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Simultaneous object perception deficits are related to reduced visual processing speed in amnestic mild cognitive impairment

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ABSTRACT

Simultanagnosia, an impairment in simultaneous object perception, has been attributed to deficits in visual attention and, specifically, to processing speed. Increasing visual attention deficits manifest over the course of Alzheimer's disease (AD), where the first changes are present already in its symptomatic predementia phase: amnestic mild cognitive impairment (aMCI). In this study, we examined whether patients with aMCI due to AD show simultaneous object perception deficits and whether and how these deficits relate to visual attention. Sixteen AD patients with aMCI and 16 age-, gender-, and education-matched healthy controls were assessed with a simultaneous perception task, with shapes presented in an adjacent, embedded, or overlapping manner, under free viewing without temporal constraints. We used a parametric assessment of visual attention based on the Theory of Visual Attention. Results show that patients make significantly more errors than controls when identifying overlapping shapes, which correlate with reduced processing speed. Our findings suggest simultaneous object perception deficits in very early AD, and a visual processing speed reduction underlying these deficits.

1. Introduction

Deficient memory is considered the hallmark of Alzheimer's disease (AD), already manifesting in mild dementia and amnestic mild cognitive impairment (aMCI) as a symptomatic predementia phase of AD (Albert et al., 2011; Morris et al., 2001; Petersen, 2004). However, growing evidence suggests the presence of visual attentional impairments early in the course of AD (Alescio-Lautier et al., 2007; Bonney et al., 2006; Bublak et al., 2011; Finke et al., 2013; Perry and Hodges, 1999; Perry et al., 2000; Rapp and Reischies, 2005; Redel et al., 2012; Rizzo et al., 2000). Significant relationships of such impairments to hypometabolism and functional connectivity changes in frontoparietal attention systems have been documented (Neufang et al., 2011, 2014; Sorg et al., 2007, 2012). Of note, frontoparietal hypometabolism and atrophy overlapping with β-amyloid accumulation at the aMCI stage have been revealed even to precede similar changes in memory-relevant temporal structures (Drzezga et al., 2011; Engler et al., 2006; Kemppainen et al., 2007; Mattsson et al., 2014; Mintun et al., 2006; Sorg et al., 2012). Among the affected attention functions, for example, visual processing speed shows a staged decline (Bublak et al., 2011), implying that individual cases suffer from more or less severe slowing. Critically, for diverse patient groups, it has been suggested that reduced visual processing speed can lead to impairments in the ability to perceive several objects at the same time, that is, to perceive symptoms of simultanagnosia (Chechlacz et al., 2012; Duncan et al., 2003; Finke et al., 2007). Thus, in the present study, we asked whether patients with aMCI show deficits in simultaneous object perception and, if so, whether these deficits are associated with a reduction of processing speed.

Patients with simultanagnosia are not able to integrate the objects within a visual scene to achieve a meaningful interpretation, although recognition of single objects is usually preserved (Bálint, 1909; Coslett and Saffran, 1991; Holmes, 1918; Wolpert, 1924). In patients with full-blown simultanagnosia, perception

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appears to stick to a single object at a time in the scene, resulting in the acquisition of visual information in a piecemeal fashion (Rizzo and Vecera, 2002). Particular severe problems occur if 2 or more objects are presented in an overlapping manner (e.g., Bálint and Harvey, 1995; Luria, 1959). For example, Luria reported that patients with simultanagnosia were not able to identify 2 overlapping triangles of different colors that formed the "star of David"; rather, they reported only one of them (Luria, 1959). Interestingly, the neural damage in cases with simultanagnosia due to acquired lesions typically involves extensive bilateral frontoparietal areas (Chechlacz et al., 2012; Ptak, 2012), including the same regions (e.g., Corbetta, 1998) that are affected in predementia phases of AD (Perry and Hodges, 1999). Thus, some degree of simultanagnosia can be expected to be present in aMCI patients, too.

A crucial step towards a systematic analysis of processing speed and visual short-term memory (VSTM) as putative causes of simultaneous object perception deficits was taken by applying parametric measurement of attention based on the "Theory of Visual Attention" (TVA; Bundesen, 1990) to patients with simultanagnosia. TVA is a unified computational account for visual single-stimulus recognition and attentional selection from multielement displays (Bundesen, 1990), essentially implementing a mathematical formalization of the biased competition model (Desimone and Duncan, 1995). Within TVA, both visual recognition and attentional selection consist in making perceptual categorizations (Bundesen, 1998). There are 2 fundamental capacity parameters that can be independently estimated based on the TVA formalization: visual processing speed C and VSTM storage capacity K. Parameter C is a quantitative estimate of the number of objects that can be processed in parallel per second; parameter K, in turn, is the estimate of the maximum number of objects that can be maintained simultaneously in the VSTM store. Both C and K parameters can be derived from an individual's performance in a whole-report task, where observers' ability to perceive and report multiple letter stimuli is assessed as a function of the effective array exposure duration (Bundesen, 1990) (for application in clinical samples, see Bublak et al., 2011; Finke et al., 2005; McAvinue et al., 2015). Using TVA assessment, Duncan et al. (2003) found severely reduced visual processing speed, even with single-item presentation, in 2 patients with both dorsal and ventral simultanagnosia, while VSTM storage capacity appeared to be preserved (Duncan et al., 2003). Furthermore, Finke et al. (2007) conducted a first group analysis based on TVA: an assessment of patients with Huntington's disease, who typically suffer from increasingly severe visual processing speed deficits (Finke et al., 2006). Finke et al. (2007) found that patients with more pronounced slowing displayed greater impairments in simultaneous object perception. They concluded that a slowing of the rate of visual information uptake gives rise to impaired perception of multiple overlapping stimuli in Huntington's disease (Finke et al., 2007). These results were also replicated in a recent study in patients with posterior cortical dementia (Neitzel et al., 2016). Of note, a staged decline of visual processing speed was also found in the amnestic form of Alzheimer's disease (Bublak et al., 2011). Thus, given the relevance of deficient visual processing speed in diverse patient groups, in the present study we, too, focused on the role of this specific attentional (dys)function with regard to potential deficits in simultaneous object perception in aMCI patients.

In particular, we aimed to ascertain whether there are deficits in simultaneous object perception in aMCI due to AD, and, if so, whether these deficits are associated with a reduction of visual processing speed. To this end, we compared aMCI patients and healthy control (HC) participants on several simultanagnosia tests and a TVA-based whole-report paradigm.

2. Materials and methods

2.1. Participants

Sixteen patients with a diagnosis of aMCI due to AD (9 females; mean age 70.9 ± 7.8 years; 11.6 mean years of education) and 16 age-, gender-, and education-matched HCs (9 females; 69.9 ± 7.4 years old, 11.6 mean years of education) participated in our study. Patients were diagnosed at, and recruited from, the Memory Clinic of the Department of Psychiatry, Technische Universität München, Germany, and controls were recruited from the general community through flyers and word-of-mouth recommendation. All participants gave written informed consent to take part in this study according to the Declaration of Helsinki II, and the study had local ethical committee approval.

Participants underwent a standardized diagnostic process that included medical, psychiatric, and neurological examinations. Patients had additionally brain-imaging diagnostics including structural magnetic resonance imaging and fluorodeoxyglucose positron emission tomography. All participants had undergone an informant-derived Clinical Dementia Rating (Morris, 1993), with patients having values of 0.5 and controls of 0, and neuropsychological assessment using the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; German version; Berres et al., 2000), including the Mini–Mental State Examination (MMSE; Folstein et al., 1975) and the clock-drawing test (Shulman et al., 1993). Based on this assessment, aMCI patients fulfilled cognitive impairment criteria according to Petersen (Petersen et al., 1999, 2001), along with largely preserved activities of daily living (Bayer ADL scale; Hindmarch et al., 1998), and no dementia according to the International Classification of Diseases, Tenth Revision criteria (WHO, 2010). Furthermore, all aMCI patients of this study met the criteria for MCI due to AD (Albert et al., 2011). Beyond patients' MCI, they had biological signs of AD in terms of bilateral temporoparietal hypometabolism as shown in fluorodeoxyglucose positron emission tomography (Albert et al., 2011). Criteria for exclusion from the study were history of other neurological diseases and imaging evidence of marked brain lesions that affected cognition (e.g., stroke lesions). Three of the 16 patients were under antidepressant medication (n = 1 with selective serotonin reuptake inhibitors, n = 1 with tricyclic, and n = 1 with noradrenergic and specific serotonergic antidepressants). Concerning genotyping, 11 patients had either 1 (n = 9) or 2 (n = 2) alleles of the APOE $\varepsilon 4$ allele.

HCs were free of any current, or history of, psychiatric or neurological condition. Patients and controls did not differ in age, gender, or education (see Table 1). As expected from the diagnosis, aMCI patients had significantly lower MMSE scores, that is, a lower global cognitive state, than controls [$t(30) = -4.025$, $p < 0.001$] (Table 1 for all demographic details). All aMCI patients were able to follow verbal instructions and to concentrate sufficiently during the tasks. All participants had normal or corrected-to-normal vision and were not color-blind.

2.2. Procedure

After their routine clinical assessment, aMCI patients and controls underwent testing of simultanagnosia and visual attention, specific for the present study. This testing was conducted in 2–3 one-hour sessions. Well-established clinical test batteries known to be sensitive to simultanagnosia symptoms were administered to most of our study participants (n = 13 aMCI and n = 10 HC). Moreover, the simultaneous perception task (SPT), a time-unlimited experimental task that allows for different levels of

Table 1
Demographic variables of both groups

Variable	aMCI patients, $n = 16$	Control participants, $n = 16$	t (30)	p-value
Sex (female [%]/male [%])	7/9 (43.8)/(56.3)	7/9 (43.8)/(56.3)	—	—
Age (y)	70.86 (7.81)	69.95 (7.39)	0.34	0.369
Education (y)	11.63 (1.86)	11.63 (1.02)	0.00	0.500
MMSE/30	26.69 (1.49)	28.44 (0.89)	**−4.02**[a]	<0.001
Handedness (right/left/ambidextrous)	15/1/0	12/2/2	—	—

Bold value indicates statistical significance at $p = 0.0004$.
Key: MMSE, Mini–Mental State Examination; aMCI, amnestic mild cognitive impairment.
[a] Statistically significant at $p < .05$, 1-tailed. Means (standard deviation, SD) are shown if not otherwise stated (Folstein et al., 1975).

difficulty and has proved useful to reveal simultanagnosia symptoms in neurodegenerative samples, such as Huntington's disease (Finke et al., 2007), was applied in all participants. To assess visual attention, TVA-based whole and partial reports were applied in all participants, but we only focus on the whole-report results here. In both the SPT and the TVA whole-report (TVA-WR), stimuli were shown on a 17-inch monitor (1024 × 768 pixels screen resolution). The viewing distance was approximately 50 cm.

2.3. Assessment of simultanagnosia symptoms

2.3.1. Neuropsychological assessment of simultanagnosia—BORB and VOSP

Specific tasks were taken from 2 standardized and widely used neuropsychological batteries that are employed to assess impairments in the simultaneous perception of visual objects and spatial locations in patient populations. More specifically, the overlapping figures–line drawings subtest of the Birmingham Object Recognition Battery (BORB) (Riddoch and Humphreys, 1993) and the subtests Dot Counting, Position Discrimination, and Number Location of the Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991) were used. For the BORB, we obtained the time (in seconds) per sheet in paired nonoverlapping and overlapping line drawing condition and a ratio between the 2 (i.e., overlapping time divided by nonoverlapping time). For the VOSP, we used the total score of correct responses in each subtest.

2.3.2. Experimental assessment of simultaneous object perception—SPT

The SPT (Finke et al., 2007) is an experimental task that assesses simultaneous object perception deficits. We consider the SPT as complementary to the standard neuropsychological simultanagnosia batteries because it is time-unconstrained (i.e., it sets no time limit for participants to respond to stimuli), uses basic geometric shapes for which no elaborated semantic knowledge is needed, and delivers more detailed information on the pattern of deficits in simultaneous object perception because set sizes and condition types vary. In short, the SPT consists of the digital presentation of 9 different black line drawings of shapes on a white background without time limit. These 9 line drawings correspond to basic shapes including square, triangle, heart-shape, pentagon, hexagon, moon, cross, star, and circle (see Fig. 1). The participant's task is to identify them in each of 16 trials under 4 conditions that increase in the complexity of simultaneous object perception. The first condition, single stimulus, is a control condition in which each of these open shapes is separately presented twice; this condition permits ensuring that the participant can correctly perceive, identify, and name all the stimuli. In the 3 following conditions, adjacent, embedded, and overlapping, the shapes are simultaneously presented in trial displays with 2 to 5 items presented in an adjacent, embedded, or overlapping manner (Fig. 1). After the participant indicates that the answer is complete, the next trial starts. A trial counts as an error if the participant is not able to identify at least one of the shapes presented on that trial. The percentage of error trials is computed for each of the conditions that include simultaneously presented shapes. Importantly, we made sure that all participants were able to correctly name all shapes presented in whatever size, small or large, in a pretest. Moreover, to reduce the influence of potential changes in verbal recall ability, or of variability of verbal productions, in patients, the verbal labels they assigned to displayed objects were scored as "correct" even if these labels were "uncommon", as long as they indicated correct visual identification.

2.4. Assessment of visual attention

TVA is a computational model that permits mathematical estimation of relevant, independent attentional capacity parameters such as visual processing speed, *C*, and VSTM storage capacity, *K* (Bundesen, 1990). The participant's task is to report verbally as many letters as possible from briefly presented arrays of letters on a black background. Only "fair certainty" of recognition, rather than the order or speed of reporting, is emphasized in the instruction. The duration of the arrays is individually adjusted in a short pretest.

Fig. 1. Example-items: (A) adjacent (B) embedded, and (C) overlapping shapes condition of the simultaneous perception task (SPT; see (Finke et al., 2007) for a presentation of all trial displays). Each condition has 4 trials of 2–5 different geometrical shapes that are presented to the participant without time limit. A trial counts as an error trial if the participant fails to identify at least one of the shapes. Before the adjacent condition, there is a control condition, in which each shape is presented alone to ensure that the participant can identify and name them all.

Table 2
BORB and VOSP results for both groups

Subtest	aMCI patients ($n = 13$)		Healthy controls ($n = 10$)		$t(21)$	p-value	95% CI	Cohen's d
	M	SD	M	SD				
BORB								
Paired nonoverlapping (seconds per sheet)	25.78	7.89	21.95	4.57	1.36	0.093	[−2.01 to 9.67]	0.59
Paired overlapping (seconds per sheet)	38.82	23.71	25.13	3.80	**1.80**	0.043	[−2.14 to 29.52]	0.79
Ratio (overlapping/nonoverlapping)	1.48	0.50	1.16	0.14	**1.92**	0.034	[−0.02 to 0.65]	0.84
VOSP								
Dot counting/10	9.31	1.11	9.70	0.67	−0.98	0.168	[−1.22 to 0.44]	−0.43
Position discrimination/20	17.92	2.46	19.50	0.85	**−2.15**	0.024	[−3.14 to −0.01]	−0.94
Number location/10	8.38	1.56	8.70	1.16	−0.53	0.299	[−1.54 to 0.91]	−0.23

In bold are statistically significant at $p < 0.05$, 1-tailed.
Key: aMCI, amnestic mild cognitive impairment; BORB, Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993); line drawings condition; CI, confidence interval of the difference; M, mean; SD, standard deviation; VOSP, Visual Object and Space Perception Battery (Warrington and James, 1991).

The experimenter enters the reported letters in the reported order and starts the next trial with a button press.

To estimate TVA parameters, an exponential growth function models the participant's letter report accuracy as a function of the effective exposure duration, according to a maximum likelihood method. The threshold for visual perception, parameter $t0$, expressed in milliseconds, is the estimated minimal exposure duration below which information uptake is assumed to be zero. The other 2 parameters estimated from TVA-WR accuracy are processing speed C, that is, the number of items that can be processed in parallel per second, and VSTM storage capacity K, that is, the number of items that can be held in a VSTM store.

2.5. Statistical analysis

The SPSS v.22 statistical package was used to perform statistical analyses. Two-sample t-tests were used to evaluate the differences between aMCI patients and controls in all demographic variables as well as in TVA-WR parameter estimates, and BORB, and VOSP results. A mixed ANOVA was conducted on SPT performance (i.e., percentage of errors) with group (aMCI, HC) as between-subjects factor, and condition type (adjacent, embedded, and overlapping) and set size (2, 3, 4, and 5) as within-subjects factors, to compare group performance in multiple object perception. Finally, a Spearman-rho analysis was performed to evaluate the association between SPT performance in the overlapping condition and TVA-WR parameter estimates (processing speed C, and VSTM storage capacity K) in the group of aMCI patients.

3. Results

3.1. Patients show simultaneous object perception deficits in clinical neuropsychological and experimental tasks

3.1.1. Simultanagnosia symptoms in standard neuropsychological tests

Participants' performance in the BORB and VOSP is presented in Table 2. In the BORB, aMCI patients needed roughly the same time as controls to name nonoverlapping pairs of line drawings [patients: M = 25.78, SD = 7.89 seconds vs. controls: M = 21.95, SD = 4.57 seconds, $t(21) = 1.36$, $p = 0.093$, Cohen's d = 0.59], but significantly more time than controls to name pairs of overlapping line drawings [M = 38.82, SD = 23.71 seconds vs. M = 25.13, SD = 3.80 seconds, $t(21) = 1.80$, $p = 0.043$, Cohen's d = 0.79]. Thus, we found higher overlapping to nonoverlapping figure ratios for aMCI patients than for controls [M = 1.48, SD = 0.50 versus M = 1.16, SD = 0.14, $t(21) = 1.92$, $p = 0.034$, Cohen's d = 0.84]. Analyzing the aMCI patients' performance based on the BORB test norm data [i.e., M = 21.5 seconds per sheet (0.9 per item) for overlapping line drawings, and M = 23.9 per sheet (1.0 per item) for nonoverlapping drawings] revealed that they were significantly impaired in their identification (i.e., naming) time for both nonoverlapping and overlapping line drawings (Riddoch and Humphreys, 1993). At the individual level, all but one aMCI patients exhibited longer identification times and higher overlapping to nonoverlapping ratios than the average values reported in the test's norms (i.e., 1.0/1.1; Riddoch and Humphreys, 1993). Of note, general performance in the BORB did not correlate with the CERAD delayed verbal recall (p-value >0.1), and only the overlapping to nonoverlapping ratio significantly correlated with the CERAD delayed visual recall (rho = −0.786, $p = 0.001$), so that longer times to identify overlapping, compared to nonoverlapping, figures were associated with lower scores in visual recall.

In the space perception battery of the VOSP, aMCI patients exhibited significantly lower performance than controls in the Position Discrimination subtest only [patients: M = 17.92, SD = 2.46 vs. controls: M = 19.50, SD = 0.85, $t(21) = -2.15$, $p = 0.024$, Cohen's d = −0.94; other subtests' p-values >0.1]. An additional comparison of aMCI patient data to the tests' norm data revealed that in Position Discrimination, aMCI patients scored on average below the 5% cut-off score (i.e., 18) for healthy participants and their numerical average was even below that of the clinical norm group with right-hemisphere damage (i.e., M = 18.7) (Warrington and James, 1991). At the individual level, almost half (46%) of the patients failed this subtest. We did not find significant differences between the groups in the Dot Counting and Number Location subtests, with the patients too performing within the norms in these tests. Unlike the BORB, the VOSP Position Discrimination scores correlated significantly negatively with the CERAD delayed verbal recall (rho = −0.724, $p = 0.003$), but not with the visual recall (rho = −0.081, $p = 0.396$). However, when the association between Position Discrimination and delayed verbal recall was assessed in the only 6 patients who failed the subtest, the correlation was no longer significant (rho = 0.088, $p = 0.434$).

In sum, aMCI patients showed deficits in simultaneous object perception in standard neuropsychological tests. These deficits were revealed chiefly in the BORB overlapping figures—line drawings subtest, sensitive to simultanagnosia symptoms. Additionally, significant deficits in position discrimination appear to indicate a deficit in simultaneous perception of spatial locations. However, normal performance in dot counting and location of numbers indicates that spatial perception was basically spared in the aMCI patients. Importantly, the deficits observed in aMCI were not related to low global cognitive state as measured by the MMSE (all p's > 0.2). Only the deficit in simultaneous perception of spatial locations was related to verbal memory performance, and only the

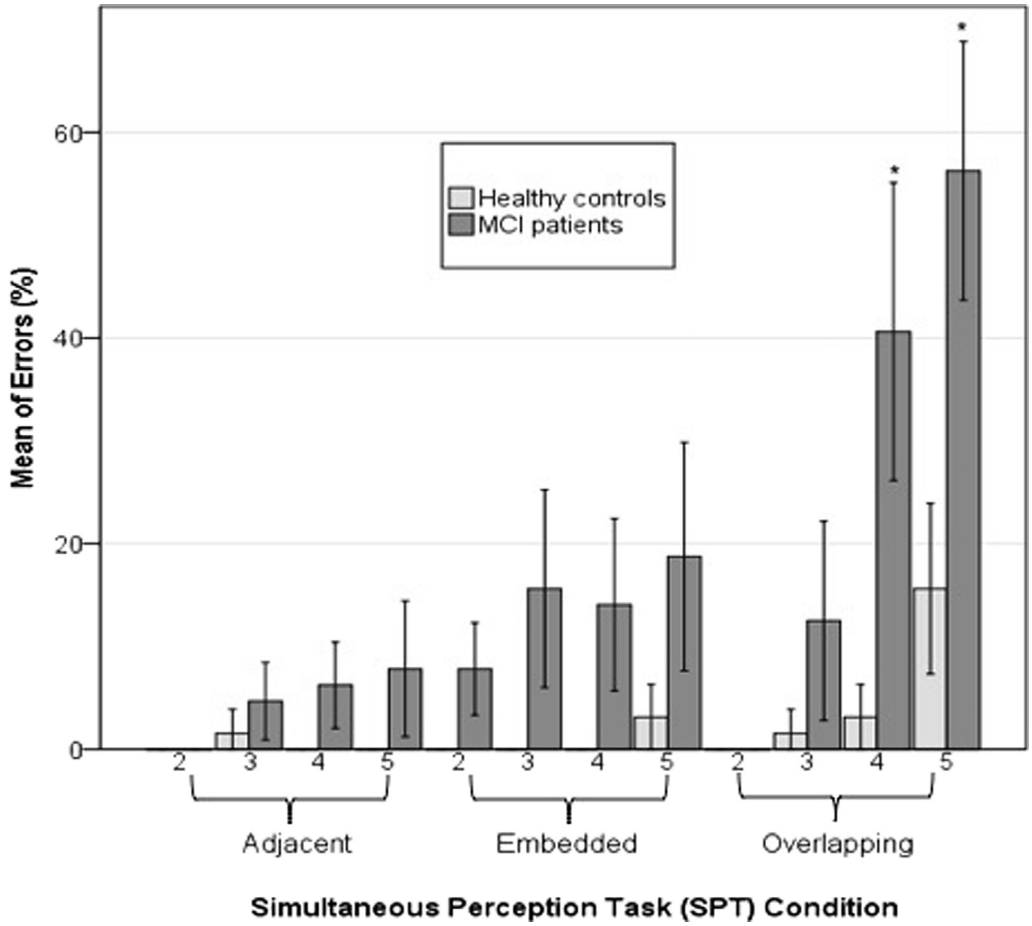

Fig. 2. Mean error percentages in the simultaneous perception task (SPT) per set size and condition type are depicted for the MCI patients group (dark gray) and the age-, gender-, and education-matched healthy control participants group (light gray). Note that aMCI patients did not make errors in the 2-shapes trials in both the adjacent and overlapping conditions of the SPT. Error bars indicate standard error of the mean. *Significantly different at $p < 0.005$, 2-tailed. Abbreviations: aMCI, amnestic mild cognitive impairment; MCI, mild cognitive impairment.

overlapping to nonoverlapping ratio was associated with visual memory performance.

3.1.2. Simultaneous object perception deficits in experimental SPT task

Average error percentages in the SPT are depicted in Fig. 2 separately for each group, condition, and set size. The mixed ANOVA, with main terms for group, condition, and set size, revealed all main effects to be significant (group: $F_{1,\ 30} = 18.482$, $p < 0.001$; condition: $F_{1.79,\ 53.66} = 20.173$, $p < 0.001$; and set size: $F_{2.93,\ 87.93} = 19.909$, $p < 0.001$). Three 2-way interactions among the factors were also observed (group by condition: $F_{1.79,\ 53.66} = 8.481$, $p = 0.001$; group by set size: $F_{2.93,\ 87.93} = 8.434$, $p < 0.001$; and condition by set size: $F_{3.47,\ 103.98} = 10.868$, $p < 0.001$). Finally, there was also a significant group by condition by set size interaction ($F_{3.47,\ 103.98} = 4.003$, $p = 0.007$). To analyze this 3-way interaction in more detail, we computed mixed ANOVAs with the factors group and set size separately for each condition (i.e., adjacent, embedded, and overlapping). In all conditions, significant main effects of group (adjacent: $F_{1,\ 30} = 5.171$, $p = 0.030$; embedded: $F_{1,\ 30} = 11.942$, $p = 0.002$; overlapping: $F_{1,\ 30} = 16.904$, $p < 0.001$) indicated that aMCI patients generally made more errors than controls. A significant main effect of set size was found only in the overlapping condition ($F_{2.652,\ 79.56} = 24.513$, $p < 0.001$; adjacent and embedded p's > 0.188). Similarly, the group by set size interaction was only significant in the overlapping condition ($F_{2.652,\ 79.56} = 9.518$, $p < 0.001$; adjacent and embedded p's > 0.188). Post hoc *t*-tests showed that aMCI patients were significantly worse than HCs when more than 3 shapes were simultaneously presented [Fig. 2; 4 shapes, mean: 40.62 vs. 3.12, aMCI patients and controls, respectively, $t(30) = 3.795$, $p = 0.001$, Cohen's $d = 1.38$; 5 shapes: 56.25 vs. 15.62, respectively, $t(30) = 4.044$, $p < 0.001$, Cohen's $d = 1.48$; both p's 1-tailed]. These results indicate that aMCI patients were in general worse than controls in identifying simultaneously presented shapes. However, only when these shapes were presented in an overlapping manner did aMCI patients show particularly severe difficulties with larger set sizes (i.e., >3 items).

3.2. Visual attention deficits

As listed in Table 3, aMCI patients exhibited significantly lower processing speed *C* estimates and significantly higher perceptual thresholds *t0* than HC participants in the TVA-WR. In other words, aMCI patients required relatively longer stimulus durations and were able to process fewer elements simultaneously compared to control participants. However, we did not find a significant difference in VSTM storage capacity *K* estimates between groups. Neither processing speed *C* (rho $= -0.242$, $p = 0.183$) nor *t0* estimates (rho $= -0.372$, $p = 0.130$) significantly correlated with global cognitive state as assessed by the MMSE.

Table 3
Whole-report TVA (TVA-WR) estimates for aMCI patients and healthy controls

TVA-WR parameters	aMCI patients ($n = 16$)		Healthy controls ($n = 16$)		$t(30)$	p-value	95% CI	Cohen's d
	M	SD	M	SD				
Processing speed *C*	13.82	5.37	17.55	5.36	**−1.97**	0.029	[−7.60 to 0.25]	−0.72
Storage capacity *K*	2.63	0.39	2.69	0.44	−0.37	0.358	[−0.35 to 0.25]	−0.13
Visual threshold *t0*	112	60.39	35.17	46.91	**4.02***	<0.001	[37.78 to 115.87]	1.47

Bold values are statistically significant at $p < 0.05$ and at $p < 0.001$ (*), 1-tailed.
Key: aMCI, amnestic mild cognitive impairment; CI, confidence interval of the difference; M, mean; SD, standard deviation; TVA, Theory of Visual Attention (Bundesen, 1990).

3.3. Overlapping figure perception deficits are associated with reduced processing speed in aMCI

To determine whether simultaneous object perception deficits in patients with aMCI are associated with a slowing in visual information uptake (i.e., a reduction in visual processing speed *C*), we correlated the percentage of errors in the SPT overlapping condition, collapsed across set size (i.e., the measure that was assumed to be most sensitive for subtle changes in simultaneous object perception and that turned out to be most affected), with processing speed *C* in patients with aMCI. As expected, higher error percentages in identifying simultaneously presented, overlapping objects were associated with lower estimates of processing speed *C* (Fig. 3; rho = −0.497, $p = 0.025$, 1-tailed), but not with VSTM capacity *K* (rho = 0.034, $p = 0.450$) or *t0* (rho = 0.148, $p = 0.292$) estimates. To examine whether the relationship between simultaneous perception deficits and processing speed would be confirmed when using clinically established tasks for the assessment of simultanagnosia, we calculated the correlations between visual processing speed and performance on those tasks on which patients performed worse than HCs. Note that complete data were available only for a subgroup of patients ($n = 13$). We found a tendency towards a negative relationship between the latencies to name pairs of overlapping objects in the BORB and processing speed *C* (rho = −0.426, $p = 0.073$). However, the correlation between errors in the Position Discrimination condition of the VOSP and processing speed *C* was nonsignificant (rho = 0.128, $p = 0.339$). The correlation between the percentage of errors in the SPT and processing speed *C* did not change for patients with at least one risk e4 allele of ApoE ($n = 11$) compared to the whole sample of patients ($n = 16$) and became nonsignificant (closed circles in Fig. 3; rho = −0.372, $p = 0.130$). Importantly, these deficits in simultaneous object perception did not relate to the relatively low global cognitive state in aMCI patients as assessed by the MMSE (rho = −0.301, $p = 0.128$), or to verbal memory as assessed in the CERAD delayed verbal recall (rho = 0.111, $p = 0.341$). However, similar to the BORB results, simultaneous object perception deficits in aMCI patients did also relate to visual memory recall (rho = −0.532, $p = 0.017$) and were, thus, not solely impaired by the patients' relatively low global cognitive state or general memory impairments.

We also examined whether a more low-level visual impairment, that is, the elevated visual threshold that was documented, might alternatively, or additionally, explain the deficits in SPT performance. Importantly, the significant association between visual processing speed *C* and percentage of errors in the SPT overlapping condition was replicated when controlling for *t0* (rho = −0.492, $p = 0.031$). Accordingly, the simultaneous object perception deficits displayed by aMCI patients are not so much related to a more basic

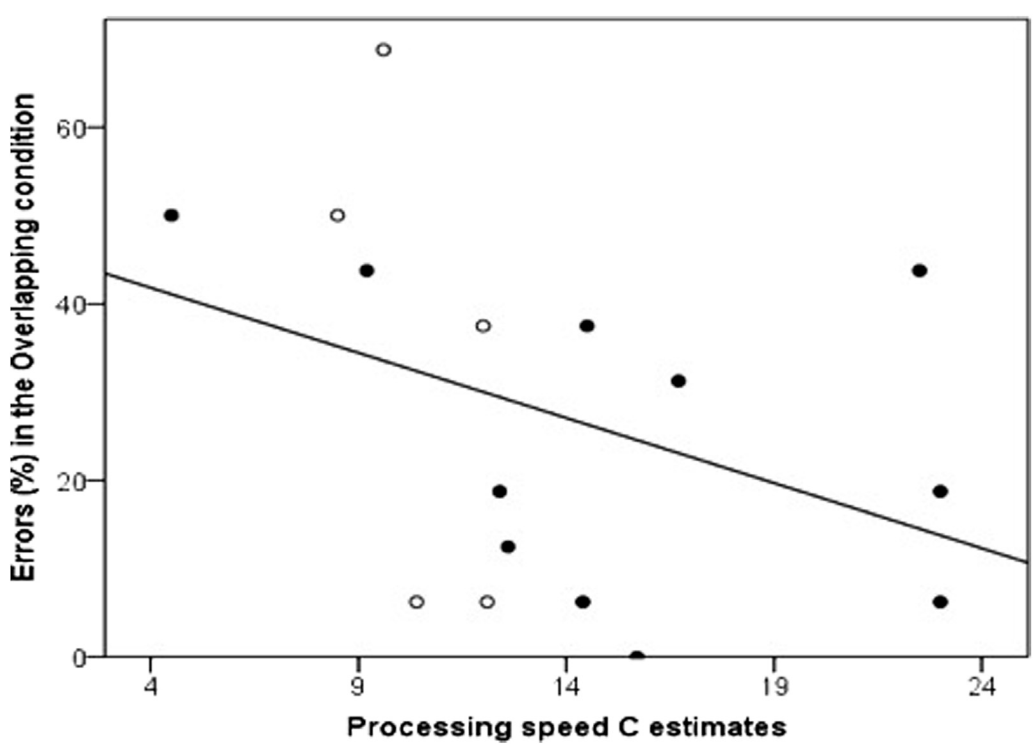

Fig. 3. Scatterplot relating aMCI patients' individual parameter estimates of visual processing speed *C* and their percentage of errors in the overlapping condition of the simultaneous perception task (SPT). *C* estimates are significantly negatively correlated with errors; rho = −0.497, $p = 0.025$, 1-tailed. Closed circles are aMCI patients with at least one risk allele (4 allele) and open circles are aMCI patients with the 3 allele or 2 allele. Abbreviation: aMCI, amnestic mild cognitive impairment.

elevation of the visual threshold than to a reduction of visual processing speed per se.

Finally, we examined for a more general association between the rate of visual information uptake and simultaneous object perception also in our normal observers. The respective correlation between the percentage of errors in the SPT overlapping condition and visual processing speed C was not significant in the HC group (rho = −0.162, $p = 0.274$, 1-tailed). However, the difference between the respective correlation coefficients of the patient and healthy groups was not significant either ($Z = 0.97$, $p = 0.166$, 1-tailed).

4. Discussion

The present study investigated whether aMCI patients show a deficit of simultaneous object perception and whether such a deficit is attributable to a reduced visual processing rate. We provide direct evidence for (1) simultaneous object perception deficits in aMCI as an early symptomatic predementia phase of AD and (2) reduced visual processing speed underlying simultaneous object perception deficits. Three main findings support this evidence. First, aMCI patients show deficits in simultaneous object perception. More specifically, when aMCI patients had to identify each one of a set of overlapping shapes in the BORB, they needed significantly more time than age-, education-, and gender-matched HCs, resulting in significantly higher overlapping to nonoverlapping time ratios. Second, compared to HCs, aMCI patients showed significantly lower processing speed C in a TVA-based whole-report paradigm. Finally, specifically the individual severity of the processing speed reduction was significantly related to—and would, thus, appear to underlie—the simultaneous object perception deficits in aMCI.

4.1. Simultaneous object perception deficits in aMCI

We found that patients with aMCI had significant difficulties compared to HCs in 2 tasks of simultaneous object perception, the BORB and the SPT. In both tasks, deficits occurred in particular when objects were presented in an overlapping manner, that is, under conditions that are conducive for simultanagnosia symptoms to become manifest (Bálint and Harvey, 1995; Laeng et al., 1999; Luria, 1959; Riddoch and Humphreys, 2004; Valenza et al., 2004). More precisely, in the BORB, aMCI patients were slow particularly in the overlapping condition, as indexed by a higher overlapping to nonoverlapping time ratio; in the SPT, they exhibited an increasing number of errors with increasing set size particularly in the overlapping condition. Importantly, aMCI patients showed relatively normal speed in identifying nonoverlapping drawings in the BORB, and all patients were able to name the single shapes presented at all (large and small) sizes in the screening part of the SPT, as well as in the adjacent condition. Thus, importantly, the deficit in identifying overlapping shapes does not relate to reduced visual acuity, semantic memory deficits, or visual object agnosia. Remarkably, although simultaneous object perception deficits as reported here are characteristic of posterior cortical atrophy (Neitzel et al., 2016; Tang-Wai et al., 2004) and quite common in AD dementia (Mendez et al., 1990; Rizzo et al., 2000), whether they are also present in individuals with aMCI at a symptomatic predementia phase of the more typical form of AD had, to the best of our knowledge, not been systematically tested before.

The use of the experimental SPT delivered fine-grained information on the nature of the multiple object perception deficits in aMCI. Specifically, we observed that only when stimuli were presented in an overlapping manner did aMCI patients show increased set size effects compared to HCs. Of note, the simultaneous object perception deficits were not only evident in our experimental task, but were also revealed in the BORB. As the diagnosis of aMCI focuses on memory impairments, simultaneous object perception is usually not evaluated in routine neuropsychological assessment; thus, it is unsurprising that such deficits in an established standard neuropsychological test for simultanagnosia had not been reported before. Furthermore, it is worth noting that both tasks use free viewing conditions without any time restrictions, and yet performance was particularly compromised in conditions with multiple overlapping shapes. In most previous studies, the duration of stimulus exposition to patients with simultanagnosia had been limited (Coslett and Saffran, 1991; Duncan et al., 2003; Huberle and Karnath, 2006; Pavese et al., 2002). In the present study, by contrast, we used the nonspeeded SPT to enable us to examine separately processing speed and simultaneous object perception. In other words, we used the SPT to determine whether indications of slowing of visual processing in a whole-report task using briefly presented letter arrays (Duncan et al., 2003; Finke et al., 2007) can make valid predictions regarding deficits under unconstrained viewing conditions.

Furthermore, the present study revealed a positive association between the degree of simultaneous object perception deficits and the degree of visual memory impairment in aMCI patients. In the BORB, higher overlapping to nonoverlapping time ratios related to lower scores in visual recall. In the SPT, more errors in the overlapping condition related to lower scores in visual recall. Thus, our results shed light on the question as to why especially visual memory tests using complex visual material such as the Rey—Osterrieth and the Benton tests are exceptionally sensitive for the earliest AD-related decline even in the preclinical phase (Kawas et al., 2003). Difficulties in these tasks might result from basic impairments in the encoding of multiple visual stimuli or stimuli containing multiple parts. Thus, while appropriate for cognitive screening, conclusions about the deficits underlying low performance in these tests should be drawn with caution.

Unlike with visual memory impairments, simultaneous object perception deficits were not associated with relatively low global cognitive state or verbal memory impairments in aMCI. This lack of association strongly suggests that simultaneous object perception deficits constitute an independent aspect in their own right in aMCI, which might, in turn, underlie low performance in visual memory tasks. In the context of evidence suggesting that aMCI is a heterogeneous entity in its clinical progression (Li and Zhang, 2015), assessing simultaneous object perception might help disclose multidimensionality in aMCI patients who, at first glance, present as a single-domain aMCI individuals. The simultaneous object perception deficits displayed by aMCI patients are, however, not comparable to those shown by the classical cases reported by Bálint (1909); rather, they would be classified only as “mild” (Hecaen and De Ajuriaguerra, 1954).

Concerning daily-life functioning, we usually do not perceive and handle objects in an isolated manner. Thus, arguably, increasing deficits in the simultaneous perception of objects likely contribute to the incipient problems of daily living during aMCI, including impairments in spatial navigation (Laczo et al., 2009), such as in way-finding (Allison et al., 2016), which might signal the clinical start of AD dementia.

4.2. Visual processing speed reduction leads to simultaneous perception deficits in aMCI

In the present study, we followed the group study—based approach to neurodegenerative diseases advocated by Rizzo and Vecera (2002) and first applied by Finke et al. (2007) in research on simultanagnosia and its underlying attentional deficits. Based on a staged decline in visual attention functions and in particular processing speed in individual cases of aMCI (Bublak et al., 2011), and on previous reports that visual processing speed reduction can lead to symptoms of simultanagnosia (Chechlacz et al., 2012; Duncan et al., 2003; Finke et al., 2007; Neitzel et al., 2016), we hypothesized that reduced visual processing speed underlies simultaneous object perception deficits in aMCI. In agreement with the results in patients with stroke (Duncan et al., 2003) and Huntington's disease (Finke et al., 2007), we observed a significant association between visual processing speed and simultaneous object perception in aMCI patients. Taken together, these results indicate that aMCI patients' reductions in visual processing speed underlie their simultaneous object perception deficits. Moreover, our results complement the previous findings in indicating that, despite heterogeneous causes, the relationship between a reduced speed of visual information uptake and deficient simultaneous objects perception constitutes a general principle across patients with symptoms of simultanagnosia. Likewise, our results add to the existing evidence that sufficient visual processing speed provides the necessary basis for identifying, integrating, and making sense of the components of complex visual scenes. Accordingly, the association between processing speed (reductions) and simultaneous object perception (errors) would not be exclusive to aMCI patients, but may hold for healthy participants too. In the present study, such an association may simply have been obscured by healthy participants performing near ceiling on the simultaneous object perception task. Consistent with a general association, we did not find a significant difference in the correlation coefficients between the aMCI patients and the control participants. However, further studies using experimental conditions best suited to assess simultaneous object perception in healthy samples are required to settle the generalizability of this association.

At a first glance, it might seem astonishing that reduced visual processing speed would affect the identification of overlapping shapes only, leaving the speed and accuracy of identifying multiple shapes presented in an embedded or adjacent fashion relatively unaffected. As similarly argued before (Duncan et al., 2003; Finke et al., 2007), patients with slow visual processing might use a strategy of serial selection. Consistent with the piecemeal perception known from patients with simultanagnosia (Paterson and Zangwill, 1944; Rizzo and Vecera, 2002), such a strategy would engender the selection of one stimulus after the other. For example, with adjacent stimuli, adaptive concentration of the available, reduced processing resources on a given stimulus location at a time will increase the likelihood of successful encoding, though the overall time taken for the whole set of stimuli will be increased and patients will appear to perform slower. Embedded stimuli, too, might be processed and reported in series, starting with the outer- or inner-most object and reporting them in a sequential manner, ordered by stimulus size. When objects are overlapping, as they typically are in multielement complex daily scenes, according to biased competition models (Bundesen, 1990; Bundesen et al., 2005; Desimone and Duncan, 1995), objects would compete for selection and access to VSTM. Moreover, the amount of processing capacity that is distributed among objects is limited, and, thus, only those objects that are processed fastest are selected and stored in VSTM (Bundesen, 1990). If processing capacity is overall reduced—as in patients with simultaneous perception deficits—only the most salient object can be selected; the others, by contrast, will not gain access to VSTM and will thus not be consciously represented (Duncan et al., 2003).

One might expect that processing speed would also be related to performance in the adjacent and embedded conditions, given that multiple objects must be perceived and categorized across all SPT conditions. In nonoverlapping conditions, however, the receptive fields are not shared, as a result of which the neural competition is not as severe as in the overlapping condition (Bundesen et al., 2005; Desimone and Duncan, 1995). In our overlapping condition, the stimulus array contained multiple objects that were superimposed at the same location, that is, they were segmented into shape parts, or fragments, with overlapping contours. In this situation, a serial selection strategy cannot be successful. Due to the concentration of processing resources on one single location, 2 or more objects that share the same position will also have to share processing capacity. Thus, when patients with slowed visual processing are forced (to attempt) to divide their limited processing resources among multiple objects, their capacity will be exhausted (Humphreys and Price, 1994; Riddoch and Humphreys, 2004). Consequently, the likelihood of making errors or omitting some objects will be high, because patients cannot muster the resources necessary to reach the depth of discrimination required for successful (whole-) object identification. Thus, all but the most salient objects will have only a low probability of being identified.

The association with visual processing speed C was only borderline significant with performance in the paired overlapping condition of the BORB, and not reliable for the Position Discrimination condition of the VOSP. These results differ from a previous report of significant correlations in patients with posterior cortical atrophy (Neitzel et al., 2016). As clinical neuropsychological batteries designed to assess severe symptoms, the BORB and VOSP may not be sensitive to more subtle deficits in simultaneous object perception, as displayed by aMCI patients. In the BORB, only pairs of overlapping objects are presented, while in the SPT aMCI patients showed a significantly increased error rate only at higher set sizes in the overlapping condition (see Fig. 2 and Table 2). Thus, the more complex SPT, with up to 5 overlapping stimuli, yielded a greater variation of responses, permitting a significant relationship between simultaneous object perception deficits and reduced processing speed to be successfully established in aMCI.

Since the first analyses of patients with simultanagnosia, the precise underlying cognitive deficit has been a matter of debate. For example, a "general weakening" of visual traces (Luria, 1959) or visual representations (Bálint, 1909) was suggested to slow even the perception of single objects, thereby disproportionately affecting the perception of multiple objects. This view received support from evidence that single-item processing too is slowed in patients with simultanagnosia (Friedman and Alexander, 1984; Kinsbourne and Warrington, 1962; Levine and Calvanio, 1978). Other authors (Coslett and Saffran, 1991; Friedman-Hill et al., 1995; Pavese et al., 2002) proposed that a deficit in VSTM storage gives rise to an inability to bind shape and position properties of more than 1 object and, as a result, in storing multiple objects. Accordingly, Rizzo and Vecera (2002) proposed to take attentional functions and specifically VSTM into consideration to gain a clearer understanding of simultanagnosia. However, research examining whether VSTM or processing speed deficits underlie symptoms of simultanagnosia has found that the latter are primarily related to visual processing speed, rather than to VSTM storage capacity, reductions (Duncan et al., 2003; Finke et al., 2007; Neitzel et al., 2016).

It is well known that with increasing encoding time, more items can be encoded into VSTM (Vogel et al., 2006). Thus, appropriate methodological procedures are required for validly measuring (individual) VSTM capacity in participants with reduced visual processing speed. In the TVA-based whole-report paradigm, exposure durations are adjusted individually so as to ensure that even participants displaying severely reduced processing speeds and/or an elevated visual threshold can fill their VSTM store up to its limit (Bundesen, 1990; Finke et al., 2005). Following this approach (which permits processing speed and storage capacity to measured independently), we were able to demonstrate that VSTM storage capacity is actually relatively spared in aMCI patients. For subsequent stages of the disease—that is, AD dementia—, by contrast, previous reports have already documented reduced VSTM capacity (Bublak et al., 2011; Vecera and Rizzo, 2004).

4.3. Possible neural mechanisms underlying simultaneous object perception deficits in aMCI

According to the neural TVA, processing capacity is directly related to the number and activation of cortical neurons that are devoted to the processing of a visual object, so that (potentially) important objects are represented by more cells than less important ones (Bundesen et al., 2005, 2015). Consequently, any disease process that hampers neuronal function can reduce processing capacity.

In the typical aMCI, structural and functional changes of a frontoparietal network are well documented (Mattsson et al., 2014; Perry and Hodges, 1999; Sorg et al., 2007, 2012). Frontoparietal regions, as well as the white-matter tracts connecting them, are considered relevant for attentional processing (Coull et al., 1996; Ptak, 2012; Thiebaut de Schotten et al., 2011). Early in the process of AD, at the aMCI stage, frontal and posterior parietal regions show hypometabolism even without signs of gray matter atrophy (Kljajevic et al., 2014) and decreased functional connectivity (Sorg et al., 2007), and amyloid deposition, metabolic changes, and atrophy when AD is already established (Buckner et al., 2005).

Another factor that might contribute to reduced processing speed is the dysfunction of the cholinergic system, like that occurring in AD (Coyle et al., 1983), as cholinergic neurotransmission is known to be relevant for fast perceptual processing (Schliebs and Arendt, 2011). The cholinergic system is assumed to play a decisive role in the attentional processing of sensory stimuli (e.g., Rizzo, et al., 2000) due to its innervation of attention-related (i.e., frontal and parietal) areas (Lawrence and Sahakian, 1995). In sum, the simultaneous object perception deficits that we observed in patients with aMCI find an explanation in the reduction of visual processing speed, which, in turn, might be attributable to the neural changes in a frontoparietal attention network.

4.4. Limitations

Visual crowding due to contour interactions (Hess et al., 2000; Huurneman et al., 2012) might, conceivably, also explain simultaneous object perception deficits in aMCI patients. If so, the deficits would be indicative of a low-level visual, rather than a higher level cognitive, limitation. Indeed, in our sample of aMCI patients, the perceptual threshold *t0* was significantly increased (see Table 3). However, the association between visual processing speed *C* and SPT performance remained unaffected even when we controlled for this low-level factor. Future studies might more systematically vary contour interactions to examine for possible effects of visual crowding on simultaneous object perception in aMCI patients. Further, as deficits in attentional selection parameters have previously been described in aMCI (Redel et al., 2012), follow-on studies might also profitably investigate the association between TVA partial-report and SPT performance. Moreover, further research would be necessary in order to determine whether visual processing speed is a basic mechanism underlying simultaneous object perception in healthy observers generally.

4.5. Outlook

The findings of significant simultaneous object deficits have clinical implications and demonstrate the relevance of analyzing cognitive domains beyond memory in aMCI patients in both clinical and research settings. Investigating in a longitudinal manner the neural mechanisms of reduced visual processing speed in aMCI and their relation to the spread of AD pathology and brain connectivity measures could help us better understand when and how these deficits start to appear.

5. Conclusion

In this study, we report simultaneous object perception deficits in patients with aMCI and show that these deficits are particularly severe in patients with reduced visual processing speed. Collectively, our results and those of previous studies allow us to conclude that visual processing speed reduction is a crucial process that underlies deficits in simultaneous object perception.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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