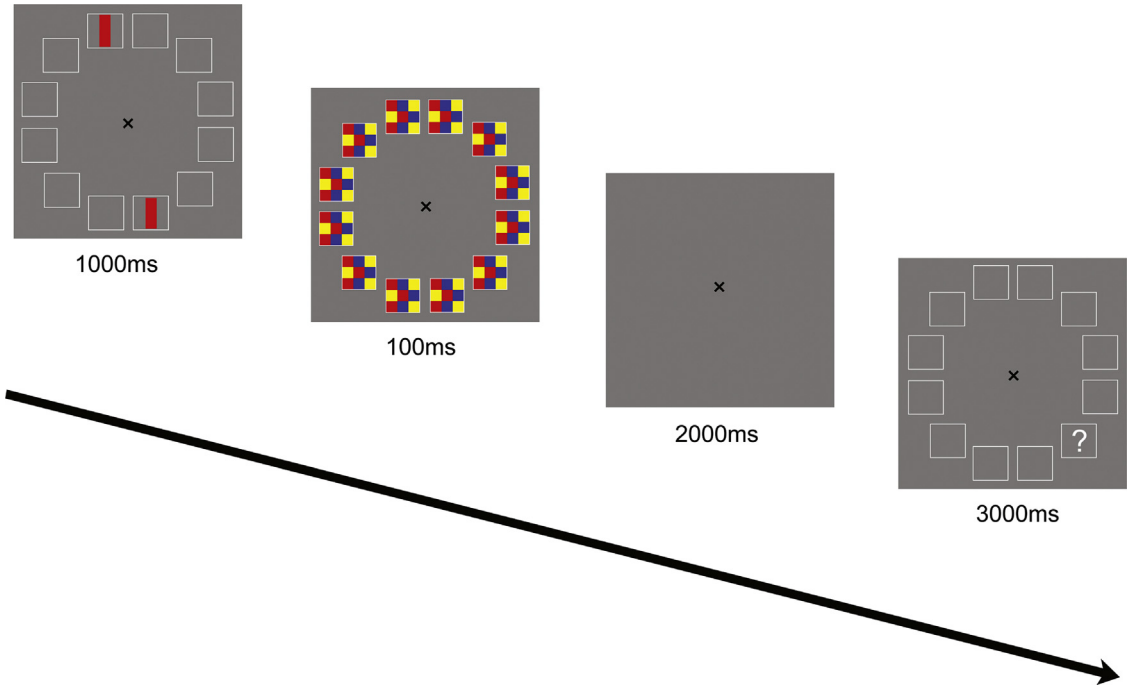

Fig. 2. Example for a LL (low load) trial. Here, the correct answer would have been "no".

necessary trials. Onset of the next trial varied by ± 500 ms to render appearance of the stimuli less predictable.

A total of 180 trials were subdivided equally into three runs with each run comprising 20 trials of each condition. Trials were not blocked but mixed and presented in pseudo-randomized order. Between runs, there was a short break of 1–2 min. Total duration of the experiment was about 30 min with the entire session taking about 1.25 h including screening tests, a questionnaire, instructions and training.

The visuo-spatial WM task was performed on a laptop computer (monitor width 15.1″). Subjects would answer by pressing two different keys on the keyboard with their left and right index fingers. Probes would disappear as soon as subjects pressed an answer key. After reading the instructions, subjects performed a training episode of 15 trials (five of each condition). If necessary, training was repeated once.

2.3. Data analysis

Differences in the distribution of sex across groups were analyzed by means of a chi-square test, differences for age, education years, overall cognitive abilities (MMSE), and olfaction (Sniffin' sticks) by a univariate ANOVA.

Eighteen aMCI patients, 22 PD patients and 25 controls completed the test. Data from 10 additional subjects (two aMCI, six PD and two controls) were excluded from the analyses because of results at chance level in the high load and/or distracter condition or because of slowed motor performance.

Our main question was related to the effects of different neurotransmitters' deficits on two components of WM, namely filtering ability and storage capacity. Hence, we computed the sensitivity measure $q=(H-FA)/(1-FA)$ (H being hits, FA being false alarms) for all three task conditions (MacMillan & Creelman, 2005). From the q values cognitive scores were computed to assess for storage and filtering abilities among our subjects: storage score (qLL−qHL) and filtering score (qLL−qLLDIS). This procedure eliminates baseline differences in working memory performance across groups (Baier et al., 2010).

For statistical analysis, we first computed a 2×2 ANOVA with repeated measures with the two patient groups (aMCI, PD) as between and cognitive score (storage score, filtering score) as within-subject factor. Here, our primary hypothesis predicted an interaction group by cognitive score. In order to assess whether this supposed interaction only reflects relative differences between the patient groups or indicates a general deficit with respect to normal function, in a next step we performed pairwise comparisons between each patient and the control group for the filtering and storage scores, respectively. For this analysis, one-sided t-tests were applied, as lower performance was predicted in the patients than the controls. The statistical threshold applied to the data was $p<0.05$.

3. Results

3.1. General results

Groups did not differ significantly concerning sex, age, education years and general cognitive function as assessed with MMSE. However, there was a significant group difference for the olfactory test [$F(2,62)=11.32$; $p<0.01$]. Both patient groups performed

Table 1
Demographic and clinical details on patients. Table shows mean and standard deviation, unless marked differently.

	MCI	PD	CG
No.	18	22	25
Male:female	10:8	13:9	14:11
Age	70.0 (4.6)	64.1 (9.5)	67.1 (8.0)
Education years	13.6 (2.4)	12.4 (2.7)	14.0 (3.3)
Duration of illness	1.1 (0.9)	2.1 (2.4)	–
Lumbar puncture specific for DAT (No.)	5	–	–
Hoehn &Yahr scale	–	1.9 (0.7)	–
MMSE	28.1 (1.5)	28.7 (0.9)	28.9 (1.1)
Sniffin' sticks	8.8 of 12 (2.8)	6.1 of 12 (3.3)	10.0 of 12 (2.5)

Table 2
Behavioral data and computed scores for filtering and storage. Table shows mean and standard error of mean.

	*q*LL	*q*HL	*q*LLDIS	Storage score	Filtering score
aMCI	0.95 (0.01)	0.73 (0.04)	0.77 (0.06)	0.23 (0.03)	0.18 (0.05)
Parkinson's disease	0.94 (0.01)	0.63 (0.04)	0.81 (0.03)	0.31 (0.04)	0.12 (0.03)
Control group	0.96 (0.01)	0.76 (0.03)	0.87 (0.03)	0.20 (0.03)	0.13 (0.03)

worse than the control group. This deficit underlines the suspected neurodegenerative alterations in the patients. Demographic and clinical details are provided in Table 1.

3.2. Experimental results

Behavioral data (sensitivity measure q) for the three conditions as well as the computed scores for filtering and storage along with the standard error of mean can be depicted from Table 2.

The computed scores for storage and filtering are further illustrated in Fig. 3. This figure also displays the data of the five MCI patients (MCI+) in which CSF analysis had yielded a biomarker pattern consistent with AD pathology. Note that the higher the score the more impaired subjects were in the respective function, i.e. the score represents the costs of increasing filtering and storage demands.

The 2×2 factorial analysis with the two patient groups revealed no main effect for group [$F(1,38)=0.063$; $p=0.803$], indicating that no group was generally more impaired than the other. A main effect for cognitive score [$F(1,38)=11.32$; $p=0.002$] reflects higher scores for storage than for filtering. Most importantly, there was an interaction between cognitive score and patient group [$F(2, 38)=4.49$; $p=0.041$] confirming that patients were differently impaired in the two cognitive functions challenged by the present WM task.

Next, pairwise comparisons between the patient groups and the control group were performed. The comparison aMCI vs. controls revealed a nearly significant deficit in the filtering [$T(41)=1.61$; $p=0.058$] but not in the storage score [$T(41)=0.49$; $p=0.315$], whereas PD patients relative to controls were significantly impaired in the storage score [$T(45)=0.43$; $p=0.025$] but not the filtering score [$T(45)=0.75$; $p=0.229$]. The subgroup of five MCI patients with positive CSF biomarkers in comparison to healthy controls showed a highly significant filtering deficit [$T(28)=3.58$; $p<0.001$] but no significant storage deficit [$T(28)=1.80$; $p=0.084$].

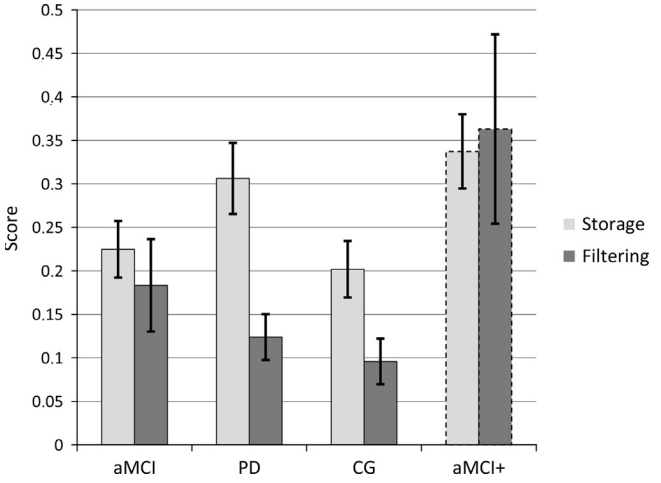

Fig. 3. Storage and filtering abilities of the two patient groups and the control group. aMCI+ refers to the subgroup of aMCI patients ($n=5$) with CSF biomarkers indicative of AD pathology.

4. Discussion

In this study we found a clear dissociation between aMCI and PD patients' ability to filter and store information in WM, respectively. MCI patients mainly had difficulties in trials in which they had to cope with distracting stimuli, indicating a deficit in their ability to inhibit irrelevant information. PD patients, on the other hand, were specifically impaired when memory load was increased, suggesting problems with storing information in WM. This effect not only emerged as an interaction in patient group × cognitive score but was further confirmed in the pairwise comparison between each patient and the control group. In other words, there was not only a relative difference between patients but a process and disease specific deficit in relation to healthy aging. With respect to our initial hypotheses, the results support the role of acetylcholine, the transmitter presumably deficient in aMCI, for attentional selection. Regarding the proposed effects of dopamine, the results favor the importance of this transmitter for memory storage rather than for attentional filtering. In this respect it is noteworthy that overall cognitive abilities as assessed with the MMSE were comparable across all groups and that we assessed behavioral scores as difference values. Hence, unspecific discrepancies in general cognitive abilities between groups are an unlikely source of the observed effects.

Nevertheless our interpretation of the present results can be challenged based on the fact that we cannot provide a direct evidence for the assumed disease-related neurotransmitter deficits. Hence, strictly speaking our results do not show a dissociation between the contribution of acetylcholine and dopamine to working memory processes but a dissociation between aMCI and PD patients in this matter. However, at least for PD it is clear that the

dopaminergic deficit constitutes the core feature of the disease. Indeed, clinicians establish their diagnosis based on the effects of dopaminergic drugs on the patient's symptoms and consequently all of our PD patients received respective medication (see below for a discussion of possible consequences of this treatment on the present results). However, other neuromodulatory deficits or degenerative processes can be present in PD as well (Crucian et al., 2010). For example some PD patients suffer from additional deficits in the cholinergic pathway, which then may contribute to the observed behavioral deficits (Dubois et al., 1987; Bohnen & Albin, 2011). However, given the well accepted role of acetylcholine in attention processes it seems unlikely that our PD patients suffered from a marked deficit in acetylcholine in addition to that in dopamine. A cholinergic deficit should have resulted in impaired performance in the task condition that was especially designed to challenge acetylcholine-dependent attentional filtering.

Whilst we did not observe filtering deficits in our PD sample others have reported such. Applying a visuo-spatial working memory task similar to ours Lee et al. (2010) reported both the presence of a filtering and a storage deficit in their PD patients. However, the study by Lee et al. differed from ours in several respects: first, they used lateralized displays that always involved the necessity to ignore information at the unattended hemifield even in no-distractor trials. Second, their distractors within the attended hemifield were defined by color rather than spatial orientation. Third, their patients were all medication-withdrawn. Hence, the observed deficits in attentional filtering in the Lee et al. study might a) have been driven by the fact that their patients had to filter stimuli based on localization and color at the same time, thereby increasing demands on selective attention, or b) they might indicate that their patients other than ours had an additional cholinergic deficit or c) they emerged because their unmedicated patients had a more pronounced lack in dopamine whilst our medicated patients were not depleted of dopamine enough to reveal this neurotransmitter's additional role in attentional filtering. In any case, the fact that our potentially less dopamine deficient patients showed only storage but no filtering deficits indicates that dopamine is likely more crucial for the first than the latter process.

We had decided to refrain from withdrawing the drugs both for ethical reasons and because we presumed that the patients would still have a dopaminergic deficit as otherwise they would have been symptom-free (Kulisevsky et al., 2000). Nevertheless, the dopaminergic medication which all of our PD patients received may at least in part have compensated for some of their cognitive deficits and it is conceivable that unmedicated patients would have revealed additional deficits in attentional filtering. However, dopaminergic medication has been postulated to interfere with distracter processing rather than with storage (Moustafa, Sherman, & Frank, 2008). Contrary to that, we found that our Parkinson subjects had more difficulties in storing targets than in ignoring distracters. We take this as evidence that the observed deficits were driven by the underlying disease of the patients and not by their medication.

Unlike the Lee et al. study, other studies support our idea that dopamine is primarily involved in the storage aspect of WM: dopaminergic medication could ameliorate the WM manipulation deficit but not attentional set-shifting capabilities or even reinstated susceptibility to distraction while rendering performance in a backward span task normal again in comparison to healthy age-matched controls (Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Cools, Rogers, Barker, & Robbing, 2010; Cools, Miyakawa, Sheridan, & D'Esposito, 2010).

Apart from differences across studies discussed above like medication there are many more reasons for the inconsistency of reported cognitive deficits in PD patients: we, for example, excluded demented PD patients who are known to suffer from additional brain pathology (Svenningsson, Westman, Ballard, & Aarsland, 2012). Also the task used to assess attention processes is of crucial importance. Some studies employed tasks that challenged executive attention rather than selective attention processes (Robbins & Roberts, 2007; Wit et al., 2012). In executive attention an influence of dopamine is to be expected, given the well-known role of this neurotransmitter on frontal lobe-mediated executive processes. Selective attention may not rely on this circuitry and hence is less dopamine dependent.

MCI constitutes an even more heterogeneous condition and it must remain unclear how many of our patients were really in the prodromal stage of AD with its associated deterioration of the nucleus basalis Meynert and the resulting cholinergic deficit. Although we selected the amnestic subtype which has the strongest association with AD (Winblad et al., 2004) for example in the corticospinal fluid analysis that was performed in a subset of our aMCI patients only five out of nine had a biomarker pattern consistent with AD pathology. Hence, not every of our aMCI patients can be assumed to have suffered from a condition nowadays often termed 'MCI due to AD' (Albert et al., 2011). Moreover, the comparison between the MCI group and the healthy controls barely missed the significance level.

However, in spite of the necessary prudence in drawing conclusions in this patient group it is important to note that all the above mentioned shortcomings which are almost inevitably inherent in clinical samples should have resulted in diluting our results, thereby revealing unspecific deficits across patient groups rather than driving group specific deficits in subprocesses of WM, which is what we observed. In this respect it is very unlikely that the attentional deficit which we observed in the aMCI group was solely caused by a conceivable subgroup of 'MCI not due to AD' patients without a cholinergic deficit. Rather, we suggest that had we been able to recruit a more homogenous sample of pure 'aMCI due to AD' patients (who for example all show an Alzheimer's disease specific corticospinal fluid protein pattern) our findings regarding the attentional deficit should have emerged even more clearly. The findings in our (small) subgroup of MCI patients with CSF biomarkers indicative of AD pathology support this notion: these patients showed the most pronounced filtering deficit stressing the role of acetylcholine in this process.

Moreover, our findings of attentional deficits in the aMCI patients are well in line with previous reports including animal and computational models of acetylcholine as a neuromodulator (Picciotto, Higley, & Mineur, 2012). For example Okonkwo, Wadley, Ball, Vance, and Crowe (2008) observed decrements in selective and especially divided attention in aMCI subjects in comparison to healthy controls using the UFOV (useful field of view) assessment. Another comprehensive study was conducted by Saunders and Summers (2010) who examined neuropsychological performance in aMCI, sMCI (subjective MCI with no objective impairment in verbal or visual episodic memory), AD patients and healthy controls: aMCI patients displayed more deficits in selective attention compared to the group that was classified as sMCI. Comparing aMCI to AD patients by means of the TVA (theory of visual attention)-based partial-report task, Redel et al. (2012) found significantly reduced top-down controlled selection abilities in an aMCI group with deficits in task-related selection and a pathological attentional imbalance. On the other hand some animal studies suggest that acetylcholine supports holding information in spatial WM online (Chudasama, Dalley, Nathwani, Bouger, & Robbins, 2004; Yang et al., 2013). With respect to our findings this could mean that acetylcholine does not sustain attentional monitoring per se but more specifically makes information kept online in memory resistant to distraction.

In sum, the present findings in our view suggest that the observed filtering and storage difficulties resulted from the proposed cholinergic deficit in aMCI and from the lack of dopamine in PD, respectively. Future research that makes use of dedicated PET

imaging methods to directly demonstrate the proposed neurotransmitter deficits is required to make our case stronger. Nevertheless, we believe that this study illustrates that even in the era of advanced imaging techniques behavioral studies with brain-damaged patients can shed light in our understanding of the neurophysiologic bases of higher cognitive functions.

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