Specific deficit of colour–colour short-term memory binding in sporadic and familial Alzheimer's disease

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Abstract

Short-term memory binding of visual features which are processed across different dimensions (shape-colour) is impaired in sporadic Alzheimer's disease, familial Alzheimer's disease, and in asymptomatic carriers of familial Alzheimer's disease. This study investigated whether Alzheimer's disease also impacts on within-dimension binding processes. The study specifically explored whether visual short-term memory binding of features of the same type (colour-colour) is sensitive to Alzheimer's disease. We used a neuropsychological battery and a short-term memory binding task to assess patients with sporadic Alzheimer's disease (Experiment 1), familial Alzheimer's disease (Experiment 2) due to the mutation E280A of the Presenilin-1 gene and asymptomatic carriers of the mutation. The binding task assessed change detection within arrays of unicoloured objects (Colour Only) or bicoloured objects the colours of which had to be remembered separately (Unbound Colours) or together (Bound Colours). Performance on the Bound Colours condition (1) explained the largest proportion of variance between patients (sporadic and familial Alzheimer's disease), (2) combined more sensitivity and specificity for the disease than other more traditional neuropsychological tasks, (3) identified asymptomatic carriers of the mutation even when traditional neuropsychological measures and other measures of short-term memory did not and, (4) contrary to shape-colour binding, correlated with measures of hippocampal functions. Colour-colour binding and shape-colour binding both appear to be sensitive to AD even though they seem to rely on different brain mechanisms.

Introduction

In the early stages of visual processing, stimuli undergo a fine-grained analysis through multiple dimensions (i.e. colour, shape, size, location, etc.) yet they reach perception and memory as integrated units (Kandel & Wurtz, 2000; Treisman, 1982; Treisman & Gelade, 1980). Binding processes are required to link features across and within these dimensions to enable an accurate representation of these complex events at different levels of cognitive processing (Gray, 1999; Zimmer, Mecklinger, & Lindenberger, 2006). The efficiency of these binding processes seems to depend on the type of features which comprise the complex stimuli (Alvarez & Cavanagh, 2004; Treisman, 1998; 1999), the memory system by means of which stimuli are processed (Colzato, Raffone, & Hommel, 2006; Logie, Brockmole, & Vandenbroucke, 2008; Moses & Ryan, 2006), and the population in which these functions are assessed (Brockmole, Parra, Della Sala, & Logie, 2008; Brown & Brockmole, 2010; Cowan, Naveh-Benjamin, Kilb, & Saults, 2006; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003; Old & Naveh-Benjamin, 2008; Parra et al., 2009a; Parra, Abrahams, Logie, & Della Sala, 2009b; Parra, Abrahams, Logie, & Della Sala, 2010b).

Studies on memory binding involving healthy older adults suggest that age dissociates binding functions across memory systems. As people age, the ability to represent complex events in long-term memory (LTM) (i.e., associative learning) declines more dramatically than the ability to represent single items (Chalfonte & Johnson, 1996; Naveh-Benjamin, Brav, & Levy, 2007; Naveh-Benjamin et al., 2003; Old & Naveh-Benjamin, 2008). This age-related LTM binding deficit has been observed with a wide range of stimuli and procedures (Old & Naveh-Benjamin, 2008). Similar age-related binding deficits have been observed in visual short-term memory (VSTM) when

spatial information is involved (object-location; Cowan et al., 2006; Mitchell, Johnson, Raye, & D'Esposito, 2000a; Mitchell, Johnson, Raye, Mather, & D'Esposito, 2000b; Mitchell, Raye, Johnson, & Greene, 2006). However, preserved VSTM binding functions have been observed in older adults when features are processed across different dimensions (shape-colour binding; Brockmole et al., 2008) or within the same dimension (colour-colour binding; Parra et al., 2009b).

Studies on LTM binding involving patients with Alzheimer's disease (AD) have reported impairments with a wide range of stimuli (Gallo, Sullivan, Daffner, Schacter, & Budson, 2004; Granholm & Butters, 1988; Lee, Rahman, Hodges, Sahakian, & Graham, 2003; O'Connell et al., 2004; Sperling et al., 2003; Swainson et al., 2001). Recent studies suggest that AD also impairs VSTM binding, including those combinations preserved in healthy older adults (Parra et al., 2010b). Parra et al. (2010b) reported that patients with sporadic AD (SAD) present with paramount difficulties in representing shape-colour bindings in VSTM compared to both healthy older adults and patients with chronic depression. Using a version of the same VSTM task, Parra et al. (2010a) also found impaired binding in patients with E280A-PS1 familial AD (FAD) and in asymptomatic carriers of the mutation E280A-PS1 who will develop FAD. In sum, retaining object-colour bindings in VSTM is not affected by age but is extremely sensitive to the effects of AD regardless of its clinical variant (i.e., SAD or FAD).

The effect of AD on within dimension binding has never been investigated and its outcome is difficult to predict. On the one hand, binding features which are processed within a single dimension seems to be a more demanding task than binding features processed in different dimensions (Olson & Jiang, 2002; Wheeler & Treisman, 2002). This is because when resources are drawn from a single dimension, memory operations are more

prone to capacity limitations than when different dimensions support these operations (Olson & Jiang, 2002). However, binding features within dimension in VSTM (i.e., colour-colour) has been shown to be preserved in older adults (Parra et al., 2009b).

On the other hand, whereas binding shapes and colours in VSTM appears to yield integrated objects (Brockmole et al., 2008; Gajewski & Brockmole, 2006; Vogel, Woodman, & Luck, 2001), binding colours into bicoloured objects does not result in object-based representations (Olson & Jiang, 2002; Parra et al., 2009b; Wheeler & Treisman, 2002). Recently, two diverse processes have been suggested which may explain such memory operations (Moses & Ryan, 2006). One process, labelled "conjunctive" is responsible for the type of binding which results in blended representations of features and which can be retrieved only by accessing the integrated unit or object. The other process, labelled "relational", is responsible for the representation of multi-feature objects which can be retrieved either by remembering individual parts or the whole representation. Colour combinations are not represented as integrated units in VSTM but are retained as individual features (Parra et al., 2009b). Moreover, conjunctive and relational processes are proposed to have dissociable neurological substrates. Conjunctive binding functions have been found to be preserved in patients with hippocampal amnesia, a condition which instead is known to cause severe relational memory deficits (Baddeley, Allen, & Vargha-Khadem, 2010; Mayes, Montaldi, & Migo, 2007; Mayes et al., 2004b; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002). These two processes also appear to be differentially vulnerable to FAD. Parra et al. (2010a) reported normal associative memory functions (Paired Associates Learning) which is more dependent on relational processes, in asymptomatic carriers of the mutation

E280A-PS1 who on the contrary showed a dramatic impairment in shape-colour binding in VSTM.

The aim of this study was to investigate whether AD could provide further evidence for the dissociability of within-dimension binding and between dimensions binding and determine whether performance of people with AD will differentiate between the two processes. We have previously shown that between dimensions binding is impaired in AD (Parra et al., 2010a & b). The present study was set out to investigate whether VSTM binding operations performed within the colour dimension are impaired in AD. We investigated this hypothesis in SAD (Experiment 1) and in FAD (Experiment 2). If AD affects binding processes regardless of the involved dimensions, and if this impairment is a general feature of AD regardless of its clinical form, we would observe that both SAD and FAD patients show VSTM colour-colour binding deficits. Alternatively, if those processes responsible for binding within dimension features in VSTM are less sensitive to the effects of AD, patients with mild AD may show preserved VSTM binding functions after adjusting the task for their memory capacity (Experiment 1). Similarly, if those processes responsible for binding within dimension features in VSTM are less sensitive to the early stages of AD (i.e., pre-dementia), asymptomatic carriers of a gene mutation that leads to FAD, who have previously shown impairments in VSTM for shape-colour bindings (Parra et al., 2010a), may show preserved colour-colour binding (Experiment 2).

Experiment 1

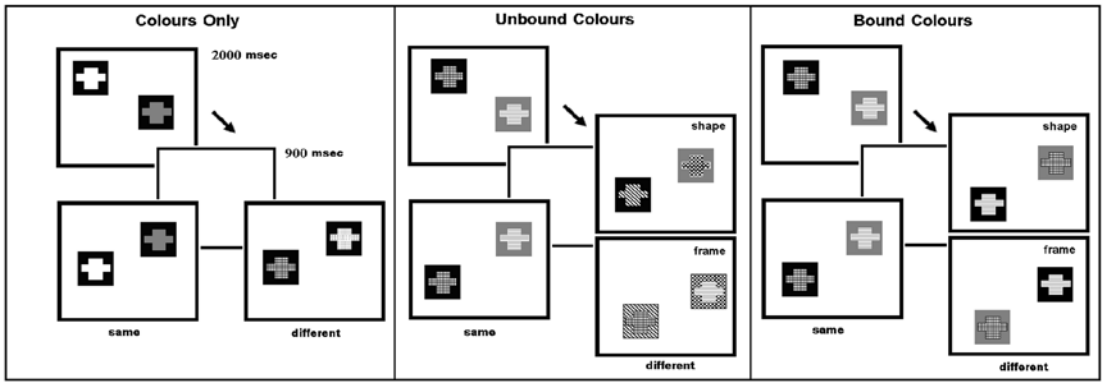
Methods

Participants

A group of 14 SAD patients diagnosed according to the criteria established by the DSM-IV-TR and the NINCDS-ADRDA (McKhann et al., 1984) and a group of 14 Healthy Controls matched for age and years spent in formal education entered Experiment 1 (Table 1). Patients were referred by local old age consultants. Healthy Controls were recruited through the panel of volunteers of the Psychology Department of the University of Edinburgh. All participants gave their informed consent to take part in the study. The study was approved by the relevant Ethics Committees.

The inclusion criteria set for the study were: 1) Normal colour vision as assessed by the Colour Blindness Test (Dvorine, 1963). 2) No other neurological or psychiatric disorders. 3) Score above 14 in the Mini-Mental State Examination (MMSE). 4) Brain CT or MRI scan ruling out cerebrovascular diseases. 5) Normal perceptual binding functions as assessed by the task described below.

----- Insert Table 1 and Figure 1 about here -----



Perception for colour-colour binding was assessed with a task that simultaneously presented two arrays of three bicoloured objects (see Figure 1 for an example of these objects). Each array, one in the upper half of the screen and one was in the lower half, comprised two or three objects. On each of the 20 trials, participants searched for changes between the two arrays. The

arrays and the changes were the same as those described below for the Bound Colours condition. Threshold for participation in the study was set at 90% accuracy on this visual perception test (18 out of 20 trials correct). None of the patients or healthy older adults recruited for the study had to be excluded due to perceptual binding problems.

Assessment

Neuropsychology

The Neuropsychological assessment comprised the MMSE, Trail Making Test Part A (Reitan, 1958), Verbal Fluency Tests - Letters (FAS) (Sumerall, Timmons, James, Ewing, & Oehlert, 1997) and Animals, The Complex Figure of Rey-Osterrieth - Copy and Recall (Osterrieth, 1944).

VSTM task

The VSTM was constructed using a change detection paradigm (Luck & Vogel, 1997; Parra et al., 2010a & b; Wheeler & Treisman, 2002). During the task the participants were presented with arrays of object shapes in random positions on a 15" PC screen using a 3x3 virtual grid. At the viewing distance of 65 cm, objects subtended 0.75^{o} and the minimum distance between them was 0.5^{o}. Objects were constructed using six different layouts, each defined by a shape and a frame area (see Figure 1; also see Parra et al., 2009b and http://www.era.lib.ed.ac.uk/bitstream/1842/2441/1/08-278-MAP.doc for examples of these figures). The shape or frame area of each object (each representing 50% of the surface) was filled with a colour. The procedures used to select the colours and the psychophysical features of the colours selected were reported in Parra et al. (2009b) and can be found in supplementary materials at http://www.era.lib.ed.ac.uk/bitstream/1842/2441/1/08-278-MAP.doc.

During the task Healthy Controls were presented with arrays of three object shapes while SAD patients were presented with arrays of two object shapes (i.e., Set Sizes = 3 for Healthy Controls and 2 for SAD patients). Previous studies have demonstrated that these memory loads allow performance levels in the baseline memory condition to be equated across groups while keeping the performance of patients above floor and performance of the controls below ceiling (e.g. Logie, Cocchini, Della Sala S., & Baddeley, 2004; Logie, Della Sala S., MacPherson, & Cooper, 2007; Parra et al., 2010a & b; Parra et al., 2009a). In the present experiment, it permits the investigation of VSTM binding performance in SAD patients when the demands of the baseline conditions are adjusted for their memory capacity.

Trials began with a fixation screen shown for 250 msec. This was followed by a study display for 2000 msec (Figure 1). After an unfilled retention interval of 900 msec, the test display was presented until the participant responded. There was then a gap of 1000 msec until the next trial. In half of the trials objects on both displays were the same. In the other half, two of the objects in the test display showed different colours from those in the study display. Object locations in the test display were always randomly changed to make location an uninformative feature. Participants were requested to detect whether the study and test displays consisted of the "same" or "different" items and to respond verbally accordingly.

Three experimental conditions were used (Figure 1). In the *Colour Only* condition the shape area displayed a different single colour for each object while the frame area was black for all. In the "different" trials the shape colour of two objects was replaced by a new colour which was not presented at study. In the *Unbound Colours* condition both the shape and frame area of each object were shown in different colours. In the "different" trials one colour from either the shape (50%) or the frame (50%) area in two of the

objects was replaced by a new colour that had not appeared in the study display. Participants were told to focus on colours and not on their associations as the change would consist of new colours. In the condition assessing memory for *Bound Colours* both the shape and frame area were of different colours. In the "different" trials two objects swapped one colour either from the shape (50%) or from the frame area (50%). Participants were told that colours and their associations were both relevant as sometimes colours would be rearranged in different combinations during the test display. In less than 30% of the trials, colours were repeated within a display no more than twice. This occurred in the Unbound and Bound Colours conditions for controls and only in the Unbound Colours condition for SAD patients (to avoid undermining the need for binding when only two items were presented). This manipulation was aimed at increasing participants' awareness of the need to attend to all the features and to all the combinations (e.g., a blue-yellow object is different from a yellow-purple object). Supplementary material shows neither difference across trials with and without repeated features or group differences that could be explained by this manipulation. For each condition participants performed 15 practice trials followed by 32 test trials. The "same" and "different" trials were fully randomized and conditions were blocked and counterbalanced across participants. Percentage of correct recognition (Hits in the "different" trials + Correct Rejections in the "same" trials) was used as the dependent variable.

Analysis

The scores on the Neuropsychological Battery were compared across groups using independent-sample t-tests (when control values were obtained) or one-sample t-tests (when standard norms were available) (Table 1). To analyse performance on the VSTM task, a two-way mixed ANOVA was used. The

between-subjects factor was Group (Healthy Controls vs. SAD) and the within-subjects factor was Condition (Colour Only vs. Unbound Colours vs. Bound Colours). Following the ANOVA, Linear Regression analysis was performed to identify which of the three conditions used in the VSTM task (dependent variables) accounted for the largest proportion of variance when Group was entered as the predictor. Then, we carried out ROC analysis to determine the sensitivity and specificity of the three conditions of the VSTM task.

Results

Neuropsychological assessment

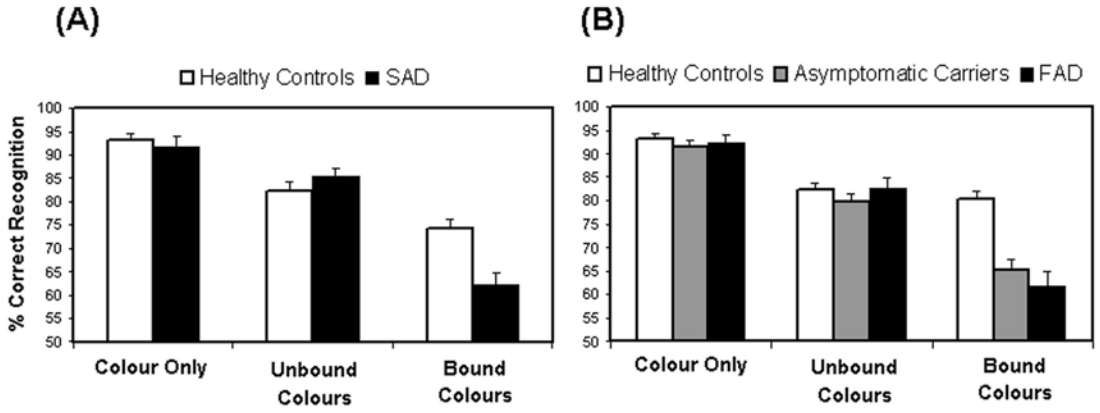
SAD patients performed significantly more poorly than controls (or below published norms) in tests of global functioning (MMSE), attention (TMT-A), memory (Rey-Figure Recall) and executive functions (Verbal Fluency - Animals) (Table 1).

VSTM task

Mean performance for SAD patients and Healthy Controls is shown in Figure 2A. The ANOVA resulted in a main effect of Condition [$F(2,52) = 99.03$, $p < 0.001$] but not of Group [$F(1,26) = 2.03$, n.s.]. The Condition by Group interaction was significant [$F(2,52) = 11.37$, $p < 0.001$]. Nine post-hoc comparisons (three across groups and six across conditions) were carried out to investigate the interaction (corrected p-level = 0.005). They revealed that SAD patients performed worse than Controls in the Bound Colours condition ($t = 3.66$, $p = 0.001$). None of the other contrasts across Groups resulted in significant differences. Contrasts performed across Conditions showed that Healthy Controls' performance in the Colour Only condition was better than in the Unbound and Bound Colours conditions. Performance on these last

two conditions did not differ statistically (all significant effects at $p < 0.005$). For SAD patients, the pattern of performance was in the form of Colour Only > Unbound Colours > Bound Colours. Hence, the significant interaction was driven by the poor performance of SAD patients in the Bound Colours condition only.

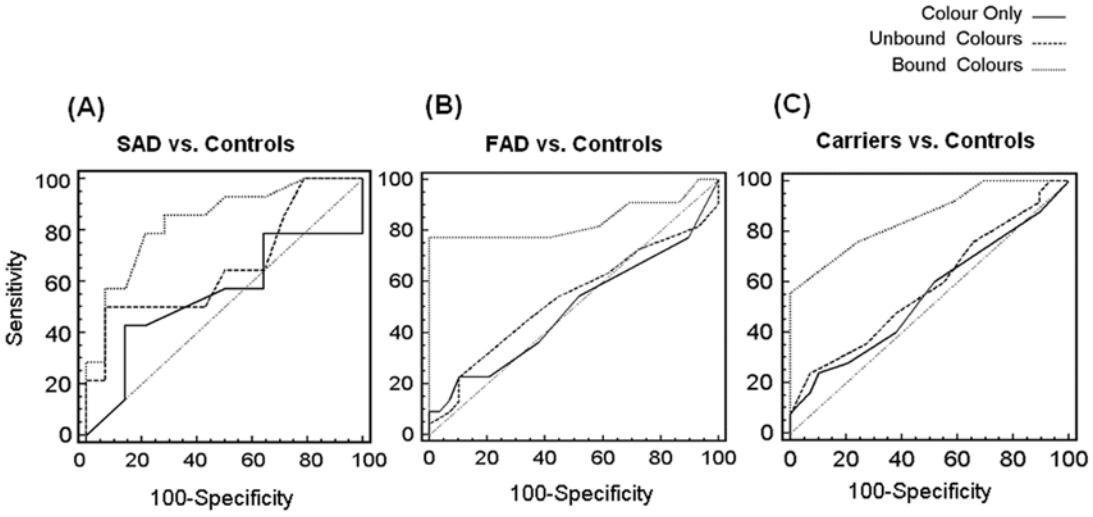
----- Insert Figure 2 – A and B - about here -----



Further Regression and ROC analyses (Table 2) confirmed that performance on the Bound Colours condition accounted for the largest proportion of variance across groups (34.1%) and combined more sensitivity (78.57%) and specificity (78.57%) for SAD than Colour Only (5.0% of variance, 42.86% sensitivity and 85.71% specificity) and Unbound Colours conditions (9.7% of variance, 50.0% sensitivity and 92.86% specificity). Analysis of the area under the curve (AUC) performed across Group showed that Bound Colours was the only condition that resulted in a significant effect (Figure 3A).

----- Insert Table 2 about here -----

----- Insert Figure 3 – A, B and C - about here -----



Comments

Experiment 1 confirmed that patients in the mild stages of SAD present with difficulties in retaining in VSTM bound features which are processed within the same dimension (i.e., colour). This difficulty seems not to be accounted for by deficits in memory for single colours or by limitations in memory capacity. Therefore, the impairments observed in SAD patients to represent bicoloured objects in VSTM seem to reflect a specific deficit in retaining how colours combine within complex objects. Previous studies have suggested that colours are not integrated into unified representations but that they are rather remembered as individual features belonging together (Olson & Jiang, 2002; Parra et al., 2009b; Wheeler & Treisman, 2002). This view considers binding between colours as an additional piece of information necessary for retrieving how colours were combined. The present data suggest that it is retaining this piece of information (i.e., the binding) that is more vulnerable to SAD (see Supplementary Material for data across "same" and "different" trials). It is worth noting that it was the Bound Colours condition that accounted for the largest proportion of variance across groups and the only condition of the VSTM task that combined sensitivity and specificity of SAD. Hence, different individual strategies could not explain the observed group effects (also see

Supplementary Material for data in both conditions across "same" and "different" trials).

Therefore, the results presented here lend support to the hypothesis that SAD affects VSTM binding operations regardless of the involved dimensions (e.g., colour-colour as assessed in the present experiment and shape-colour as it was assessed by Parra et al., 2010a & b). Whether binding in VSTM is affected by AD regardless of its clinical form was the question addressed in Experiment 2.

Experiment 2

Experiment 2 was aimed at investigating VSTM colour-colour binding in patients with FAD and in asymptomatic carriers of the single mutation E280A in the Presenilin-1 gene which leads to FAD in 100% of cases. This second group is of particular interest considering that they will develop FAD but have not yet the disease. Our previous work (Parra et al., 2010a) has shown that this group does show a specific deficit in across dimension binding (colour-shape). Hence, if those processes responsible for binding in VSTM are less sensitive to the pre-demented stages of AD, asymptomatic carriers should show preserved binding functions.

Methods

Participants

The selection protocol consisted of three phases. The genetic screening, which was carried out using the methodology reported by the Alzheimer's Disease Collaborative Group (1995) (see also Lemere et al., 1996 and Lendon et al., 1997), was aimed at confirming the presence of the mutation. The genetic screening phase ran in parallel with a neurological and a neuropsychological

phase. The Neurologists and Neuropsychologists were therefore blind to the genetic condition of the referrals.

Twenty two were FAD patients diagnosed according to the criteria established by the DSM-IV-TR and the NINCDS-ADRDA group (McKhann et al., 1984), twenty five were Asymptomatic Carriers positive to the E280A mutation who met neither AD nor Mild Cognitive Impairment (MCI) criteria (Petersen, 2004) and twenty nine were Healthy Controls who were relatives of FAD patients or Asymptomatic Carriers but were negative to the E280A mutation and healthy according to the outcomes of the assessment phases described above. Additional inclusion criteria for Healthy Controls and Asymptomatic Carriers were (1) negative history of neurological or psychiatric disorders, (2) MMSE score equal to or greater than 24 (3) and no memory complaints as documented by a self-report and a family questionnaire. All the participants recruited for the present experiment successfully underwent the Colour Vision and the Binding Perception assessment described in Experiment 1.

The three groups were matched according to the number of years spent in formal education (see Table 1). Asymptomatic Carriers were significantly younger than FAD patients and than Healthy Controls. Previous studies in this population have shown that age per se does not explain variability in performance on the VSTM task across groups (Parra et al., 2010a). Hence, age was not further considered in the analysis presented here. All participants gave informed consent to take part in the study which was approved by the relevant Ethics Committees.

Assessment

Neuropsychology

The Neuropsychological Battery comprised the MMSE (Folstein, Folstein, & McHugh, 1975), Spanish versions of Verbal Fluency Tests (Letters-FAS, adapted from Sumerall et al., 1997, and Animals), the Copy and Recall of the Complex Figure of Rey-Osterrieth (Osterrieth, 1944; Rey, 1941), and Part-A of the Trail Making Test (TMT) (Reitan, 1958). We additionally used a Spanish version of the Paired Associates Learning (PAL) Task from (Wechsler, 1945). Paired associates learning is a function known to be sensitive to the early stages of AD (Gallo et al., 2004; Granholm & Butters, 1988; Lee et al., 2003; Swainson et al., 2001). Therefore, we compared the sensitivity of this test with that of the VSTM task to determine the usefulness of the novel VSTM measure relative to a more standard test in the investigated population.

VSTM task

For Experiment 2 we used the same task described in Experiment 1. Asymptomatic Carriers and Healthy Controls were presented with arrays of three object shapes while FAD patients were presented with arrays of two object shapes (Set Sizes = 3 for Healthy Controls and Asymptomatic Carriers and 2 for FAD patients). The aim of this manipulation was as described in Experiment 1. Asymptomatic Carriers and Healthy Controls were assessed with the same number of items as we knew nothing about the genetic condition during the testing sessions. Hence, they were treated as non-patient referrals throughout the protocol.

Analyses

Performance on the neuropsychological tests was compared across groups using one-way ANOVA. Bonferroni-corrected post-hoc tests were then performed with the scores that resulted in significant main effects (Table 1). To analyse performance on the VSTM task, a two-way mixed ANOVA was

used. The between-subjects factor was Group (Healthy Controls vs. Asymptomatic carriers vs. FAD patients) and the within-subjects factor was Condition (Colour Only vs. Unbound Colours vs. Bound Colours). Linear Regression and ROC Analyses were also performed as described in Experiment 1. In Experiment 2 separate analyses were carried with the Predictor Group to investigate the accuracy of the VSTM task to distinguish between (1) Healthy Controls and FAD patients and between (2) Healthy Controls and Asymptomatic Carriers. Additionally, we considered performance on the PAL task and on the Recall of the Complex Figure of Rey as these tests were found to be sensitive to FAD and Carriers in a previous study (Parra et al., 2010a). A measure of executive functioning (Verbal Fluency - Animals) was also entered in the analysis as previous reports suggest that this form of FAD presents as an amnesic and dysexecutive syndrome resembling in most of its features SAD (Ardila et al., 2000; Lopera et al., 1997; Parra et al., 2010a).

Results

Neuropsychological assessment

FAD patients performed significantly more poorly than Healthy Controls on all of the neuropsychological tests. FAD patients also performed significantly worse than Asymptomatic Carriers on all of the neuropsychological tests except on the Copy of the Complex Rey Figure. The performance of Asymptomatic Carriers and Healthy Controls did not significantly differ in any of the neuropsychological tests (Table 1).

VSTM task

Mean performance for the three groups is shown in Figure 2B. The ANOVA outcomes revealed main effects for Group [$F(2,73) = 8.16$, $p = 0.001$] and for

Condition [$F(2,146) = 183.42$, $p < 0.001$]. The Condition by Group interaction was significant [$F(4,146) = 14.11$, $p < 0.001$]. Eighteen post-hoc comparisons (nine across groups and nine across conditions) were carried out to investigate the interaction (corrected alpha level = 0.003). Comparisons carried out across Group revealed that both FAD and Asymptomatic Carrier performed significantly worse than Healthy Controls only in the Bound Colours Condition (Mean Differences = 18.69, $p < 0.001$ and 15.14, $p < 0.001$ respectively). Comparisons across Condition using paired-sample t-tests showed that the pattern of performance was in the form of Colour Only > (Unbound Colour = Bound Colours) for Healthy Controls and in the form of Colour Only > Unbound Colour > Bound Colours for both Asymptomatic Carriers and FAD patients (all significant effects at $p < 0.003$). Therefore, the significant interaction was driven by FAD patients and Asymptomatic Carriers performing worse than Healthy Controls and no differently from each other in the Bound Colours condition only.

Linear Regression analysis (Table 2) showed that three standard neuropsychological variables (PAL = 35.5%; Rey-Recall = 60.2%; and Verbal Fluency-Animal = 46.3%) and the Bound Colours condition from the VSTM task (39.8%) accounted for a significantly large proportion of the variance when performance of FAD patients and Healthy Controls was entered in the model (Table 2). Analysis of the AUC supported the results of the Regression analysis. However, ROC analysis revealed that it was the Bound Colours condition only that combined sensitivity and specificity for FAD (77.27% and 100% respectively) (Figure 3B). None of the other measures used in the present study achieved this classification power. When performance of Asymptomatic Carriers and Healthy Controls was entered in the Regression model, none of the standard neuropsychological measures was found to significantly account for the variability across groups (PAL = 1.7%; Rey-Recall

= 5.2%; and Verbal Fluency-Animal = 3.5%). Performance on the Bound Colours task however was able to explain 37.6% of the variance across groups. Analysis of the AUC supported the results of the Regression analysis and showed that it was Bound Colours condition only that combined sensitivity and specificity for Asymptomatic Carriers (76.0% and 76.0% respectively) (Figure 3C).

In our previous investigations we have demonstrated that shape-colour binding is sensitive to the effects of AD (see Parra et al., 2010a & b). In the current study a similar outcome emerged for colour-colour binding. We capitalised on these two sets of data to further investigate whether there was any evidence that performance on these two binding tasks were dissociable. The performance of AD patients that took part in the present study and the studies reported by Parra et al. (2010a & b), and who were assessed with the same protocol, were entered into an overall analyses. For the purposes of this analysis, performance on single feature conditions (i.e., Shape and Colour Only for the Shape-Colour Binding task and Colour Only and Unbound Colours for the Colour-Colour Binding task) were collapsed into two variables (Single Features 1 and 2 respectively, see Table 1 in Supplementary Material). The full set of results from a Pearson correlation analysis is presented in Supplementary Material. Performance on the Bound Colours and Shape-Colour Binding conditions were found to significantly correlate [$r = 0.64$, $p < 0.001$] suggesting that both processes deteriorate in the course of AD. However, performance on the Bound Colours condition did not correlate with any condition assessing memory for single features but showed a significant correlation with performance on the PAL task [$r = 0.88$, $p < 0.05$]. The opposite pattern was observed for the Shape-Colour Binding condition (see Supplementary Material) which showed a significant correlation with both conditions assessing memory for single features (Single Features 1 and 2)

but not for the PAL task. This suggests that although both types of binding are sensitive to AD, their deterioration may occur via different mechanisms.

Finally, as both SAD (Exp. 1) and FAD (Exp. 2) patients were assessed with the same VSTM task (Set Size = 2), their scores were comparable. However, FAD patients were younger than SAD patients (t = 17.47, p< 0.001) and were also less educated (t = 3.09, p < 0.01). Education did not prove to be relevant in VSTM binding tasks (see e.g. Parra et al., 2010a). Therefore, an education-uncorrected two-way mixed ANOVA was performed to verify the lack of age effect (see Parra et al., 2009b). Group (Healthy Older Controls – Exp 1 vs. Healthy Younger Adults – Exp 2) was the between-subjects factor and Condition (Colour Only vs. Unbound Colours vs. Bound Colours) was the within-subjects factor. Healthy Controls could be compared across Experiments 1 and 2 because they too performed the same VSTM task (Set Size = 3). There was no effect of Group [F(1,41) = 2.01, n.s.]. The effect of Condition was found to be significant [F(2,82) = 60. 83, p < 0.001] whereby performance on the Colour Only condition was better than on the Unbound Colour condition which in turns was better than on the Bound Colours condition (all with p < 0.001). The Group by Condition interaction did not reach significance [F(2, 28) = 2.91, n.s.]. Given that age does not effect on the task, uncorrected ANOVAs were performed to assess performance difference between the SAD and the FAD samples. Hence, data from the SAD vs. FAD patients (Group) were entered in a two-way mixed ANOVA. There was no effect of Group [F(1,34) = 0.14, n.s.]. The effect of Condition was found to be significant [F(2,68) = 122.13, p < 0.001]. The Group by Condition interaction was non significant [F(2,68) = 0.30, n.s.]. Therefore, colour-colour binding was clearly affected by different variants of AD; of note is that in our previous work, this type of binding was not affected by healthy ageing (Parra et al., 2009b).

Comments

Experiment 2 demonstrated that patients with FAD due to the single mutation E280A of the Presenilin-1 gene and carriers of this mutation, who, at the time of testing were still asymptomatic according to self-reports and standard neuropsychological tests, do present with difficulties in retaining colour-colour bindings in VSTM. Furthermore, the results of Experiment 2 showed that retaining the binding between colours in VSTM is vulnerable to both SAD and FAD. Relative to the other measures used in this study, impairment of VSTM binding explained the greatest proportion of variance when patients (or asymptomatic carriers) and controls were compared. When the outcome of Exps. 1 and 2 were compared, no differences were found between FAD and SAD patients, although both performed significantly more poorly than Healthy Controls (Healthy Controls of Experiments 1 and 2 did not differ in performance on the VSTM task).

General Discussion

The present study sought to investigate whether VSTM binding deficits are a general characteristic of AD. Patients with sporadic Alzheimer's disease (SAD, Experiment 1) and familial Alzheimer's disease (FAD, Experiment 2) were assessed with a neuropsychological battery and a colour-colour VSTM binding task. Patients that met AD criteria (Experiments 1 and 2) performed worse than Healthy Controls on standard neuropsychological tests and on the binding condition of the VSTM task. Asymptomatic carriers of the E280A mutation and Healthy Controls only differed significantly in the VSTM binding scores. Regression and ROC analyses with Group as the independent variable confirmed that the binding condition offers the best combination of

sensitivity and specificity for SAD, FAD and for Asymptomatic Carriers of the mutation that leads to FAD. VSTM binding deficits for features processed within colour dimension seem to be a common phenotypic expression of AD regardless of its clinical variant.

The literature on associative memory and AD is vast. Previous studies have consistently demonstrated the usefulness of Associative Learning Tasks to investigate both patients with AD (Gallo et al., 2004; Granholm & Butters, 1988; Lee et al., 2003; Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002; Sperling et al., 2003; Swainson et al., 2001) and individuals at risk for developing the disease (Fowler, Saling, Conway, Semple, & Louis, 2002; Swainson et al., 2001). Recent studies have suggested that the mechanisms responsible for retaining bindings in STM are different from those subserving the representation of bindings as associations in LTM (Colzato et al., 2006; Logie et al., 2008). However, AD seems to impact on these mechanisms irrespective of the memory systems which subsume them (Della Sala, Kinnear, Spinnler, & Stangalino, 2000; Lloyd-Jones, 2005; Parra et al., 2010a; Parra et al., 2009a & b), the dimensions involved (Parra et al., 2009a; 2010a & b), and the clinical form of the disease (Parra et al., 2009a; 2010a & b).

In the present study we have demonstrated that those processes required to bind features which are processed within a single dimension are specifically affected by FAD and SAD. These findings, particularly in Asymptomatic Carriers, are relevant as they suggest that even when other measures of cognitive functioning fail to detect AD-related changes, VSTM binding tasks achieve this goal with high efficiency. VSTM binding deficits were observed in SAD with a task that proved insensitive to the effects of age (Parra et al., 2009b). This represents an important development for tasks aimed at assessing AD as the Associative Learning Tasks reported in the aforementioned literature are also sensitive to the effects of normal ageing (de

Jager, Milwain, & Budge, 2002; De, Blackwell, Budge, & Sahakian, 2005; Naveh-Benjamin et al., 2007; Naveh-Benjamin et al., 2003; Old & Naveh-Benjamin, 2008), hence they are sensitive but not specific to the effects of AD.

Moreover, in the current study binding colours in VSTM was found to combine more sensitivity and specificity for FAD than the PAL task used. The PAL task places a great demand on language functions which in turns depend on the cultural background (see Ardila et al., 2000; Parra et al., 2010a). Tests insensitive to socio-demographic factors (e.g., age and education) offer a valuable tool to reliably assess and compare patients with different form of AD.

The results presented here also have implications for our understanding of the underpinnings of VSTM binding deficits in AD. Memory binding is assumed to be responsible for linking and connecting the different elements of complex events either in perception or in memory (Treisman, 1996; 1999; 2006; Treisman & Gelade, 1980; Zimmer et al., 2006). The hippocampus has been long thought of as a brain structure involved in binding operations in LTM (Hannula & Ranganath, 2008; Hannula, Tranel, & Cohen, 2006; Mayes et al., 2007; Moses, Cole, & Ryan, 2005; Moses & Ryan, 2006). However, STM binding has been less thoroughly investigated. Studies involving older and younger populations have found that the functions responsible for binding information or holding bindings in STM are only sensitive to the effects of age when spatial information is relevant to the task (Cowan et al., 2006; Mitchell et al., 2006; 2000a & b). If the to be bound information leads to the formation of an integrated object representation with its own identity, older people can process these events in STM as well as younger participants (Brockmole et al., 2008; Brown & Brockmole, 2010; Parra et al., 2009b). A mechanism which has been proposed to explain this dissociation is that binding to spatial locations requires the functions of the

hippocampus whereas binding features within single objects does not require such functions (Hannula & Ranganath, 2008; Mitchell et al., 2000a; 2006). This proposal was tested and corroborated in healthy young individuals (Piekema, Kessels, Mars, Petersson, & Fernandez, 2006) and has been also supported by patient studies (Baddeley et al., 2010; Mayes et al., 2002; 2004a; 2007; Moses & Ryan, 2006).

Nonetheless, there is limited evidence available to explain the observed dissociation within VSTM binding in healthy ageing (i.e., affected when location is relevant and unaffected when object's identity is involved), which contrasts with a general non-domain specific impairment in AD. Object processing relies on the function of the ventral pathway which seems to be reorganised in older adults (Grady, 1998 see also Schiavetto, Kohler, Grady, Winocur, & Moscovitch, 2002). This functional reorganization has been used to explain why older people can achieve the same level of performance as younger adults in tasks requiring the identification of singular objects such as faces, which are known to require intra-item binding functions (see Mayes et al., 2002; 2004b). For example Chee et al. (2006) observed differential brain activation in older adults when objects had to be processed relative to their background (i.e., contextual binding) as compared to when they had to be processed independently. Only in the contextual binding condition was an age-related effect observed. This literature suggests that the ability to process object in VSTM is preserved in the old. The observation that older adults can process objects as well as younger adults suggests that the processes required to integrate features into objects with their own identity seem to operate in an age-insensitive manner. Recent evidence suggests that this holds from perception (e.g., Habak, Wilkinson, & Wilson, 2009) to short-term memory (Mitchell et al., 2000b), and it relies on structures other than the hippocampus (Baddeley et al., 2010; Piekema et al., 2006).

Further analyses that combined data from the studies reported here on colour-colour binding with comparable data on colour-shape binding previously collected with the same AD patients (Parra et al., 2010a & b) also offered some insight into a dissociation. Performance on the Bound colours condition of the current task did not correlate with performance on single feature conditions but did significantly correlate with performance on the PAL task. The opposite pattern was observed for the shape-colour binding task. This new evidence seems to fit well with the proposed relational and conjunctive accounts of binding (Moses et al., 2006) and provides insight into the potential links between STM and LTM in these memory operations. Whereas shape-colour binding has been found to lead to integrated objects in VSTM (Brockmole et al., 2008; Logie et al., 2008; Vogel et al., 2001), colour-colour bindings appear to be represented as separate features linked together (Parra et al., 2009b; Wheeler & Treisman, 2002). Therefore, one would expect to see an association between performance on a task assessing the retention of binding of a pair of items (e.g., PAL) within dimension but not between dimensions. However, following this assumption one would also expect within dimension binding to be more sensitive to the effects of ageing than between dimension binding, but this contrasts with recent findings (Parra et al., 2009b). The hippocampus is known to be affected by ageing (Grady & Craik, 2000; Mitchell et al., 2000a), However, functional brain reorganization has been found to compensate for reduced hippocampal function so as to reduce the impact of age on memory performance in older adults (Grady, 1998). Further insight may be provided by the dual-process model of memory recognition (Yonelinas, 1994; 1999) that distinguishes between the processes of familiarity and recollection, both of which contribute to performance on change detection tasks. This model suggests that recollection is dependent on the functions of the hippocampus, whereas familiarity, which may be used as

a basis for source judgments (e.g., comparing items in a recent array with those previously experienced) is more dependent on medial temporal lobe structures other than the hippocampus (e.g., entorhinal and perirhinal cortices) (Ranganath et al., 2004). These regions are not affected by ageing per se, but are dramatically affected by AD (Insausti et al., 1998; Juottonen, Laakso, Partanen, & Soininen, 1999). This could help explain why AD patients, but not healthy older adults, show an impairment in change detection tasks assessing colour-colour binding and shape-colour binding (see Haskins, Yonelinas, Quamme, & Ranganath, 2008 for further evidence) as both familiarity and recollection may be affected. Therefore, although colour-colour binding and shape-colour binding may be supported by different brain mechanisms, they both remain insensitive to healthy ageing while being extremely sensitive to AD.

An alternative hypothesis is the loss of connectivity between medial temporal lobe structures and cortical regions required for memory processing (Golob, Miranda, Johnson, & Starr, 2001; Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001).

In sum, associative learning declines in normal ageing and more remarkably in the course of AD because both conditions impact on the integrity of the hippocampus and other medial temporal lobe structures known to be involved in LTM (Eichenbaum, Yonelinas, & Ranganath, 2007; Grady, 1998; Grady et al., 2001; Mayes et al., 2007; Schiavetto et al., 2002). These deficits are expressed clinically when substantial neuronal loss has occurred (Bobinski et al., 1997; Velez et al., 2004; West, Coleman, Flood, & Troncoso, 1995). This suggests that when people with AD or at risk of developing AD are identified with Associative Learning tasks, the mechanisms leading to the disease have already started and have caused substantial damage. The expression of the STM binding deficits investigated

here and in previous studies might be less reliant on the hippocampus but more dependent on the integrity of extra-hippocampal regions (i.e., perirhinal and entorhinal cortices) which degenerates in AD but not in the course or normal ageing. Loss of brain connectivity across feature dimensions could also account for our findings with VSTM binding tasks. Recent studies with FAD also due to mutations in the Presenilin-1 gene suggest that the integrity of the white matter is affected in the early course of AD (Ringman et al., 2007). Although colour-colour binding and shape-colour binding in VSTM appear to rely on different brain mechanisms, both are sensitive to AD and insensitive to healthy ageing at least within an age range where most of the new AD cases are detected.

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Figure Captions

Figure 1. Trial design for the three conditions of the VSTM tasks.

Figure 2. Mean performance on the VSTM task for the groups that entered Experiment 1 (A) and 2 (B).

Figure 3. ROC analysis with performance on the three conditions of the VSTM task for the groups that entered Experiment 1 (A) and 2 (B and C).

Table Headings

Table 1. Demographic and Neuropsychological variables of participants entering Experiments 1 and 2.

Table 2. Regression and ROC analyses with the VSTM and Neuropsychological variables from Experiments 1 and 2.

Table 1.

Experiment	Groups	Age	Education	MMSE	TMT-A	Rey-Figure Copy	Rey-Figure Recall	Verbal Fluency Letters - FAS	Verbal Fluency – Animals	PAL
1	**SAD**	76.29 (5.78) §	12.71 (3.77)	23.36 (2.73) §	138.42 (139.36) §	26.89 (11.74)	3.18 (4.79) §	24.86 (12.11)	9.07 (4.91) §	
	Controls/Norms*	70.71 (4.30)	15.57 (3.32)	28.83 (1.47)	57.6 *	31 *	13 *	22 *	12.1 *	
2	**Asymptomatic Carriers**	37.24 (5.21) ¥	9.12 (3.68)	29.52 (0.83) ¥	61.96 (25.90) ¥	26.86 (5.89)	16.48 (5.67) ¥	11.62 (3.79) ¥	21.07 (3.88) ¥	12.93 (3.91) ¥
	FAD	45.18 (4.82) §	8.45 (4.18)	25.55 (3.69) §	114.76 (61.07) §	21.14 (7.78) §	3.98 (4.35) §	8.41 (3.61) §	14.14 (3.62) §	7.43 (3.50) §
	Controls	39.55 (8.82)	9.21 (2.90)	29.29 (1.12)	69.38 (38.37)	25.10 (6.86)	13.69 (6.50)	11.88 (5.91)	19.30 (5.58)	11.88 (4.33)

MMSE: Mini Mental State Examination; TMT-A: Trail Making Test Part A; PAL: Paired Associates Learning; * Age appropriate norms from: letter fluency (FAS) (Sumerall et al., 1997); verbal fluency (animals) (Tombaugh, Kozak, & Rees, 1999); TMT (Tombaugh, 2004); Rey Figure (Fastenau, Denburg, & Hufford, 1999); §: Different from Controls (or from norms * using one-sample t-tests) ($p < 0.05$); ¥: Different from FAD

Table 2.

Experiment	Predictor (Group)	Dependent Variable	Regression		ROC Analysis			
			R^2	ANOVA - F(p)	Criterion	Sensitivity	Specificity	AUC (p)
1	SAD vs. Controls	Colour Only	0.005	0.12 (0.730)	<= 81	21.4	100	0.47 (0.79)
		Unbound Colours	0.097	2.81 (0.106)	> 87.5	50.0	85.7	0.59 (0.44)
		Bound Colours	0.341	13.45 (0.001)	<= 66	78.6	78.6	0.81 (< 0.001)
2	FAD vs. Controls	Colour Only	0.006	0.27 (0.605)	<= 84	22.73	89.66	0.49 (0.93)
		Unbound Colours	0.000	0.02 (0.887)	> 88	22.73	89.66	0.53 (0.69)
		Bound Colours	0.398	32.45 (<0.001)	<= 69	77.27	100	0.84 (< 0.001)
		PAL	0.355	27.02 (< 0.001)	<= 9	77.27	79.31	0.85 (< 0.001)
		Rey-Recall	0.602	73.99 (< 0.001)	<=7	90.91	96.55	0.95 (< 0.001)
		Verbal Fluency-Animals	0.463	42.30 (< 0.001)	<= 16	77.27	86.21	0.89 (< 0.001)
	Asymptomatic Carriers vs. Controls	Colour Only	0.019	0.98 (0.326)	<= 84	24.0	89.66	0.55 (0.55)
		Unbound Colours	0.029	1.56 (0.217)	<= 72	24.0	93.10	0.59 (0.27)
		Bound Colours	0.376	31.33 (< 0.001)	<= 72	76.0	76.00	0.86 (< 0.001)
		PAL	0.017	0.88 (0.353)	<= 12	68.0	62.07	0.58 (0.32)
		Rey-Recall	0.052	2.80 (0.101)	<= 15	56.0	62.07	0.61 (0.17)
		Verbal Fluency-Animals	0.035	1.80 (0.185)	<= 21	76.0	51.72	0.63 (0.09)

Supplementary Material

Supplementary Table 1. Results of the Pearson Correlation Analysis with performance of AD patients (both SAD and FAD) on the shape-colour binding task (n = 36) (Parra et al., 2010a & b), on the Bound and Unbound Colours conditions (n = 36) (Parra et al., 2010a & b) and on the Paired Associates Learning (PAL) task (PAL only for FAD patients, n = 22) (Parra et al., 2010a).

		Bound Colours	**Single Features [1]**	**Single Features [2]**	**PAL**
Shape-Colour Binding	**Pearson Correlation**	**0.64**	**0.34**	**0.41**	0.31
	p-value	**0.000**	**0.049**	**0.016**	0.176
Bound Colours	**Pearson Correlation**		0.13	0.27	**0.48**
	p-value		0.460	0.124	**0.026**
Single Features [1]	**Pearson Correlation**			**0.88**	0.26
	p-value			**0.000**	0.264
Single Features [2]	**Pearson Correlation**				0.24
	p-value				0.293

Single Features [1] = shape-colour binding task; Single Features [2] = colour-colour binding task

Supplementary Table 2. Analysis across "different" and "same" trials with data from Experiment 1 collected with the Unbound and Bound Colours conditions.

	Different Trials			Same Trials		
	Controls	**SAD**	***t*-test p-value**	**Controls**	**SAD**	***t*-test p-value**
Unbound Colours	78.13 (10.6)	80.43 (11.57)	0.275	90.18 (10.02)	89.50 (11.02)	0.435
Bound Colours	61.16 (16.8)	40.00 (16.5)	**0.000**	87.50 (10.96)	87.64 (12.68)	0.488
***t*-test p-value**	**0.012**	**0.006**		0.221	0.204	

Supplementary Table 3. Analysis with performance of SAD patients and controls across trials with and without repeated features and across conditions (11 participants per group). No differences were observed across these factors because of this manipulation.

Mean (SE)	Unbound Colours		Bound Colours	
	No Repeated	**Repeated**	**No Repeated**	**Repeated**
Controls	89.39 (3.82)	82.58 (3.31)	80.00 (5.71)	81.70 (4.29)
SAD	81.63 (5.59)	84.96 (3.11)		
Total	84.61 (3.96) *Two-way ANOVA* $F(1,351) = 0.28$, ns		80.85 (5.04) *t-test* $t(382) = 1.34$, ns	