Working Memory in Alzheimer's Disease and Parkinson's Disease

Nahid Zokaei and Masud Husain

Contents

Abstract Working memory impairments are frequently observed in patients with Alzheimer's disease (AD) and Parkinson's disease (PD). Recent research suggests that the mechanisms underlying these deficits might be dissociable using sensitive tasks, specifically those that rely on the reproduction of the exact quality of features held in memory.

In patients with AD, working memory impairments are mainly due to an increase in *misbinding errors*. They arise when patients misremember which features (e.g., color, orientation, shape, and location) belong to different objects held in memory. Hence, they erroneously report features that belong to items in memory other than the one they are probed on. This misbinding of features that belong to different objects in memory can be considered a form of interference between stored items. Such binding errors are evident even in presymptomatic individuals with familial AD (due to gene mutations) who do not have AD yet. Overall, these findings are in line with the role of the medial temporal lobes, and specifically the hippocampus, in

N. Zokaei (✉)
Oxford Centre for Human Brain Activity, University of Oxford, Oxford, UK

Department of Experimental Psychology, University of Oxford, Oxford, UK
e-mail: nahid.zokaei@psy.ox.ac.uk

M. Husain
Department of Experimental Psychology, University of Oxford, Oxford, UK

Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK

Curr Topics Behav Neurosci
DOI 10.1007/7854_2019_103

retention of feature bindings, regardless of retention duration, i.e., in both short- or long-term memory.

Patients with PD, on the other hand, do not show increased misbinding. Their working memory deficits are associated with making more *random errors* or guesses. These random responses are not modulated by manipulations of their dopaminergic medication and hence may reflect involvement of non-dopaminergic neurotransmitters in this deficit. In addition, patients with PD demonstrate impairments in gating of information into relevant vs. irrelevant items in memory, a cognitive operation that is modulated by dopaminergic manipulation in line with a frontal executive effect of this neurotransmitter. Thus, although AD and PD are both associated with working memory impairments, these surface manifestations appear to be underpinned by very different mechanisms.

Keywords Alzheimer's disease · Parkinson's disease · Working memory

Working memory (WM) impairments are a common feature of many neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Muslimovic et al. 2005; Verbaan et al. 2007; Wolk et al. 2010). The importance of understanding the exact nature of these deficits in disease is twofold. On the one hand, WM underlies and constrains our abilities for a variety of cognitive processes including language, problem-solving, and executive functions (Baddeley 2003) which impact greatly on functional independence for patients with neurodegenerative disorders (Lau et al. 2015). Isolation of the precise nature of WM deficits in disease may assist in providing a comprehensive cognitive fingerprint of these disorders and also aid in the development of training regimens. On the other hand, given that WM impairments can be one of the earliest cognitive impairments in these disorders (Owen et al. 1993, 1997; Blackwell et al. 2004), a clearer distinction from normal healthy aging might aid in early diagnosis as well as monitoring disease progression and the impact of new treatments.

1 Binding Deficits in Working Memory in Alzheimer's Disease

Classically, long-term memory (LTM) dysfunction has been widely linked to early stages of AD (Linn et al. 1995; Fox et al. 1998; Yau et al. 2015). Medial temporal lobe (MTL) subregions, including the hippocampus, are known to contribute to LTM and are key brain areas associated with AD pathology, with respect to both neurofibrillary tangle disposition and as an early site of atrophy (Braak and Braak 1998; Ridha et al. 2006; Brier et al. 2016). Some models of memory argue that although other parts of the MTL may be involved in retention of information regarding an event, or contextual information, the hippocampus binds features belonging to a memory episode, for example, an item to its context (Davachi 2006; Eichenbaum et al. 2007; Konkel and Cohen 2009; Nadel and Peterson 2013).

More specifically, it has been hypothesized that the hippocampus does not play a role in all aspects of memory but rather performs a specific computation: high-resolution binding of features in perception as well as working and long-term memories, *regardless of duration* (Pertzov et al. 2013; Yonelinas 2013). For example, maintenance of complex scenes or tasks that require precise retention of bound information appears to require hippocampal contributions (Hartley et al. 2007; Koen et al. 2016). Recent neurophysiological studies provide further evidence for the role of MTL – and specifically the hippocampus – in integration and coordination of disparate cortical representations, supporting relational binding of features that belong to a specific episode in LTM (Cashdollar et al. 2011; Watrous et al. 2013). There is also evidence from lesion studies that the hippocampus and/or MTL structures play a similar role in binding feature information together over far shorter periods (seconds) in WM (Hannula et al. 2006; Olson et al. 2006).

Consistent with these models, an important line of research has provided evidence that the ability to retain bound features in WM is also critically affected in AD, a disorder that, as mentioned above, is classically associated with hippocampal and MTL dysfunction. Traditionally, WM has been measured using neuropsychological tasks that index span. In such tests, participants are presented with increasing digit, word, or spatial location sequences and have to recall the sequence of the array, in forward or backward order. The maximum sequence length successfully recalled by the participants is taken as a measure of WM capacity.

Several studies using digit and word spans have found reduced WM capacity in patients with AD compared to healthy controls (Miller 1973; Spinnler et al. 1988; Becker 1988; Hulme et al. 1993). However, these findings are not always reliably replicable (Martin et al. 1985; Carlesimo et al. 1994; Perry and Hodges 2000) and importantly are not sensitive enough to detect subtle variations in performance in the healthy populations, for example, between elderly and young healthy participants (Belleville et al. 1996). Moreover, span measures of WM do not provide any further detail on the exact nature of the deficits, that is, whether any reduced WM capacity observed in a patient group such as AD is due to encoding, retention, or retrieval aspects of this cognitive process.

1.1 Change-Detection Tasks

More in-depth experimental studies however provide a means to better quantify the nature of WM impairments in AD patients. In a series of studies, Parra and colleagues demonstrated that maintenance of bound features, for example, color and shape, is selectively impaired in AD (Parra et al. 2009, 2010, 2011; Della Sala et al. 2012). In one such report (Della Sala et al. 2012), patients with AD and non-AD dementias as well as healthy controls performed a visual WM task in which they were presented with memory arrays consisting of either single features (color squares or objects), multiple features bound together in a single object (colored objects), or unbound features (colored squares and black and white line

drawing objects presented separately). Participants were asked to keep in mind and recall as many features or bound objects following a brief delay interval.

Importantly, performance for single-feature conditions was matched between patients and healthy controls. This avoided ceiling- and floor-level performance in healthy controls and patients, respectively, and also attempted to minimize the contribution of task difficulty in the two conditions of interest: binding and unbound multiple-feature conditions. AD patients performed significantly worse compared to non-AD dementia patients only in the binding condition (Della Sala et al. 2012).

Binding deficits have also been observed in both sporadic and familial AD (FAD) patients and importantly in asymptomatic carriers of genes that have been shown to cause FAD (Parra et al. 2010, 2011). Mutations in three genes associated with amyloid processing – amyloid precursor protein (APP), presenilin-1, and presenilin-2 – have been identified in FAD; all are inherited in an autosomal dominant fashion. That is, inheritance of the abnormal gene from only one parent will result in the development of the disease. Furthermore, mutation carriers have increased hippocampal and whole-brain atrophy which is evident prior to a clinical diagnosis of AD (Ridha et al. 2006).

WM binding deficits have now been reported in both patients with FAD and asymptomatic carriers of these genetic mutations. In one study (Parra et al. 2011), participants were presented with a memory array and were asked to keep in mind either single features (colors) or bound features of objects (colored objects). Following a short-delay interval, a probe array appeared, and participants had to indicate whether the probe array was the same or different to the memory array. Patients with FAD and clinically asymptomatic carriers performed similar to sporadic AD patients, demonstrating impaired performance in only the bound condition. Impaired retention of bound features in WM even in clinically asymptomatic carriers highlights the sensitivity of this deficit in detecting AD-related changes even in the absence of other cognitive deficits.

The studies employed by Parra and his colleagues employed a change-detection paradigm, which can be used to measure the capacity of WM or the *number of items* which participants can recall correctly from the WM array in a binary manner (Luck 1997; Zhang and Luck 2008). Although these "quantal" measures of WM performance have been essential to our understanding of WM and its impairments in disease, they might not be sensitive to detect changes in memory resolution. In other words, change-detection paradigms require participants to make a binary response: either the item was remembered correctly or it was not remembered at all, in an all-or-none manner.

However, it is important to highlight that just because an individual fails to recall an item, it does not necessarily mean that information regarding that item is completely lost from memory. Conversely, a correct response does not inform us regarding the quality with which an item was retained in memory. Furthermore, the condition of interest (i.e., the binding condition) required an additional operation compared to single-feature trials. In this condition, participants have to remember both single features and their associations with one another. Thus, direct comparison of such trials to unimpaired single-feature trials should be considered with caution,

especially since the single-feature capacity of patients differed from healthy controls in some of these studies (Parra et al. 2011).

1.2 Delayed Reproduction Tasks

A more recent theoretical and empirical approach aims to examine the resolution with which items are retained in memory, in a continuous manner (for a review, see Fallon et al. 2016; Ma et al. 2014). Instead of asking participants to report whether a change occurred between the memory and the probe array, they are requested to reproduce the exact quality of the remembered feature in an analogue response space (e.g., Bays et al. 2009; Gorgoraptis et al. 2011). These delayed reproduction tasks (Fig. 1) measure the resolution or precision of recall by calculating the difference in the response from the true value of the feature from the memory array and hence provide an index of the quality of memory representation.

The delayed reproduction tasks have now been successfully used to study memory for a range of features, including color, orientation, motion direction, location, and even auditory pitch (Bays et al. 2009; Zokaei et al. 2011; Gorgoraptis et al. 2011; Joseph et al. 2016). Using this methodology, it has been found that memory does not reach a capacity limit, but rather the precision with which these features are retained, as measured by variability in recall error, increases gradually

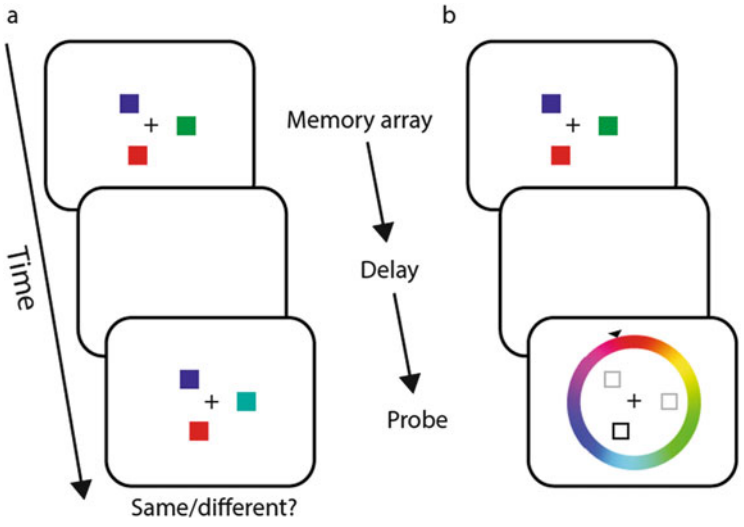

Fig. 1 Example of a color change-detection and delayed reproduction tasks. In the change-detection task, participants have to identify whether the probe array was the same or different to the memory array. In the delayed reproduction tasks, observers must report the color of the item probed by location by selecting it from the color wheel. (**a**) Change-detection. (**b**) Delayed reproduction

and continuously with memory array set size. Importantly, these tasks have been shown to be more sensitive in detecting subtle changes in WM compared to conventional span measures of WM, such as digit or spatial spans (Zokaei et al. 2014a).

On a delayed reproduction task, FAD patients with pathological mutations in presenilin-1 or APP genes demonstrated significant WM deficits for object locations compared to healthy controls (Liang et al. 2016). Participants were presented with one or three colored shapes (fractals) on a touchscreen computer and were asked to keep in mind both their identity and locations (Fig. 2a). Following a delay, they were presented with two shapes, one from the memory array and a novel foil. They first had to select the shape that appeared in the memory array by tapping on it (identification memory) and then drag it to its remembered location (localization memory).

Localization memory error, i.e., the difference in the reported location and the true location of the object from the memory array, was larger in patients with FAD (Fig. 2b). Importantly, an advantage of these delayed reproductions tasks, such as the one employed in this study, is that it is possible to dissect out different sources of error that contribute to impaired WM. Specifically, error can arise from misreporting features of "other" none-probed items that were presented in the memory array, instead of reporting the features of the probed item. These *binding errors* are often labelled as "swap errors."

For example, in the object-location WM task, a swap occurs if participants pick the correct item at identification but drags it to the location of one of the other objects on the screen (Fig. 2c). Importantly, unlike change-detection paradigms, the proportion of binding errors – or swaps – can be estimated from the same trial rather than requiring participants to actively retain bound vs. unbound features in WM on different trials.

In line with previous research, FAD patients showed greater binding errors compared to healthy controls and hence mislocalized a correctly identified object to the location of other items held in WM. Significantly, asymptomatic carriers (people with an FAD gene who were not yet showing cognitive deficits on standard neuropsychological tests) also made increased binding errors (Fig. 2c). Consistent with the role of hippocampus in feature-binding (Yonelinas 2013; Libby et al. 2014), decreased hippocampal volume across familial AD participants was associated with deficits of WM performance and the proportion of swap errors (Fig. 2d).

In a similar study, using an identical object-location memory task, WM performance was examined in another group of individuals with a genetic risk factor of AD: carriers of the apolipoprotein-E (APOE) ε4 allele gene. APOE ε4 confers the highest-known genetic risk for developing AD in the older age, with 30–60% of those diagnosed with AD carrying one or two copies of the APOE ε4 allele (Saunders et al. 1993; Myers et al. 1996; Sando et al. 2008). This high risk of conversion makes individuals with ε4 allele ideal candidates for investigating cognitive impairments that may point to early signs of AD. Importantly, variants of the APOE allele occur normally in the population and are not causative of AD, but rather the APOE ε4 allele results in a higher-than-normal risk of developing this disorder.

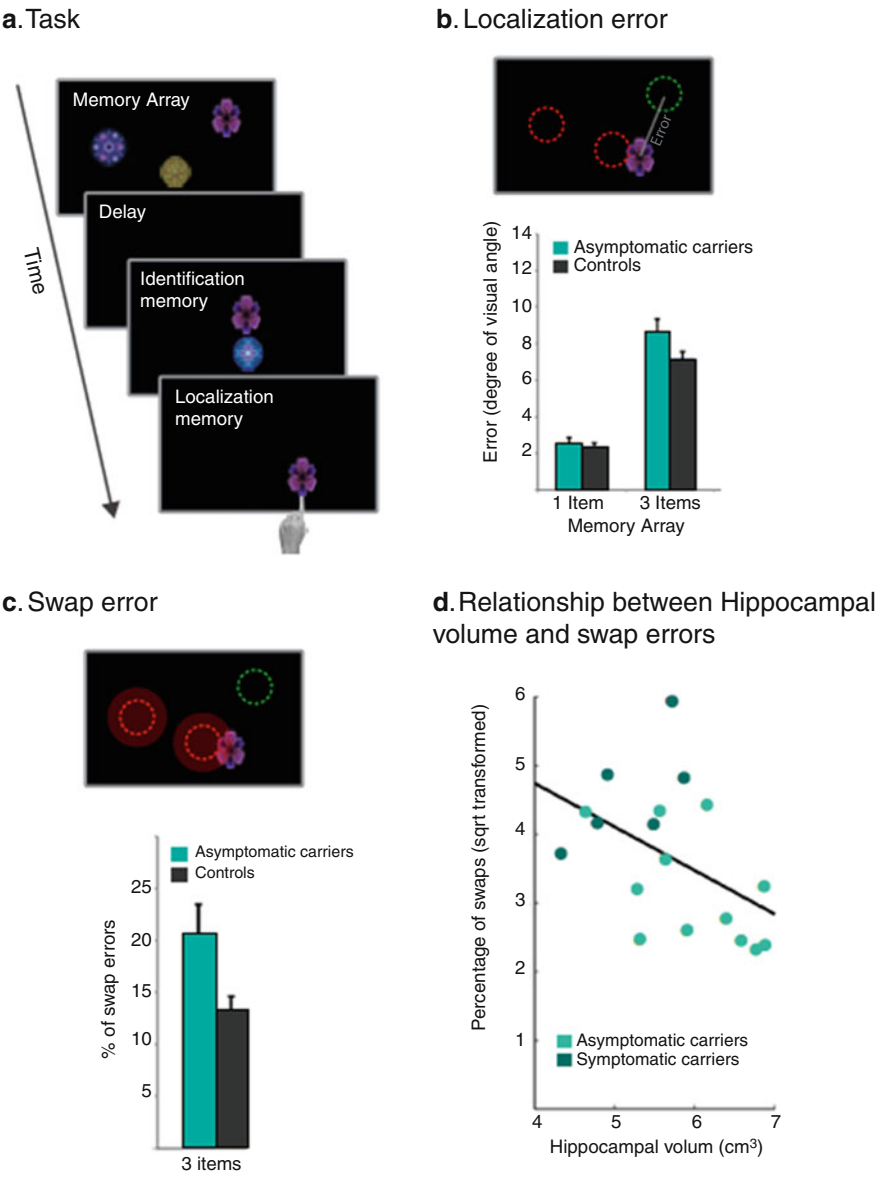

Fig. 2 Object-location memory task and performance. (**a**) Schematic of the working memory task. Participants are presented with a memory array followed by a delay. They are then presented with two items, one from the memory array and a foil. On a touchscreen computer, participants first have to touch the object they have seen before in the memory array and drag it to its remembered location. (**b**) Different types of error that can occur in this task. Localization error is measured by a difference in response location compared to the true location of the item in the memory array. Swap errors are proportion of trials where the object is dragged to a location near the location of one of the other, non-probed, items from the memory array. (**c**) Asymptomatic patients with familial AD make significantly larger errors in memory and make significantly more swap errors compared to healthy controls. (**d**) Proportion of swap errors correlated with the hippocampus volume for both symptomatic and asymptomatic carriers (figure from Liang et al. 2016)

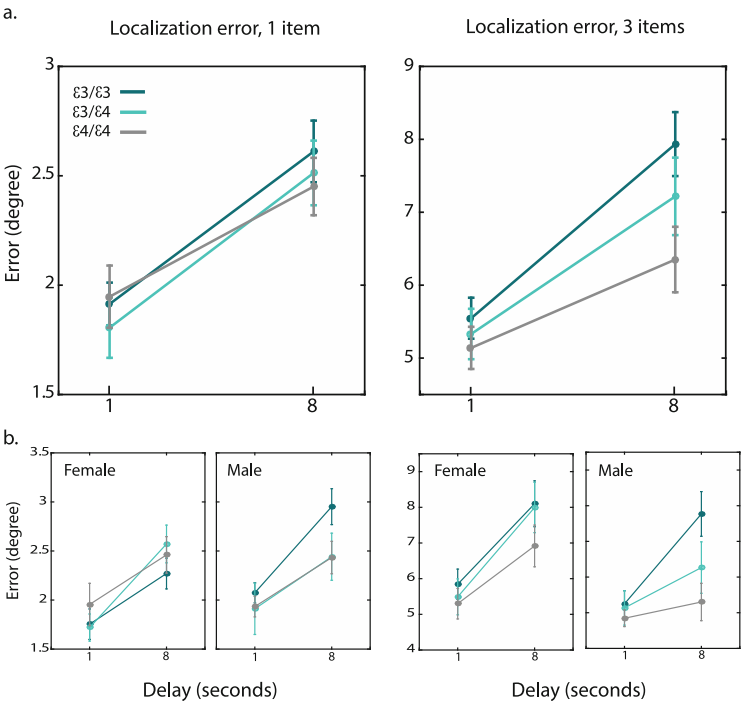

Fig. 3 Localization performance according to genotype and gender in middle age Localization error, indexed by the difference in angular degrees between the target location and the response, for different memory set sizes and delays (**a**) for all participants and (**b**) broken down by sex. Location memory was more precise and decayed less in male APOE ε4/ε4 carriers than male ε4/ε3 or ε3/ε3 carriers, particularly, when more items had to be retained in memory for longer durations (figure from Zokaei et al. 2017)

Interestingly, middle-aged carriers of the APOE ε4 allele demonstrated enhanced WM performance, indexed by both reduced memory decay and a decrease in number of swap errors, in a gene dosage-dependent manner (Zokaei et al. 2017, 2019a). That is, individuals with two copies of the ε4 allele performed better than those with a single copy compared to noncarriers, specifically in male compared to female carriers (Fig. 3). These results are consistent with an antagonistic pleiotropy hypothesis (Williams 1957), which proposes that carrying the APOE ε4 allele might actually confer a WM advantage earlier in life. Detrimental effects associated with this allele become evident only at a point beyond normal reproductive age and would not have been a factor until only relatively recently in human history when people have begun to live far longer than in previous centuries. Although the presence of the APOE ε4 allele reduced swap errors in middle age, the exact effects of the APOE gene on neural mechanisms related to AD pathology and its interaction with cognition are not yet well understood but have been subject to vigorous research in the past decade (Wolk et al. 2010; Suri et al. 2013; Heise et al. 2014; Zimmermann and Butler 2018).

In other pathologies like AD that affects MTL structures, WM binding deficits have also been reported (Pertzov et al. 2013; Koen et al. 2016; Zokaei et al. 2019b). For example, individuals with focal MTL damage due to voltage-gated potassium channel antibody (VGKC-Ab)-mediated limbic encephalitis showed the binding deficit in WM, measured by an increase in proportion of swap errors in the object-location WM task, while crucially their memory for object identities and locations remained intact (Pertzov et al. 2013). Similarly, patients with hippocampal lesions also appear to have a binding deficit in memory, regardless of retention duration (Olson et al. 2006; van Geldorp et al. 2014; Esfahani-Bayerl et al. 2016; Zokaei et al. 2018), although some have contested these conclusions (Jeneson et al. 2010). Together, these findings point to a specific impairment in retention of bound objects in WM in MTL disorders, such as sporadic and familial AD.

2 Working Memory in Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder characterized by depletion of nigrostriatal and mesocortical dopamine, although it is now established that other neurotransmitter systems such as noradrenaline (Zarow et al. 2003), serotonin (Kish et al. 2008), GABA (Emir et al. 2012), or acetylcholine (Dubois et al. 1983) are also affected in PD. The neurotransmitter dopamine nevertheless is thought to play a crucial role in many complex cognitive functions such as WM. Considering the link between dopamine depletion and PD, cognitive deficits, including those in WM, are an important feature of PD, often apparent at very early stages of the disease (Owen et al. 1993, 1997; Dujardin et al. 1999; Muslimovic et al. 2005; Verbaan et al. 2007; Savica et al. 2010).

The influence of disease progression on WM performance, however, is highly complex, and some studies have failed to identify impairments in unmedicated PD patients at earlier stages of the illness using variants of span tasks (e.g., Owen et al. 1997). For example, in the previously described study by Della Sala et al. (2012), WM performance for memory arrays consisting of single features or multiple features – bound or unbound – was intact in patients with PD compared to healthy controls. More sensitive delayed reproduction tasks, however, have been successful in identifying the pattern of impairment in PD patients and in at-risk cohorts.

2.1 Delayed Reproduction Tasks

In one study, unmedicated PD patients (those who had not yet been started on any drug therapy by their clinician) were tested on a sequential delayed reproduction task within a few months of being diagnosed in order to identify the nature of WM impairments in early PD (Zokaei et al. 2014a). Participants were presented with a sequence of four colored oriented bars and were asked to keep in mind both the color

and the orientation of these bars. At the end of the sequence, they were presented with a probe orientation in the color of one of the orientations from the memory array. They were asked to "dial up" the orientation of the probed item to match the one from memory (Fig. 4a). WM orientation precision, as measured by the difference in angular deviation between the response orientation and the target angle, was significantly impaired in these unmedicated patients with PD compared to healthy controls.

But what is the source of error of the impaired WM precision in patient with PD? As mentioned earlier, delayed reproduction tasks allow us to dissect out sources of error contributing to impaired performance (Fig. 4b). In addition to misbinding errors, participants may make random errors because, on some trials, they may be simply guessing because of failure to encode or retrieve the probed item. Patients with PD made significantly more *random responses* when performing the described delayed reproduction task (Zokaei et al. 2014b). Moreover, in this study, patients with PD – regardless of the presence or absence of a genetic risk factor for PD: glucocerebrosidase (*GBA*) mutation – were making significantly more guesses (Fig. 4c).

Mutations in the gene encoding the lysosomal enzyme GBA, classically associated with Gaucher's disease (Pastores and Hughes 1993), have been identified as the highest genetic risk factor for developing PD (Clark et al. 2009; Neumann et al. 2009; Sidransky et al. 2009). However, it is important to note that this gene also constitutes a rare susceptibility factor for PD (Sato et al. 2005). Individuals with GBA mutation, regardless of whether they had PD, showed increased *binding errors* (Zokaei et al. 2014b). Interestingly, both mouse models of *GBA* mutation (Sardi et al. 2011) and human Gaucher's disease patients with dementia or PD have pathological changes in MTL regions (Wong et al. 2004), in line with the role of MTL in binding of information.

Unlike people with *GBA* mutations, individuals with idiopathic rapid eye movement (REM) sleep behavior disorder (RBD) provide an "enriched" at-risk cohort to examine whether WM impairments, specifically increased random responses, are present in prodromal PD – the period between the onset of neurodegeneration and the diagnosis. In healthy people, the body is atonic and motionless during dreaming during REM sleep. RBD is a parasomnia typified by simple or complex motor behaviors associated with vivid dreams occurring during REM sleep (Boeve 2010). Prospective cohort studies have reported a very strong association between RBD and subsequent development of neurodegenerative disorders, with up to 80% of cases affected (Iranzo et al. 2006; Postuma et al. 2009; Boot et al. 2012; Schenck et al. 2013). While some patients with RBD may develop dementia with Lewy bodies, most will eventually develop PD (Boeve 2010).

Moreover, dysfunction within the dopaminergic systems has also been reported in RBD prior to the onset of clinically defined neurodegenerative disorders. For example, in one study using single-photon emission computed tomography (SPECT), a decrease in ^{123}I-FP-CIT uptake in the striatum of RBD patients was demonstrated with approximately 40% of cases having an abnormal scan (Selikhova et al. 2009; Lawton et al. 2015). Similarly, loss of dopaminergic neurons as

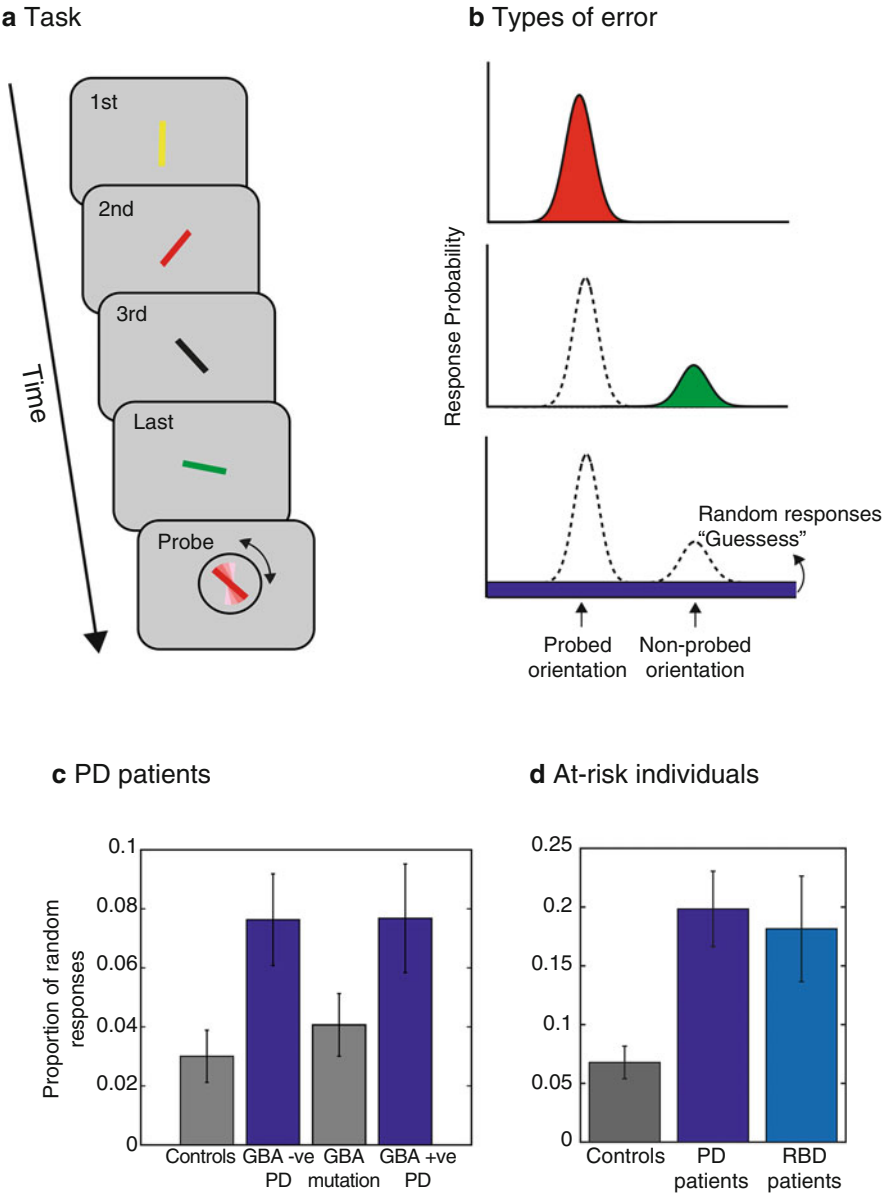

Fig. 4 Sequential orientation task and performance. (**a**) Sequences of four colored oriented bars were presented. Participants had to adjust the orientation of the probe stimuli to the orientation of the bar with the same color in the memory array. (**b**) Sources of error in memory. Error can arise due to increased variability in responses to the probed orientation, due to responses toward the non-probed items or misbinding error, and lastly due to random responses or guesses. Patients with PD with or without GBA mutation (**c**) as well as those at risk of developing PD due to RBD (**d**) made significantly more random responses/guesses compared to healthy controls (figures from Zokaei et al. 2014a, b; Rolinski et al. 2015)

measured by a decrease in ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ) striatal binding on positron emission tomography (PET) scanning has also been reported in RBD patients without PD (Ferini-Strambi et al. 2004). Importantly though, patients with RBD, who were not yet diagnosed with PD, also had a similar deficit in WM to patients with PD, that is, they made an increased proportion of guesses or *random responses* as measured by delayed reproduction tasks (Rolinski et al. 2015; Fig. 4d).

The precise mechanisms underlying this type of error however are yet to be established. Increased random responses could be a consequence a decrease in signal-to-noise ratio due to deficits in the dopaminergic dysfunction in PD patients resulting in responses to fall within the random range (Sawaguchi and Goldman-Rakic 1991; Winterer and Weinberger 2004; Kroener et al. 2009). On the other hand, WM deficits might arise because of non-dopaminergic pathologies present in PD, such as disruptions in noradrenaline (Zarow et al. 2003), serotonin (Kish et al. 2008), GABA (Emir et al. 2012), or acetylcholine (Dubois et al. 1983). For example, cholinergic disruptions in PD may result in fluctuations in attention leading to encoding or retrieval failure and therefore increased probability of guesses (Kehagia et al. 2010; Hasselmo and Sarter 2011). To better understand and isolate the mechanisms associated with WM deficits in PD, researchers have relied on studying the effects of drugs that selectively alter an individual neurotransmitter by investigating performance both on and off medication (Poewe et al. 1991; Lange et al. 1992; Lewis et al. 2005; Hughes et al. 2013).

Using this approach, studies investigating WM performance both on and off dopaminergic medication have resulted in conflicting findings. Dopaminergic medication has been reported to both improve (Lange et al. 1992) and impair WM performance (Poewe et al. 1991; Cools et al. 2010; Uitvlugt et al. 2016), sometimes depending on modality of the memory array (Owen et al. 1997; Postle et al. 1997; Gruszka et al. 2016), in tasks employing span or change-detection methodology. To better quantify the effect of dopaminergic medication on WM, a recent study (Fig. 5) examined the effect of dopaminergic medication on a delayed reproduction task examining retention over time (simple maintenance), as well as recall when people either had to ignore distracting information or update the contents of WM (Fallon et al. 2017).

Dopaminergic medication selectively improved PD patients' ability to precisely recall items from memory *in the presence of irrelevant information*, irrespective of whether the information had to be ignored or updated. On the other hand, dopaminergic medication did not influence WM retention in the absence to competing information, that is, in trials that required participants to retain a memory array for either short- or long-delay intervals – maintenance conditions. Simple retention of information however was impaired in PD patients compared to healthy controls, pointing to possible involvement of non-dopaminergic neurotransmitters involved in WM maintenance processes.

Together these findings point to the possibility of two distinct mechanisms that may contribute to WM deficits in PD. Firstly, a frontal dysexecutive effect which is modulated by dopamine and deals with gating of information into relevant vs. irrelevant information in WM (Dalrymple-Alford et al. 1994; Gruszka et al.

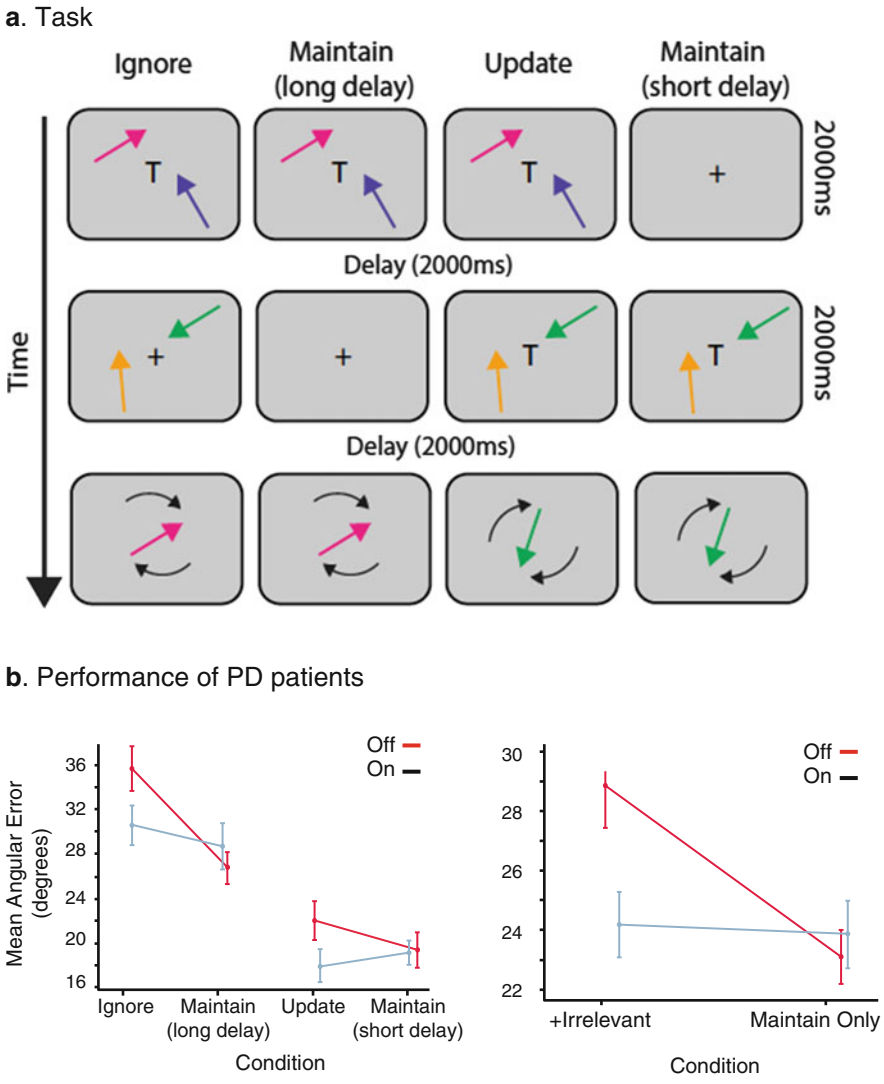

Fig. 5 Working memory task with and without irrelevant information. (**a**) Participants are presented with two colored arrows to keep in mind either for short or long duration (conditions maintain long and short delay) in half of the trials. In the remaining half, they will be presented with a second array of arrows that they either have to ignore (ignore condition) or replace with the array in mind (update). (**b**) Dopaminergic medication only influenced by the trials with irrelevant information, that is, ignore or update conditions (figures from Fallon et al. 2017)

2016). Secondly, studies reported here also support the possibility of a non-dopaminergic syndrome that influences the successful retention of information and may result in increased forgetting over short periods of time (Kehagia et al. 2010; Gratwicke et al. 2015).

3 Summary

Working memory impairment is a central feature of cognitive dysfunction, often reported in both patients with AD and PD. However, the exact nature of these deficits and the underlying mechanisms resulting in such impairment are dissociable. More detailed and sensitive reproduction WM tasks have helped shed light on the distinction in sources of error in WM in these two groups of patients. These are tasks that allow us to distinguish between errors arising from changes in resolution of memory, increased misbinding of retained features, and increased guessing or random responses.

In AD (and other disorders affecting MTL function), patients make more swaps or misbinding errors, in line with the role of hippocampus in retention of bound objects. More specifically, even though the retention of single features can be intact in these individuals, the binding of features into objects is significantly affected compared to both healthy individuals and patients with PD. Moreover, a similar pattern of increased swap errors is also found in individuals with a genetic risk of developing familial AD, even prior to manifestation of any clinical symptoms of the disease.

In PD, on the other hand, two distinct underlying mechanisms may contribute to WM impairments. Firstly, there is an increased proportion of random responses or guesses. This deficit is not influenced by dopaminergic medication, highlighting the role of a non-dopaminergic contributions to impairments associated with simple retention of information over brief periods of time. However, impairments in gating of information in WM in PD can be attributed to a frontal dysfunction and are modulated by dopamine, in studies that manipulate the effects of drug to selectively alter this neurotransmitter system.

Acknowledgments This work is supported by the Wellcome Trust, British Academy, NIHR Oxford Biomedical Research Centre, and Wellcome Centre for Integrative Neuroscience.

References

Baddeley A (2003) Working memory: looking back and looking forward. Nat Rev Neurosci 4:829–839. https://doi.org/10.1038/nrn1201

Bays PM, Catalao RFG, Husain M (2009) The precision of visual working memory is set by allocation of a shared resource. J Vis 9:7. https://doi.org/10.1167/9.10.7

Becker JT (1988) Working memory and secondary memory deficits in Alzheimer's disease. J Clin Exp Neuropsychol 10:739–753. https://doi.org/10.1080/01688638808402811

Belleville S, Peretz I, Malenfant D (1996) Examination of the working memory components in normal aging and in dementia of the Alzheimer type. Neuropsychologia 34:195–207

Blackwell AD, Sahakian BJ, Vesey R, Semple JM, Robbins TW, Hodges JR (2004) Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. Dement Geriatr Cogn Disord 17:42–48. https://doi.org/10.1159/000074081

Boeve BF (2010) REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. Ann N Y Acad Sci 1184:15–54. https://doi.org/10.1111/j.1749-6632.2009.05115.x

Boot BP, Boeve BF, Roberts RO, Ferman TJ, Geda YE, Pankratz VS, Ivnik RJ, Smith GE, McDade E, Christianson TJH, Knopman DS, Tangalos EG, Silber MH, Petersen RC (2012) Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. Ann Neurol 71:49–56. https://doi.org/10.1002/ana.22655

Braak H, Braak E (1998) Evolution of neuronal changes in the course of Alzheimer's disease. J Neural Transm Suppl 53:127–140

Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, Owen C, Aldea P, Su Y, Hassenstab J, Cairns NJ, Holtzman DM, Fagan AM, Morris JC, Benzinger TLS, Ances BM (2016) Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. Sci Transl Med 8:338ra66. https://doi.org/10.1126/scitranslmed.aaf2362

Carlesimo GA, Fadda L, Lorusso S, Caltagirone C (1994) Verbal and spatial memory spans in Alzheimer's and multi-infarct dementia. Acta Neurol Scand 89:132–138

Cashdollar N, Duncan JS, Duzel E (2011) Challenging the classical distinction between long-term and short-term memory: reconsidering the role of the hippocampus. Future Neurol 6:351–362. https://doi.org/10.2217/fnl.11.12

Clark LN, Kartsaklis LA, Wolf Gilbert R, Dorado B, Ross BM, Kisselev S, Verbitsky M, Mejia-Santana H, Cote LJ, Andrews H, Vonsattel J-P, Fahn S, Mayeux R, Honig LS, Marder K (2009) Association of glucocerebrosidase mutations with dementia with lewy bodies. Arch Neurol 66:578–583. https://doi.org/10.1001/archneurol.2009.54

Cools R, Miyakawa A, Sheridan M, D'Esposito M (2010) Enhanced frontal function in Parkinson's disease. Brain J Neurol 133:225–233. https://doi.org/10.1093/brain/awp301

Dalrymple-Alford JC, Kalders AS, Jones RD, Watson RW (1994) A central executive deficit in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 57:360–367

Davachi L (2006) Item, context and relational episodic encoding in humans. Curr Opin Neurobiol 16:693–700. https://doi.org/10.1016/j.conb.2006.10.012

Della Sala S, Parra MA, Fabi K, Luzzi S, Abrahams S (2012) Short-term memory binding is impaired in AD but not in non-AD dementias. Neuropsychologia 50:833–840. https://doi.org/10.1016/j.neuropsychologia.2012.01.018

Dubois B, Ruberg M, Javoy-Agid F, Ploska A, Agid Y (1983) A subcortico-cortical cholinergic system is affected in Parkinson's disease. Brain Res 288:213–218

Dujardin K, Degreef JF, Rogelet P, Defebvre L, Destee A (1999) Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. J Neurol 246:783–788

Eichenbaum H, Yonelinas AP, Ranganath C (2007) The medial temporal lobe and recognition memory. Annu Rev Neurosci 30:123–152. https://doi.org/10.1146/annurev.neuro.30.051606.094328

Emir UE, Tuite PJ, Öz G (2012) Elevated pontine and putamenal GABA levels in mild-moderate Parkinson disease detected by 7 tesla proton MRS. PLoS One 7:e30918

Esfahani-Bayerl N, Finke C, Braun M, Düzel E, Heekeren HR, Holtkamp M, Hasper D, Storm C, Ploner CJ (2016) Visuo-spatial memory deficits following medial temporal lobe damage: a comparison of three patient groups. Neuropsychologia 81:168–179. https://doi.org/10.1016/j.neuropsychologia.2015.12.024

Fallon SJ, Zokaei N, Husain M (2016) Causes and consequences of limitations in visual working memory. Ann N Y Acad Sci 1369:40–54. https://doi.org/10.1111/nyas.12992

Fallon SJ, Mattiesing RM, Muhammed K, Manohar S, Husain M (2017) Fractionating the neurocognitive mechanisms underlying working memory: independent effects of dopamine and Parkinson's disease. Cereb Cortex 27:5727–5738. https://doi.org/10.1093/cercor/bhx242

Ferini-Strambi L, Di Gioia MR, Castronovo V, Oldani A, Zucconi M, Cappa SF (2004) Neuropsychological assessment in idiopathic REM sleep behavior disorder (RBD): does the idiopathic form of RBD really exist? Neurology 62:41–45

Fox NC, Warrington EK, Seiffer AL, Agnew SK, Rossor MN (1998) Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease. A longitudinal prospective study. Brain J Neurol 121(Pt 9):1631–1639

Gorgoraptis N, Catalao RFG, Bays PM, Husain M (2011) Dynamic updating of working memory resources for visual objects. J Neurosci 31:8502–8511. https://doi.org/10.1523/JNEUROSCI.0208-11.2011

Gratwicke J, Jahanshahi M, Foltynie T (2015) Parkinson's disease dementia: a neural networks perspective. Brain J Neurol 138:1454–1476. https://doi.org/10.1093/brain/awv104

Gruszka A, Bor D, Barker RR, Necka E, Owen AM (2016) The role of executive processes in working memory deficits in Parkinson's disease. Pol Psychol Bull 47:123–130. https://doi.org/10.1515/ppb-2016-0013

Hannula DE, Tranel D, Cohen NJ (2006) The long and the short of it: relational memory impairments in amnesia, even at short lags. J Neurosci 26:8352–8359

Hartley T, Bird CM, Chan D, Cipolotti L, Husain M, Vargha-Khadem F, Burgess N (2007) The hippocampus is required for short-term topographical memory in humans. Hippocampus 17:34–48. https://doi.org/10.1002/hipo.20240

Hasselmo ME, Sarter M (2011) Modes and models of forebrain cholinergic neuromodulation of cognition. Neuropsychopharmacology 36:52–73. https://doi.org/10.1038/npp.2010.104

Heise V, Filippini N, Trachtenberg AJ, Suri S, Ebmeier KP, Mackay CE (2014) Apolipoprotein E genotype, gender and age modulate connectivity of the hippocampus in healthy adults. NeuroImage 98:23–30. https://doi.org/10.1016/j.neuroimage.2014.04.081

Hughes LE, Altena E, Barker RA, Rowe JB (2013) Perseveration and choice in Parkinson's disease: the impact of progressive frontostriatal dysfunction on action decisions. Cereb Cortex 23:1572–1581

Hulme C, Lee G, Brown GD (1993) Short-term memory impairments in Alzheimer-type dementia: evidence for separable impairments of articulatory rehearsal and long-term memory. Neuropsychologia 31:161–172

Iranzo A, Molinuevo JL, Santamaría J, Serradell M, Martí MJ, Valldeoriola F, Tolosa E (2006) Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol 5:572–577. https://doi.org/10.1016/S1474-4422(06)70476-8

Jeneson A, Mauldin KN, Squire LR (2010) Intact working memory for relational information after medial temporal lobe damage. J Neurosci 30:13624–13629. https://doi.org/10.1523/JNEUROSCI.2895-10.2010

Joseph S, Teki S, Kumar S, Husain M, Griffiths TD (2016) Resource allocation models of auditory working memory. Brain Res 1640:183–192. https://doi.org/10.1016/j.brainres.2016.01.044

Kehagia AA, Barker RA, Robbins TW (2010) Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol 9:1200–1213. https://doi.org/10.1016/S1474-4422(10)70212-X

Kish SJ, Tong J, Hornykiewicz O, Rajput A, Chang L-J, Guttman M, Furukawa Y (2008) Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease. Brain 131:120–131

Koen JD, Borders AA, Petzold MT, Yonelinas AP (2016) Visual short-term memory for high resolution associations is impaired in patients with medial temporal lobe damage. Hippocampus 27:184–193. https://doi.org/10.1002/hipo.22682

Konkel A, Cohen NJ (2009) Relational memory and the hippocampus: representations and methods. Front Neurosci 3:166–174. https://doi.org/10.3389/neuro.01.023.2009

Kroener S, Chandler LJ, Phillips PEM, Seamans JK (2009) Dopamine modulates persistent synaptic activity and enhances the signal-to-noise ratio in the prefrontal cortex. PLoS One 4:e6507. https://doi.org/10.1371/journal.pone.0006507

Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM (1992) L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology 107:394–404

Lau KM, Parikh M, Harvey DJ, Huang C-J, Farias ST (2015) Early cognitively based functional limitations predict loss of independence in instrumental activities of daily living in older adults. J Int Neuropsychol Soc 21:688–698. https://doi.org/10.1017/S1355617715000818

Lawton M, Baig F, Rolinski M, Ruffman C, Nithi K, May MT, Ben-Shlomo Y, Hu MTM (2015) Parkinson's disease subtypes in the Oxford Parkinson disease Centre (OPDC) discovery cohort. J Park Dis 5:269–279. https://doi.org/10.3233/JPD-140523

Lewis SJG, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA (2005) Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry 76:343–348

Liang Y, Pertzov Y, Nicholas JM, Henley SMD, Crutch S, Woodward F, Leung K, Fox NC, Husain M (2016) Visual short-term memory binding deficit in familial Alzheimer's disease. Cortex 78:150–164. https://doi.org/10.1016/j.cortex.2016.01.015

Libby LA, Hannula DE, Ranganath C (2014) Medial temporal lobe coding of item and spatial information during relational binding in working memory. J Neurosci 34:14233–14242. https://doi.org/10.1523/JNEUROSCI.0655-14.2014

Linn RT, Wolf PA, Bachman DL, Knoefel JE, Cobb JL, Belanger AJ, Kaplan EF, D'Agostino RB (1995) The "preclinical phase" of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort. Arch Neurol 52:485–490

Luck V (1997) The capacity of visual working memory for features and conjunctions. Nature 390:279–281. https://doi.org/10.1038/36846

Ma WJ, Husain M, Bays PM (2014) Changing concepts of working memory. Nat Neurosci 17:347–356. https://doi.org/10.1038/nn.3655

Martin A, Brouwers P, Cox C, Fedio P (1985) On the nature of the verbal memory deficit in Alzheimer's disease. Brain Lang 25:323–341

Miller E (1973) Short- and long-term memory in patients with presenile dementia (Alzheimer's disease). Psychol Med 3:221–224

Muslimovic D, Post B, Speelman JD, Schmand B (2005) Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 65:1239–1245. https://doi.org/10.1212/01.wnl.0000180516.69442.95

Myers RH, Schaefer EJ, Wilson PW, D'Agostino R, Ordovas JM, Espino A, Au R, White RF, Knoefel JE, Cobb JL, McNulty KA, Beiser A, Wolf PA (1996) Apolipoprotein E epsilon4 association with dementia in a population-based study: the Framingham study. Neurology 46:673–677

Nadel L, Peterson MA (2013) The hippocampus: part of an interactive posterior representational system spanning perceptual and memorial systems. J Exp Psychol Gen 142:1242–1254. https://doi.org/10.1037/a0033690

Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, Li A, Holton J, Guerreiro R, Paudel R, Segarane B, Singleton A, Lees A, Hardy J, Houlden H, Revesz T, Wood NW (2009) Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain 132:1783–1794. https://doi.org/10.1093/brain/awp044

Olson IR, Moore KS, Stark M, Chatterjee A (2006) Visual working memory is impaired when the medial temporal lobe is damaged. J Cogn Neurosci 18:1087–1097. https://doi.org/10.1162/jocn.2006.18.7.1087

Owen AM, Beksinska M, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, Sahakian BJ, Robbins TW (1993) Visuospatial memory deficits at different stages of Parkinson's disease. Neuropsychologia 31:627–644

Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW (1997) Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia 35:519–532

Parra MA, Abrahams S, Fabi K, Logie R, Luzzi S, Della Sala S (2009) Short-term memory binding deficits in Alzheimer's disease. Brain J Neurol 132:1057–1066. https://doi.org/10.1093/brain/awp036

Parra MA, Abrahams S, Logie RH, Méndez LG, Lopera F, Della Sala S (2010) Visual short-term memory binding deficits in familial Alzheimer's disease. Brain J Neurol 133:2702–2713. https://doi.org/10.1093/brain/awq148

Parra MA, Sala SD, Abrahams S, Logie RH, Méndez LG, Lopera F (2011) Specific deficit of colour-colour short-term memory binding in sporadic and familial Alzheimer's disease. Neuropsychologia 49:1943–1952. https://doi.org/10.1016/j.neuropsychologia.2011.03.022

Pastores GM, Hughes DA (1993) Gaucher disease. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong C-T, Stephens K (eds) GeneReviews™. University of Washington, Seattle

Perry RJ, Hodges JR (2000) Fate of patients with questionable (very mild) Alzheimer's disease: longitudinal profiles of individual subjects' decline. Dement Geriatr Cogn Disord 11:342–349. https://doi.org/10.1159/000017264

Pertzov Y, Miller TD, Gorgoraptis N, Caine D, Schott JM, Butler C, Husain M (2013) Binding deficits in memory following medial temporal lobe damage in patients with voltage-gated potassium channel complex antibody-associated limbic encephalitis. Brain J Neurol 136:2474–2485. https://doi.org/10.1093/brain/awt129

Poewe W, Berger W, Benke TH, Schelosky L (1991) High-speed memory scanning in Parkinson's disease: adverse effects of levodopa. Ann Neurol 29:670–673

Postle BR, Jonides J, Smith EE, Corkin S, Growdon JH (1997) Spatial, but not object, delayed response is impaired in early Parkinson's disease. Neuropsychology 11:171–179

Postuma RB, Gagnon JF, Vendette M, Montplaisir JY (2009) Markers of neurodegeneration in idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease. Brain J Neurol 132:3298–3307. https://doi.org/10.1093/brain/awp244

Ridha BH, Barnes J, Bartlett JW, Godbolt A, Pepple T, Rossor MN, Fox NC (2006) Tracking atrophy progression in familial Alzheimer's disease: a serial MRI study. Lancet Neurol 5:828–834. https://doi.org/10.1016/S1474-4422(06)70550-6

Rolinski M, Zokaei N, Baig F, Giehl K, Quinnell T, Zaiwalla Z, Mackay CE, Husain M, Hu MTM (2015) Visual short-term memory deficits in REM sleep behaviour disorder mirror those in Parkinson's disease. Brain 139:47–53. https://doi.org/10.1093/brain/awv334

Sando SB, Melquist S, Cannon A, Hutton ML, Sletvold O, Saltvedt I, White LR, Lydersen S, Aasly JO (2008) APOE epsilon 4 lowers age at onset and is a high risk factor for Alzheimer's disease; a case control study from Central Norway. BMC Neurol 8:9. https://doi.org/10.1186/1471-2377-8-9

Sardi SP, Clarke J, Kinnecom C, Tamsett TJ, Li L, Stanek LM, Passini MA, Grabowski GA, Schlossmacher MG, Sidman RL, Cheng SH, Shihabuddin LS (2011) CNS expression of glucocerebrosidase corrects α-synuclein pathology and memory in a mouse model of Gaucher-related synucleinopathy. Proc Natl Acad Sci 108:12101–12106. https://doi.org/10.1073/pnas.1108197108

Sato C, Morgan A, Lang AE, Salehi-Rad S, Kawarai T, Meng Y, Ray PN, Farrer LA, St George-Hyslop P, Rogaeva E (2005) Analysis of the glucocerebrosidase gene in Parkinson's disease. Mov Disord 20:367–370. https://doi.org/10.1002/mds.20319

Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PHS, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD (1993) Association of apolipoprotein E allele ϵ4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43:1467–1467. https://doi.org/10.1212/WNL.43.8.1467

Savica R, Rocca WA, Ahlskog J (2010) When does Parkinson disease start? Arch Neurol 67:798–801. https://doi.org/10.1001/archneurol.2010.135

Sawaguchi T, Goldman-Rakic P (1991) D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 251:947–950. https://doi.org/10.1126/science.1825731

Schenck CH, Boeve BF, Mahowald MW (2013) Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med 14:744–748. https://doi.org/10.1016/j.sleep.2012.10.009

Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ (2009) A clinico-pathological study of subtypes in Parkinson's disease. Brain J Neurol 132:2947–2957. https://doi.org/10.1093/brain/awp234

Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, Berg D, Bras J, Brice A, Chen C-M, Clark LN, Condroyer C, de Marco EV, Dürr A, Eblan MJ, Fahn S, Farrer MJ, Fung H-C, Gan-Or Z, Gasser T, Gershoni-Baruch R, Giladi N, Griffith A, Gurevich T, Januario C, Kropp P, Lang AE, Lee-Chen G-J, Lesage S, Marder K, Mata IF, Mirelman A, Mitsui J, Mizuta I, Nicoletti G, Oliveira C, Ottman R, Orr-Urtreger A, Pereira LV, Quattrone A, Rogaeva E, Rolfs A, Rosenbaum H, Rozenberg R, Samii A, Samaddar T, Schulte C, Sharma M, Singleton A, Spitz M, Tan E-K, Tayebi N, Toda T, Troiano AR, Tsuji S, Wittstock M, Wolfsberg TG, Wu Y-R, Zabetian CP, Zhao Y, Ziegler SG (2009) Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 361:1651–1661. https://doi.org/10.1056/NEJMoa0901281

Spinnler H, Sala SD, Bandera R, Baddeley A (1988) Dementia, ageing, and the structure of human memory. Cogn Neuropsychol 5:193–211. https://doi.org/10.1080/02643298808252933

Suri S, Heise V, Trachtenberg AJ, Mackay CE (2013) The forgotten APOE allele: a review of the evidence and suggested mechanisms for the protective effect of APOE ε2. Neurosci Biobehav Rev 37:2878–2886. https://doi.org/10.1016/j.neubiorev.2013.10.010

Uitvlugt MG, Pleskac TJ, Ravizza SM (2016) The nature of working memory gating in Parkinson's disease: a multi-domain signal detection examination. Cogn Affect Behav Neurosci 16:289–301

van Geldorp B, Bouman Z, Hendriks MPH, Kessels RPC (2014) Different types of working memory binding in epilepsy patients with unilateral anterior temporal lobectomy. Brain Cogn 85:231–238. https://doi.org/10.1016/j.bandc.2013.12.009

Verbaan D, Marinus J, Visser M, van Rooden SM, Stiggelbout AM, Middelkoop HAM, van Hilten JJ (2007) Cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 78:1182–1187. https://doi.org/10.1136/jnnp.2006.112367

Watrous AJ, Tandon N, Conner CR, Pieters T, Ekstrom AD (2013) Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. Nat Neurosci 16:349–356. https://doi.org/10.1038/nn.3315

Williams GC (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398–411. https://doi.org/10.2307/2406060

Winterer G, Weinberger DR (2004) Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. Trends Neurosci 27:683–690. https://doi.org/10.1016/j.tins.2004.08.002

Wolk DA, Dickerson BC, Alzheimer's Disease Neuroimaging Initiative (2010) Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. Proc Natl Acad Sci U S A 107:10256–10261. https://doi.org/10.1073/pnas.1001412107

Wong K, Sidransky E, Verma A, Mixon T, Sandberg GD, Wakefield LK, Morrison A, Lwin A, Colegial C, Allman JM, Schiffmann R (2004) Neuropathology provides clues to the pathophysiology of Gaucher disease. Mol Genet Metab 82:192–207. https://doi.org/10.1016/j.ymgme.2004.04.011

Yau W-YW, Tudorascu DL, McDade EM, Ikonomovic S, James JA, Minhas D, Mowrey W, Sheu LK, Snitz BE, Weissfeld L, Gianaros PJ, Aizenstein HJ, Price JC, Mathis CA, Lopez OL, Klunk WE (2015) Longitudinal assessment of neuroimaging and clinical markers in autosomal dominant Alzheimer's disease: a prospective cohort study. Lancet Neurol 14:804–813. https://doi.org/10.1016/S1474-4422(15)00135-0

Yonelinas AP (2013) The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory. Behav Brain Res 254:34–44. https://doi.org/10.1016/j.bbr.2013.05.030

Zarow C, Lyness SA, Mortimer JA, Chui HC (2003) Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch Neurol 60:337–341

Zhang W, Luck SJ (2008) Discrete fixed-resolution representations in visual working memory. Nature 453:233–235

Zimmermann JF, Butler CR (2018) Accelerated long-term forgetting in asymptomatic APOE ε4 carriers. Lancet Neurol 17:394–395. https://doi.org/10.1016/S1474-4422(18)30078-4

Zokaei N, Gorgoraptis N, Bahrami B, Bays PM, Husain M (2011) Precision of working memory for visual motion sequences and transparent motion surfaces. J Vis 11:2. https://doi.org/10.1167/11.14.2

Zokaei N, Burnett Heyes S, Gorgoraptis N, Budhdeo S, Husain M (2014a) Working memory recall precision is a more sensitive index than span. J Neuropsychol 9:319–329. https://doi.org/10.1111/jnp.12052

Zokaei N, McNeill A, Proukakis C, Beavan M, Jarman P, Korlipara P, Hughes D, Mehta A, Hu MTM, Schapira AHV, Husain M (2014b) Visual short-term memory deficits associated with GBA mutation and Parkinson's disease. Brain J Neurol 137:2303–2311. https://doi.org/10.1093/brain/awu143

Zokaei N, Giehl K, Sillence A, Neville MJ, Karpe F, Nobre AC, Husain M (2017) Sex and APOE: a memory advantage in male APOE ε4 carriers in midlife. Cortex 88:98–105. https://doi.org/10.1016/j.cortex.2016.12.016

Zokaei N, Nour MM, Sillence A, Drew D, Adcock J, Stacey R, Voets N, Sen A, Husain M (2018) Binding deficits in visual short-term memory in patients with temporal lobe lobectomy. Hippocampus 29:63–67. https://doi.org/10.1002/hipo.22998

Zokaei N, Čepukaitytė G, Board AG, Mackay CE, Husain M, Nobre AC (2019a) Dissociable effects of the apolipoprotein-E (APOE) gene on short- and long-term memories. Neurobiol Aging 73:115–122. https://doi.org/10.1016/j.neurobiolaging.2018.09.017

Zokaei N, Nour MN, Sillence A, Drew D, Adcock J, Stacey R, Voets N, Sen A, Husain M (2019b) Binding deficits in visual short-term memory in patients with temporal lobe lobectomy. Hippocampus 29:63–67