FACULTY OF PSYCHOLOGY
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Coding Serial Position in Working Memory in the Healthy and Demented Brain

Maya De Belder

Supervisor: Prof. Dr. Wim Fias
Co-supervisor: Prof. Dr. Patrick Santens

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> «HISTORY AND MEMORY SHARE EVENTS; THAT IS, THEY SHARE TIME AND SPACE. EVERY MOMENT IS TWO MOMENTS.»
>
> ANNE MICHAELS

Vier jaar zwoegen en zweten hebben uiteindelijk geleid tot dit kleine boekje, een grote verwezenlijking voor elke doctoraatsstudent die dit punt bereikt. Als student droomde ik al van het ‘glamoureuze’ intellectuele leven van een doctoraatsstudent en heb vaak getwijfeld of dat doel wel haalbaar was voor mij. Het lijkt bijna onwerkelijk dat na negen jaar werken aan het bereiken van een studentendroom dit uiteindelijk het bekronende eindresultaat blijkt te zijn. Hoewel de nuchterheid voor het ware leven van de doctoraatsstudent er niet altijd even zachtaardig ingeslagen werd, geeft het overwinnen van een harde strijd een grote voldoening. Uiteraard moet de eer verdeeld worden onder allen die mij doorheen deze weg gesteund of begeleid hebben, want zonder hen zou dit nooit gelukt zijn.

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CHAPTER 1

INTRODUCTION

Daily life requires us to continuously deal with ordered information. Cooking a recipe requires the proper execution of a series of consecutive actions in order to obtain a tasty dish. Communicating with others involves the use of words in the correct order if you want your message to be understood. When retrieving a childhood memory we will re-experience the event by serially ordering specific features and moments of that memory in time. Almost anything we do in life demands the storage of serial information, in long-term memory for permanent preservation or in working memory (WM) for temporary retention. As serial order is so omnipresent in everyday functioning, serial order processing encompasses an important field of research. Following questions are fundamental to this domain of research; how do we mentally represent serial order and how does the brain deal with streams of information?

WM is an elementary cognitive function that serves to briefly maintain information in an active and accessible state, allowing to manipulate and perform operations based on temporarily stored information (Baddeley, Logie, Bressi, Della Sala & Spinnler, 1986; Jonides, Lacey & Nee, 2005). Language, reasoning and learning are some of the major cognitive skills that are considered to be fundamentally dependent on the functioning of WM and/or order processing (e.g., Baddeley, 2012; Martin & Gupta, 2004). It can be assumed that the WM system is the first instance in which serial order is encoded. All information that is received from the outer world first passes through the WM system, before being potentially transferred to long-term memory. The WM is therefore the ideal starting point to conduct research on serial order coding.

The first key question addresses the following matter: how is serial order coded within the WM? On the one hand, it can be assumed that serial order is based on spatial representations. For example, when trying to navigate from one location to another, we have to be able to construct a mental map with information about our current location, the upcoming roads, the possible obstacles and the track we have to follow to reach our goal. In order to understand sentences while reading, information read at the beginning of the sentence needs to be temporarily stored in the WM until the end of the sentence has been reached. As we utilize a left-to-right reading direction, we could ask ourselves whether we would benefit from transferring information accordingly to the WM system. On the other hand, all our actions are also bound to a specific moment in time. Time can be divided in separate sequences, but will always be characterized by the serial organization of events. In other words, serial order can manifest itself in many forms, but which forms are fundamental to the construction of order in the WM? More specifically, do we utilize spatial and/or temporal information to bind with to-be-memorized sequential item information in order to create a mental representation of serial order in WM?

A second key question addresses the fundamentality of serial order coding of WM: is all received information automatically ordered within the WM? Not all tasks require a structured storage of information in order to lead to successful performances; some information we receive is perceived as chaotic rather than inherently structured. The question is to what extent we automatically tend to order this type of information within the WM. And if we serially encode all information within the WM, does this benefit our performances?

Furthermore, specific patient groups are known to suffer from WM deficits, such as patients with dementia, patients with frontal brain lesions, children with dyslexia, patients suffering from schizophrenia (e.g., Becker, 1988; de Jong, 1998; Owen, Downes, Sahakian, Polkey & Robbins, 1990; Park & Holzman, 1992). Testing of these patient groups could make a major contribution to the understanding of WM functioning and/or serial order processing. When specific parts of the WM system or assisting processes are disrupted, these patients can be submitted to paradigms to test hypotheses that cannot be tested on a healthy functioning WM.

It is beyond doubt the coding of serial order is indispensable when it comes to everyday functioning. However, research still has to tackle many questions on the ‘how, what, when, why and what if’s’ of serial order coding. This dissertation will attempt to enlighten some of these aspects in the WM.

We will first describe the theoretical WM models that have been put forward by other researchers, followed by a broader allocation of brain areas and their known contribution to the WM and/or order processing. We then elaborate on disease-related WM functioning and its contribution to WM research. The last section of this chapter will address the origin and framework of the predominantly used paradigm of the dissertation.

SERIAL ORDER IN WORKING MEMORY MODELS

In general, models that address the learning and retrieval processes for serial order can be divided into two main theoretical fields: chaining and positional theories (Henson, 1996; 2001).

Chaining models assume that serial order is constructed by binding successive elements to each other. The strong interitem associations between elements make each separate item to act as a cue for the following item (e.g., Ebbinghaus, 1964; Lewandosky & Murdock, 1989). Going through the sequence thus happens relatively automatically. The chaining approach is one of the oldest ideas put forward to explain serial order construction in working memory. Moreover, it provides a simple and intuitive explanation and is supported by many different models (e.g., Elman, 1990; Murdock, 1993; Richman & Simon, 1994). However, several problems are encountered using this model. According to the chaining approach, sequences with repeated items (e.g., 528623) would result in slightly impaired performances as the item identity of a single element is bound to cue two different successive items (e.g., 2 cues 8 and 3). In other words, these models do not always allow for a disambiguation of elements repeated in a sequence. Compound chaining models do partially overcome this problem by assuming that earlier sequence items can also form associations with items located further within the sequence (e.g., Elman, 1990; Jordan, 1986). However, simple and compound chaining theories both have difficulty dealing with sequences with highly similar items, for example, when having to memorize words such as *fit*, *tip*, *pit*, *pif*, *itp.* According to the chaining models it would be quite hard to retrieve the correct order of the letters of these words as each letter is associated with most of the other letters and would therefore cue the wrong responses (Houghton & Hartley, 1996).

As a result of these issues, positional or contextual models have won grounds and can now be stated to be the most prominent models for serial order coding within the WM. These positional theories assume that serial order is a result of items binding to specific position markers. The nature and way of constructing these position markers differs between the several proposed theories.

The first and simplest model is Conrads 'box' model (Conrad, 1965). This model assumes that short-term memory contains a particular number of boxes in which information can be stored. During memory retrieval you can simply walk through the boxes according to a predetermined routine. According to this model, interference due to item similarity or repeated stimuli would not occur, as all item information is stored in a separate box. However, this model seems too simple. First, it describes no clear limits as to how many boxes a person can posses. If a box would be created for each element to be stored, one could memorize infinitely long sequences. Second, it does not provide an explanation for certain common situations. For example, people tend to confuse elements located close to each other more than those located further apart (Henson, 1996). Following the idea of separate boxes, this would not be expected.

However, this basic box-model provided a good stepping stone to more elaborate and applicable models. For example, the 'primacy' model assumes that order information is stored by means of the activation strength of each successive item in the sequence relative to the first item (Page & Norris, 1998). When stepping through the sequence the strength of this activation decreases across list positions, creating a primacy gradient. This model can account for often observed word-length (longer lists can be recalled more easily when consisting of short compared to long words) and list-length effects. In the context of the primacy model the length effect is attributed to decay of the item activation during item presentation, memorization and retrieval.

Another influential positional WM model is the 'start-end' model of Henson (1998), arguing that position in a sequence is coded with respect to the start and end of the sequence. The coding of each position requires a start and an end marker. The strength of the start marker is the strongest for the first item of the sequence and weakest for the last item. The end marker is the weakest for the first item and increases in strength for items located closer to the end of the sequence. This type of marking provides a first step towards the specification of position markers, which has been neglected in previously described models. The representation of start and end markers allows for a spatial position coding (Nelson & Chaiklin, 1980), but the model does experience problems because one cannot code the item's temporal position with respect to the end markers before the end of the sequence has occurred.

With respect to the actual nature of position markers, the 'oscillator-based memory for serial order' model has been proposed. It is a purely computational model that describes the coding of a serial order in the WM to be the result of binding successive states of internal temporal oscillators in the brain to list items during encoding (Brown, Preece & Hulme, 2000; Burgess & Hitch, 1996). These oscillators are assumed to cycle synchronized with the onset of the to-be-memorized list. The state of these oscillators is reset during recall; the reproduction of their states during encoding then cues the recall of the listed items. Theoretically, this model can account for many observations, such as item similarity effects, the effect of nearby-item confusion, list length effects (but see Brown, Preece & Hulme, 2000). Despite the fact that the different serial order models account for several empirical observations, a major drawback is that these models are mainly theoretical and computationally constructed (but see Botvinick & Watanabe, 2007).

The current dissertation is built on a framework described by Abrahamse, van Dijck, Majerus & Fias (2014), i.e., the 'mental whiteboard hypothesis'. The theoretical framework provided by Abrahamse et al. (2014) describes the WM to be localized within a spatial coordinate system and relies on three essential assumptions. First, information to-be-memorized is bound to specific position markers, which are localized in a spatially defined system. Second, the allocation of internal spatial attention is fundamental to search through the ordered representations. Third, retrieval from the WM occurs by selection by spatial attention.

However, just like most other models, even this model does not conclusively challenge the cognitive and neural nature of the position markers. While it suggests a spatial base for position markers, it remains unclear to what extent other modalities, such as time, would contribute to the construction of a position marker.

The current dissertation departs from the idea that memory for serial order in WM is a result of binding to-be-memorized item information to position markers, and further elaborates on the exact nature of the constructed markers, both temporal and spatial.

LOCALIZATION OF THE WORKING MEMORY IN A HEALTHY AND A DISEASED BRAIN

Many studies attempted to localize the WM within the brain using fMRI, PET and single-unit recordings in animals. These studies led to the global consensus that WM mainly relies on the recruitment of prefrontal brain areas and of parts of the parietal cortex (Cohen, Forman, Braver, Casey, Servan-Schreiber & Noll, 1994; D'Esposito, Aguirre, Zarahn, Ballard & Lease, 1998; Honey et al., 2002; Owen, 1997). Neuroimaging studies demonstrated the neural functional overlap for brain areas involved in WM and the recruitment of spatial attention (D'Esposito et al., 1998; LaBar, Gitelman, Parrisch & Mesulam, 1999); large-scale neural networks overlap at frontoparietal sites, like the precentral sulcus, frontal eye fields and intraparietal sulcus.

Previous research also tried to identify the involvement of brain areas specific to the coding of serial order, revealing the main contribution of prefrontal, parietal areas and possibly the hippocampus (for a review see Marshuetz, 2005). Patients with hippocampal damage were instructed to memorize a list of eight-word sentences or eight spatial locations. Their memory was tested for the temporal distance (the number of items) between two test items. Compared to controls, patients with hippocampal damage demonstrated attenuated distance effects, suggesting less distinct representations of items' positional codes.

Patients with hippocampal damage are not the only ones suffering from WM problems. Patients experiencing a (right) hemispherical stroke in the inferior parietal lobe often suffer from neglect and demonstrate WM impairments. Patients with hemispatial neglect exhibit difficulties with directing their attention to stimuli in the ipsilateral space of the lesion. However, the goal-directed guiding of attention is not only disrupted in external space, but also in the mental space (Fias, van Dijck & Gevers, 2011; Zorzi, Priftis & Umiltà, 2002). For example, in the experiment of Bisiach & Luzzatti (1978), patients were instructed to describe a familiar scene from mental memory. When describing the scene, many patients with left-sided neglect omitted details of the left side of the scene. While it was originally thought that neglect would only be reflected in spatial dimensions, further research found that effects of neglect extended to the verbal domain (e.g., Zorzi, Priftis & Umiltà, 2002). However, the current dissertation mainly focused on another interesting patient group; patients with Alzheimer's dementia (AD).

Alzheimer's dementia is typically known for the deteriorating performance of long-term memory, but also affects functioning of the WM and semantic memory (Baddeley et al., 1986; Baddeley, Bressi, Della Sala, Logie & Spinnler, 1991; Baudic et al., 2006; Hodges, Salmon & Butters, 1992; Miller, 1973; Perry, Watson & Hodges, 2000; Stopford, Thompson, Richardson, Neary & Snowden, 2010; Welsh, Butters, Hughes, Mohs & Heyman, 1991). Moreover, early stages of the disease are already associated with medial temporal lobe atrophy, with a progressive spread of atrophy in the general temporal lobe and global cortex with advancing AD (Killiany et al., 1993; Fox et al., 1996).

While many studies acknowledged the presence of WM impairments in AD patients, the mechanisms underlying affected WM functioning have long been under debate. On the one hand, Baddeley et al. (1986) proposed the dysfunction of the central executive to be the source of impaired WM performances. The central executive is crucial for the distribution of attentional resources. When attention needs to be divided or switched between two separate tasks, AD patients typically expressed diminished performances compared to healthy controls (Baddeley et al., 1986, 1991). On the other hand, Stopford et al. (2010) observed that the measured WM span in AD patients is typically smaller than in healthy controls, outside of dual-task settings. Performance patterns of patients suffering from frontotemporal dementia significantly differed from those of AD patients. The AD patient group expressed significantly less problems with executive tasks, while experiencing specific difficulties with the amount of information load imposed.

Research investigating the relationship between WM impairments and brain alterations in AD lead to the observation that WM performances are associated with a general measure of atrophy severity (Kaszniak, Garron & Fox, 1979). Reduced functional connectivity in posterior cingulate cortical regions, the medial frontal gyrus and ventral anterior cingulate cortex were related to impaired performance on general cognitive tasks and WM tasks (Hampson, Driesen, Skudlarski, Gore & Constable, 2006; Sambataro et al., 2010).

Only one study mentioned that AD patients appear to perform worse when having to recall order information, compared to non-ordered information (Lamar, Catani, Price, Hailman & Libon, 2008). They observed that a reduced memory for the order of an item list was linked with the observation of more severe leukoaraiosis in the left-sided posterior horn and frontal centrum.

All in all, many questions remain concerning the source of deteriorated WM functioning and converging evidence addressing the localization of affected brain areas associated with specific WM processes is missing.

Due to the fact that AD patients clearly express difficulties when utilizing WM, dedicating research to this patients group is worthwhile for several reasons. First, clarification should be brought to what mechanisms are compromised causing inefficient WM functioning in AD. We investigated whether order processing could be the main underlying problem resulting in WM impairments. Possibly, insights provided by this research could then be used to improve AD diagnostics and the development of goal-directed treatment strategies (e.g., cognitive training).

Second, working with patient groups in which WM is affected, provides the perfect opportunity to learn more about the WM system and the involved assisting processes. Hypotheses can be tested in contexts that are impossible to recreate for healthy participants by experimental manipulations. Furthermore, as will be discussed in the next section, experiments involving healthy participants allow for a vast amount of flexibility and encompassed a great deal of the research performed for this dissertation.

THE USED PARADIGM AND ITS ORIGIN

As earlier indicated, the representation of serial orders is fundamental to processes that involve both WM and long-term memory. While I previously discussed the role of WM in serial order coding, it is obvious that a great deal of discussion centers on the origin of serial order effects. In other words, during retrieval, would long-term serial order presentations drive the observed effects, or are performances driven by serial order construction that occurs within the WM?

The main paradigm we used originates in the spatial-numerical association of response codes (Dehaene, Bossini & Giraux, 1993), the so-called SNARC-effect. If people are to respond with a left- or right-hand response to a number between 0 to 10, people tend to be faster with a left hand compared to with the right hand, when responding to numbers smaller than five, while the opposite is observed for larger numbers. The generally proposed explanation for this relation between numbers and space is a long-term memory representation of a mental number line. The memory of numbers is assumed to be stored by means of a horizontal number line with increasing magnitude, coded in a left to right fashion (Dehaene et al., 1993; Restle, 1970). This idea has gained much support over the years and has been used to investigate alterations in spatial attention after unilateral brain damage due to a stroke (e.g., Hartmann, Grabherr & Mast, 2012; Vuilleumier, Ortigue & Brugger, 2004; Zorzi, Prifitis, Meneghello, Marenzi & Umiltà, 2006). Many researchers started to question the existence of a mental number line (e.g., Santens & Gevers, 2008; Swarz & Keus, 2004); we will mainly focus on one specific contribution that addresses the essential involvement of the WM (van Dijck & Fias, 2011).

One of the reasons making it harder to stick to the idea of a mental number line is the observation that the SNARC-effect is range-dependent (Dehaene et al., 1993; Fias, Brysbaert, Geypens & d'Ydewalle, 1996). When responding to numbers ranging between 4 and 9, faster left- than right-hand responses are observed for the numbers 4 and 5. However, when the numbers ranged from 1 to 5, the numbers 4 and 5 elicit faster right- than left-hand responses. Another argument against the mental number line was the observation that the SNARC-effect changes when participants have to read cooking instructions where small numbers are located on the right side of the screen and large numbers are spatially located on the left side of the screen (Fischer, Mills & Shaki, 2010). These observations led to reason that the task at hand determines the relation between the space and numbers (van Dijck et al., 2011). Van Dijck et al. (2011) put this idea to the test; when performing a task, a task set is constructed within the WM. This constructed task set determines the relation between numbers and space. The paradigm they used consisted of three main components that were successively repeated throughout the experiment. First, participants were instructed to memorize a sequence of items in the correct order (e.g., fruit/vegetables or letters), which were separately presented at a self-paced rate at the center of the screen. Second, after the memorization of these items the task of interest was initiated. In the experiment of van Dijck et al. (2011) participants were instructed to categorize presented items with a left- or right-hand response (categorize as ‘fruit’ or ‘vegetable’). Importantly, participants were only allowed to respond to presented items that were part of the memorized sequence. Non-memorized items did not allow for a response. Third, the last phase consisted of a memory verification task, to assure the participant’s memory for the to-be-memorized sequence of items. In this experiment, van Dijck et al. (2011) observed that initially memorized items were responded to faster with a left hand response. Items that were located at the end of the memorized sequence were responded to faster with a right hand response, indicating an association between position in WM and spatial location.

This three-layered structure of this paradigm provided a flexible and manipulable framework to submit to a wide variety of WM-related hypotheses. The described paradigm was used as main starting point for the behavioral studies of the present dissertation.

OUTLINE OF THE DISSERATION

In the current dissertation we aimed to investigate the way in which serial order coding occurs in WM. While many studies acknowledged the crucial role of WM in serial order coding, most theories lacked empirical support. We investigated the nature of these position markers used in the WM and tried to answer the question whether space, time and/or other modalities contribute to the construction of position markers. Last, we investigated the underlying neural substrates responsible for successful serial order within WM by means of a study with Alzheimer's patients.

The first two empirical chapters (CHAPTER 2 and CHAPTER 3) focused on the identification of the modalities of information that could be used to construct position codes within WM.

In CHAPTER 2 we mainly investigated the role of space in serially organized verbal WM. Two behavioral tasks were performed, involving spatial priming in a go/no-go task setting. On the one hand, it was observed that spatial cues could facilitate recognizing serially stored information in WM. On the other hand, it was found that memorized item information in WM sufficed to facilitate the detection of subsequently presented spatial information. In this chapter, a bidirectional link was demonstrated between the processing of space and serially memorized WM information. This observation provided the crucial and missing piece of evidence to establish that the storage of serial information in WM occurs in a spatial coordinate system (Abrahamse et al., 2014).

While the fundamental role of space in the construction of positional codes within WM is described in CHAPTER 2, this initial finding does not exclude the possible role of other information modalities in the construction of position codes. CHAPTER 3 was therefore dedicated to examine the role of time in the construction of position markers, as suggested by the oscillator-based memory model (e.g., Brown et al., 2000). Again, two experiments were conducted, consisting of a cueing paradigm similar to the paradigms used in CHAPTER 2. The results of these experiments did again confirm a bidirectional link between the processing of time and serially ordered WM. Based on these findings we concluded the functional involvement of time in the construction of position markers in WM.

The findings described in CHAPTER 2 and CHAPTER 3 emphasized the flexible nature of position coding within WM since both spatial and temporal coding can support the construction of position markers. However, further research should address the following question: do we automatically code in a spatial and temporal fashion, or is temporal coding always additionally supported by a spatial coding system?

The first two empirical chapters were critical to substantiate the theoretical model of serial order coding within WM and shape the idea of a WM memory system localized in a spatial coordinate system, in which position markers can be spatial and temporal in nature.

CHAPTER 4 provided additional insight into serial order functioning. While the subject of this chapter may sound obvious, no empirical studies so far answered the following question; if we have to memorize items, do we automatically store them in a serial fashion? In other words, this research question addresses the automaticity of serial order coding in WM. When debating with other researchers, some were strongly convinced that we always would automatically store information in a serially organized fashion. However, others contrasted their standpoint and considered it obvious that information would not be stored in a serial fashion if the context would not require this extra effort to organize to-be-memorized information. The fact that this rather simple question elicited strong viewpoints, lacking any empirical support, emphasized the importance of finding conclusive evidence. Therefore, we set up a study in which hundreds of students were submitted to a single trial, investigation their automatic tendency to bind information to position markers within WM. As the findings of CHAPTER 3 did not exclude the fact that temporal position coding could occur independent of spatial position coding, the question in CHAPTER 4 focused on the construction of spatial position markers. The results of this large-scale study demonstrated the automatic tendency to I) memorize items in a serial fashion, and additionally, II) store these items in a spatial fashion within WM, providing an answer to the heated discussion about automatic serial order coding.

CHAPTER 5 and CHAPTER 6 encompassed the behavioral and neurological part of WM research in Alzheimer's patients. As this patient group typically suffers from an impaired WM functioning, the nature of their WM problems was investigated by means of an extensive set of neuropsychological and experimental tasks and imaging of the brain. CHAPTER 5 describes the behavioral tasks performed by the patients and their partners. It was found that AD patients expressed difficulties with the processing of order, while information about (unordered) item identity remained relatively preserved in WM. Moreover, AD patients specifically reflected problems with the goal-directed steering of attention when retrieving position-specific item information from WM. In CHAPTER 6 we correlated a refined order-measure with the integrity of brain anatomy (T1), white matter tracts (DTI) and functional networks (rsfMRI). An impaired ability to effectively represent order within WM was associated with reduced cortical thickness in frontal, parietal en temporal regions, deterioration tracts connecting fronto-parietal and fronto-temporal regions, altered functional connectivity for frontal regions in the default mode network and executive control network.

The GENERAL DISCUSSION provides an overview of the obtained results and relates those to existing literature. Strengths and weaknesses of the described studies are outlined, along with future research suggestions.

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CHAPTER 2

SERIAL POSITON MARKERS IN SPACE: VISUOSPATIAL PRIMING OF SERIAL ORDER WORKING MEMORY RETRIEVAL[1]

Most general theories on serial order working memory (WM) assume the existence of position markers that are bound to the to-be-remembered items to keep track of the serial order. So far, the exact cognitive/neural characteristics of these markers have remained largely underspecified, while direct empirical evidence for their existence is mostly lacking. In the current study we demonstrate that retrieval from verbal serial order WM can be facilitated or hindered by spatial cuing: Begin elements of a verbal WM sequence are retrieved faster after cuing the left side of space, while end elements are retrieved faster after cuing the right side of space. In direct complement to our previous work - where we showed the reversed impact of WM retrieval on spatial processing - we argue that the current findings provide us with a crucial piece of evidence suggesting a direct and functional involvement of space in verbal serial order WM. We outline the idea that serial order in verbal WM is

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[1] De Belder, M., Abrahamse, E., Kerckhof, E., Fias, W., & van Dijck, J. P. (2015). Serial position markers in space: visuospatial priming of serial order working memory retrieval. *PloS one*, *10*(1), e0116469.

coded within a spatial coordinate system with spatial attention being involved when searching through WM, and we discuss how this account can explain several hallmark observations related to serial order WM.

INTRODUCTION

Working memory (WM) is a fundamental cognitive function and refers to the brief maintenance of information in an active and accessible state such that operations can be performed on it. It is considered to be crucial for major cognitive skills like language, reasoning and learning, not in the least for its major feature of maintaining serial order across multiple items (e.g., Baddeley, 2012). In this study, we address the particular nature of *verbal serial order WM*.

The question how the brain deals with serial order processing in WM has a long research tradition (for a review see Marshuetz, 2005). These research efforts have resulted in several sophisticated (computational) models and theories. In general, it can be stated that the most prominent models in this domain are built on the idea that serial order coding in WM is achieved by binding the various items to-be-maintained to specific *position markers* (e.g., begin vs. end items, Henson, 1998; encoding strength, Page & Norris, 1998; oscillatory response, Brown, Preece & Hulme, 2000; magnitude codes, Botvinick & Watanabe, 2007). Despite their (relative) success in accounting for several empirical observations, these models are largely formulated on theoretical grounds and few specifications have been provided with respect to the cognitive and/or neural nature of these position markers (but see Botvinick & Watanabe, 2007). Importantly, direct empirical evidence for the existence of (any of the proposed) position markers is sparse (Kalm & Norris, 2014).

Recently a new idea to account for serial order coding in WM was proposed – but not further developed – by Oberauer (2009; p. 53) who suggested that a "spatial medium of representation [is used] as a projection screen for relations on nonspatial dimensions" – such as serial order. In a recent paper, we further developed this into what we refer to as the *mental whiteboard hypothesis*: (I) The position markers that provide multi-item WM with a serial context should be understood as coordinates within an internal, spatially defined system; (II) internal spatial attention is involved in searching through the resulting serial order representation; and (III) retrieval corresponds to selection by spatial attention (Abrahamse, van Dijck, Majerus & Fias, 2014). We hereby assume that the spatial coding of serial order spontaneously occurs from left to right on the basis of the typically observed leftward bias in spatial processing (Della Sala, Darling & Logie, 2010; Jewell & McCourt, 2000) and/or a shaping by reading direction (cf. Bonato, Zorzi & Umiltà, 2012; Maass & Russo, 2003; Spalek & Hammad, 2005). Here we zoom in on the empirical foundation of this account, specifically for the verbal domain. To demonstrate a functional involvement of spatial processing in verbal serial order, the empirical foundation should be at least twofold:

First, it needs to be shown that retrieval from serial order WM can modulate spatial processing. Indeed, this has been confirmed across a number of recent studies (van Dijck & Fias, 2011; van Dijck et al., 2013; 2014). For example, a systematic association between the ordinal position of an item in verbal WM and the response side was observed when retrieving information from serial order WM: begin elements of a WM sequence were responded to faster with left hand responses, and end elements with right hand responses (e.g., van Dijck & Fias, 2011; Ginsburg, van Dijck, Previtali, Fias & Gevers, 2014). This suggests that verbal WM, in its serial aspects, is more strongly associated to space than one would anticipate. Moreover, building further on the notion that internal and external spatial attention strongly interface (Awh & Jonides, 2001; Nobre et al., 2004), it was found that the association between serial order in WM and space can be observed already directly at the level of spatial attention: using items from serial order WM as a cue in a Posner-like cueing paradigm van Dijck et al. (2013; 2014) showed that retrieval of an item from WM increasingly facilitated detection of right dots as the item was positioned further towards the end of the WM sequence.

Importantly, the observation that serial order WM retrieval modulates spatial processing constitutes only part of the required support. Whereas it indicates that processes in serial order WM can elicit spatial processing, they do not necessarily evidence the functional involvement of spatial processing in serial order. For example, spatial processing might have been triggered by peripheral processes unrelated to serial order per se. To this purpose, *secondly*, it is important to consider the intriguing and complementary prediction of our mental whiteboard hypothesis that verbal serial order WM retrieval can be facilitated/hindered by the processing of external *spatial* cues. That is, left-sided spatial cues should facilitate retrieval of begin elements of the WM sequence while right-sided spatial cues should facilitate retrieval of end elements. Such observations would provide a next piece of the puzzle and bring us one step closer to confirming the intrinsic role of spatial processing in serial order WM. In the current study, we tested this prediction across two experiments.

EXPERIMENT 1

Procedure

The study was approved by the ethical committee of the Faculty of Psychology and Educational Sciences of Ghent University and in agreement with the Declaration of Helsinki.

Nineteen participants (all participants reached the legal age of adulthood, i.e. 18 years; age range: 20-36 years; average age: 24.26 years, SD = 3.87; 13 females; 4 left-handed) completed the study after signing an informed consent in exchange for 10 euro. Participants were individually tested in a quiet room and seated behind a 17-inch monitor at a viewing distance of approximately 50 cm. Instructions and stimuli were presented in white on a black background. A QWERTY keyboard was used to register the responses.

Participants cycled repeatedly through the same three phases: I) WM sequence presentation, II) probe detection task, and III) WM sequence verification. Phase 1 started with the self-paced central presentation of 4 successive consonants, randomly selected from the list: c, f, h, m, p, s, t and v (each 0.72° x 0.84°). The instruction was to memorize the elements of the sequence in the order of presentation. After the fourth letter, a 2500ms rehearsal interval elapsed. Subsequently, a go/no-go probe detection task was initiated (phase II). Every trial of this task started with a central fixation cross (1000ms), followed by a dot (2.9°; 150ms) appearing randomly either on the left or right side of the fixation cross, and at either a more centralized (4.6° from center) or more distant location (16° from center) on the screen. Dots appeared on distant locations in 75% of the trials, and the instructions were to *only* execute the probe detection task when the dot appeared in one of the two distant locations on the screen to induce explicit processing of spatial information.

After dot presentation, the screen remained black (50ms) after which the probe letter appeared (1000ms). The task was to press the letter “b” as fast and accurate as possible with the dominant hand when the letter belonged to the WM sequence (and the dot was previously presented at a distant location on the screen), and to refrain from responding otherwise. In the probe detection task, all letters were presented twice in random order for each cycle, resulting in 16 trials per WM sequence. After a response or the response deadline (1500ms), the screen went black and following a 1000ms inter-trial-interval (ITI) the next trial was initiated.

Finally, after sixteen trials of the go/no-go probe detection task, sequence maintenance was verified (phase III) by two subsequent statements on serial order (e.g., “Kwam C voor V?”, Dutch for “Was C preceded by V?”). These statements were composed of 2 unique pairs of consecutive WM items of which the order either corresponded or not to the WM sequence (items were vertically arranged to avoid horizontal association). Care was taken within a block that the answer to both statements was unpredictable, but that over the entire experiment, equal amounts of correct and wrong statements were presented. After responding to the two statements, participants could take a self-paced break to move on to the next to-be-remembered sequence. The complete procedure, passing through the three phases, was repeated with 32 distinct WM sequences, with each letter equally often presented across all possible serial positions of the sequence. As we were mainly interested in the effects of spatial processing per se (and not whether the effects are induced by overt of covert shifts of spatial attention), eye movements were not monitored in the current study. Moreover, it has been shown that eye movements do not typically account for dot detection performance in general (Fischer, Castel, Dodd & Pratt, 2003; Pratt, Spalek, & Bradshaw, 1999), or even for specifically the relation between serial order and space (e.g., van Dijck et al., 2013; their Experiment 2), suggesting an important contribution of covert spatial attention.

Data Analysis

Mean reaction times (RTs) were computed per participant per condition for the probe detection task, and submitted to a 4 x 2 Repeated Measures ANOVA with *WM-position* (4 levels: position 1 to 4) and *Dot-location* (2 levels: left distant, right distant) as within-subject variables. An interaction between *WM-position* and *Dot-location* is predicted to indicate visuospatial priming of the verbal serial order in WM. Polynomial contrasts were calculated to investigate the presence of a linear relationship to further explore the nature of the interaction (van Dijck et al., 2013). Multivariate test results for repeated measures are reported.

Results

Trials from WM sequences which were correctly remembered (i.e., a correct serial order verification of the two statements presented during phase III of the experiment) (94% correct (SD = .09)) and correct go-trials (probe detection accuracy was 95% (SD = .04) and 98% (SD = .03) for go- and no-go trials, respectively) were considered. Mean RT was 572ms (SD = 67ms).

The analyses revealed a main effect of *WM-position* [Wilks' lambda = .88, F(3,16) = 5.31, p = .01, $\eta p2$ =.500]. RTs for the four different positions were 554 (SD = 66), 556 (SD = 68), 573 (SD = 77) and 587ms (SD = 78). A polynomial contrast of this latter effect confirmed a linear relationship [F(1,18) = 10.40, *p* = .005, *ηp2* = .366), suggesting serial scanning in WM from start to end items (cf. van Dijck et al., 2013). The WM-position by Dot-location interaction was significant [Wilks' lambda = .91, F(3,16) = 15.09, *p* <.001, *ηp2* = .74; Figure 1A], supporting the hypothesis that WM retrieval is influenced by the visuospatial primes. A polynomial contrast of WM-position in its interaction with Dot-location revealed a linear relationship [F(1,18) = 41.38, *p* <.001, *ηp2* = .697, slope = -25.74; Figure 1B]: the RT advantage for WM retrieval after perceiving right-sided over left-sided dots increased on average with 26ms per WM-position from start to end.

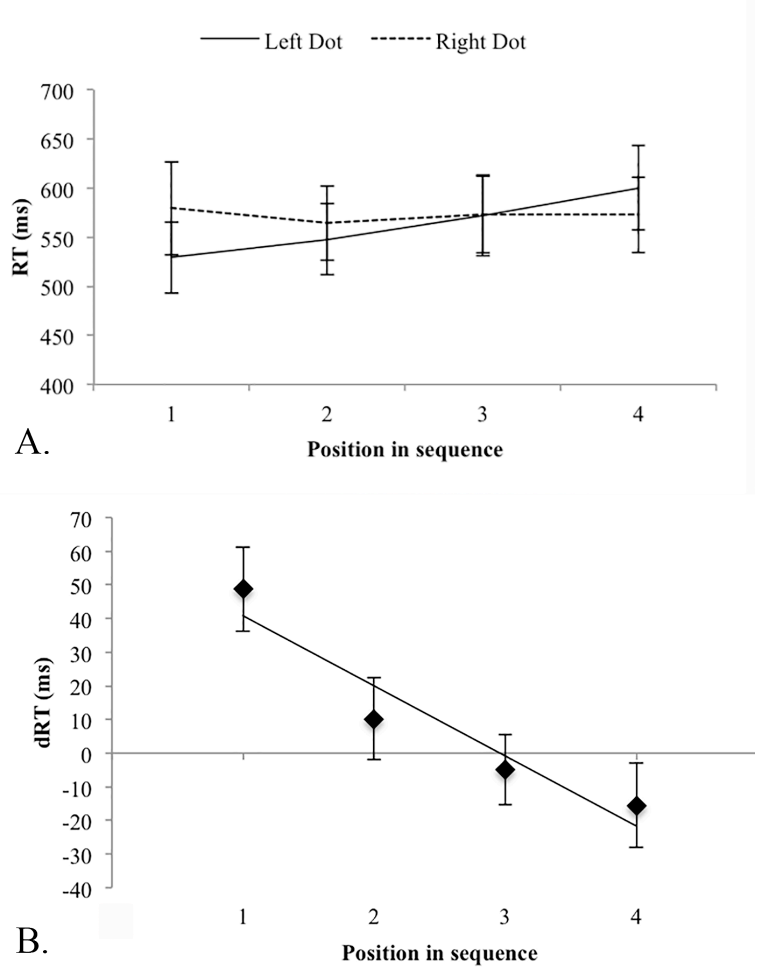

Figure 1. Experiment 1. A. Raw RTs for left- and right-sided dot presentations for each position in WM. The error bars indicate one standard error of the mean. B. Average RT differences between right and left-dot presentations as a function of the position in the WM sequence. Positive values indicate faster responses after dot presentation on the left side of space. The regression line reflects the linear relationship as expressed by the polynomial contrast.

EXPERIMENT 2

The aim of Experiment 2 was fourfold. First, we investigated whether the explicit need to process the spatial dot is a necessary condition to modulate WM retrieval or whether the mere perception of task irrelevant flashed dots is sufficient. We replicated Experiment 1 but presented task irrelevant dots unpredictably on the left or right side from the central fixation point. Second, it is known that spatial information can be encoded fast and automatically (e.g., Lu & Proctor, 1995) and then quickly decays (or is actively suppressed; e.g., Zorzi & Umiltà, 1995). Therefore we manipulated the interval between dot and probe onset (100ms before, or 100 or 300ms after probe onset). Two backward prime conditions were included with the aim to maximize the chance to create overlap between serial order retrieval and spatial attention processing (cf. Stoianov, Kramer, Umiltà, Zorzi, 2008). Third, in Experiment 1 participants could memorize the WM sequences in a self-paced fashion. However, it has been shown that encoding times can potentially impact WM (e.g., Barrouillet, Plancher, Guida & Camos, 2013). To ensure that encoding strategies did not (partly) underlie observations in Experiment 1, the presentation of WM sequences in Experiment 2 was computer-paced. Fourth, to rule out any impact of the use of the dominant hand, vocal responses were employed.

Procedure

The study was approved by the ethical committee of the Faculty of Psychology and Educational Sciences of Ghent University and in agreement with the Declaration of Helsinki.

Twenty students (all participants reached the legal age of adulthood, i.e. 18 years; age range: 18-25 years, average age: 19.60 years (SD = 2.23); 12

females; 8 left handers) provided written informed consent and participated in exchange for course credits. Participants were seated at a viewing distance of approx. 50 cm from the computer screen of the monitor. A chin-rest was used to ensure a stable viewing distance. Responses were collected with a voice-key connected to a headset microphone.

The experimental setup again involved 3 phases, but contained several differences with Experiment 1. In phase I, four letters (each 0.72° x 0.84°) pseudo-randomly sampled from the list c, f, h, k, m, p, s and v (balanced across WM positions) were sequentially presented at the center of the screen (1500ms), separated by an empty screen (200ms). Participants were instructed to memorize the stimuli in the order of presentation. After a rehearsal period (2500ms), phase II started with the presentation of a fixation cross (500ms). Two types of spatial priming were used: forward and backward priming. With forward priming, a dot (.06°; 100ms) was presented 200ms *before* probe onset (i.e. with a 100ms black screen after dot offset) appearing unpredictably on the left or right side of the screen (7.4° from center). With backward priming, the dots could appear either 100 or 300ms after probe onset. Participants were explicitly told that they could and should ignore the dots, and that they gave no useful information. Subsequently the probe letter appeared. The task was to say "JA" (Dutch for "yes") in the microphone as fast as possible when the letter belonged to the WM sequence, and to refrain from responding otherwise. During the probe detection phase, all letters were presented once in random order. After the 1200ms probe duration or 300ms after a response, the screen went black and following an ITI of 500ms the next trial was initiated. Due to technical limitations of the voice-key device, only RTs below 901ms were recorded. Finally, after the execution of eight trials of the probe detection task, sequence maintenance was verified in phase III by similar statements on serial order as in Experiment 1. The three phases were passed through 72 times, resulting in 72 distinct WM sequences, with each letter equally often presented across all possible WM sequence positions and with trials equally balanced across experimental conditions. This resulted in 12 measurements per condition, RTs collected during the probe detection task.

Results

Data of two participants were discarded from analyses because of low overall accuracy (2 SD below average and chance level performance on the Go trials); this mainly related to technical failure of the voice-key device (analyses including these two participants demonstrated qualitatively identical results to those described below). For the remaining participants, as in Experiment 1 only trials with correct serial order verification (84%, SD = .07) and correct go-trials (probe detection accuracy was 81% (SD = .09) and 97% (SD = .02) for the go and no-go trials, respectively) were considered. Mean RT was 519ms (SD = 60ms).

The mean RT of the different conditions was submitted to a repeated measures ANOVA with *Dot-probe interval* (DPI; 3 levels: -100, 100 and 300ms), *WM-position* (4 levels: position 1 to 4) and *Dot-location* (2 levels: left, right) as within subject variables. The multivariate test results for repeated measures are reported.

Main effects were observed for DPI [Wilks' lambda = .62, F(2,16) = 4.86, p = .022, $\eta p2$ = .378] and WM-position [Wilks' lambda = .25, F(3,15) = 14.84, p <.001, $\eta p2$ = .748]. RTs per DPI were 514 (SD = 15.43), 529 (SD = 13.99) and 531 (SD = 14.28) ms; and 495 (SD = 15.13), 518 (SD = 15.46), 534 (SD = 15.22) and 551ms (SD = 13.89) per WM position. A linear polynomial contrast of this latter effect [F(1,17) = 50.36, p<.001, $\eta p2$ = .748] suggested serial scanning of the WM sequence from start to end. The interaction between Dot-location and WM-position was significant [Wilks' lambda = .42, F(3,15) = 6.85, p =.004, $\eta p2$ = .578; Figure 2], and a linear relationship was observed [F(1,17) = 14.12, p = .002, $\eta p2$ = .454, slope = -15.54; Figure 3]: The advantage in RT to detect right-sided over left-sided dots increased on average with 16.95ms per WM position replicating the observation that a (task irrelevant) left or right-sided visuospatial prime selectively modulates the retrieval from verbal serial order WM.

All other main and interaction effects failed to reach significance, but the three-way interaction between DPI, WM-position and Dot-location nearly reached significance [Wilks' lambda = .41, F(6,12) = 2.85, p = .058, $\eta p2$ = .59], suggesting modulation in the interactions between WM-position and Dot-location based on the time of presentation of the Dot (DPI). Further two-way ANOVAs between WM-position and Dot-location for each DPI separately showed that a) for a dot presentation 100ms before stimulus presentation (DPI: -100) a significant interaction between WM-position and Dot-location was observed [Wilks' lambda = .50, F(3,15) = 4.99, p = .01, $\eta p2$ = .500], with a linear relationship [F(1,17) = 6.53, p = .02, $\eta p2$ = .278]; b) for a dot presentation 100 after stimulus presentation (DPI: 100) a similar interaction [Wilks' lambda = .56, F(3,15) = 3.99, p = .028, $\eta p2$ = .444] and linear relationship were observed [F(1,17) = 10.46, p = .005, $\eta p2$ = .381]; and c) for a DPI of 300ms no interaction was observed [Wilks' lambda = .87, F(3,15) = .722, p = .554, $\eta p2$ = .126]. Hence, there is weak support for the notion that irrelevant spatial information should be presented relatively close in time to the WM stimulus in order to affect WM processes.

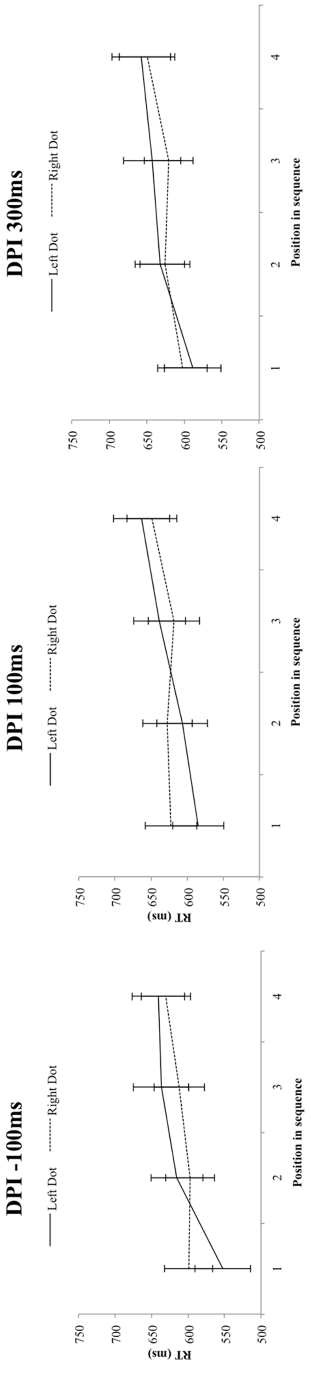

Figure 2. Experiment 2. The graphs display the raw RTs for left- and right-sided dot presentations for each position in WM, depending on DPI (-100ms, 100ms or 300ms). The error bars indicate one standard error of the mean, for all DPIs separately.

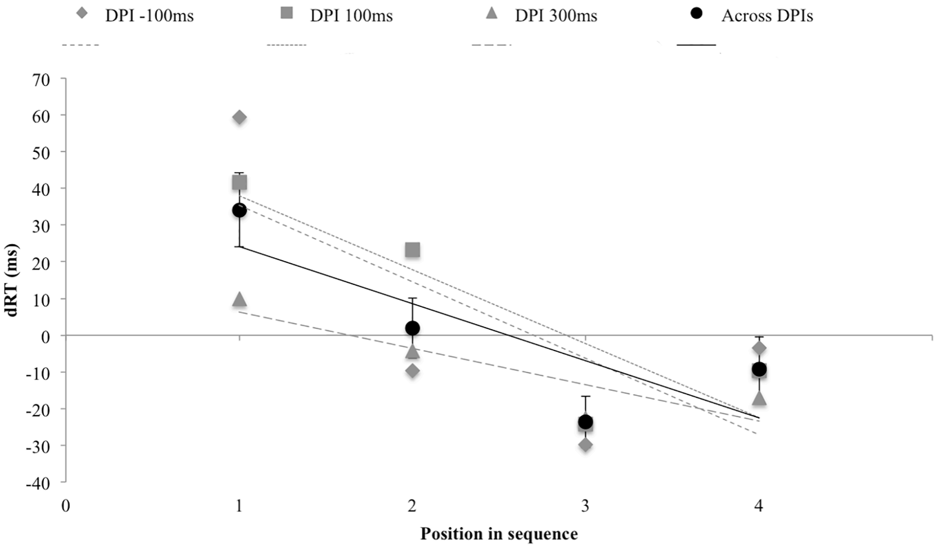

Figure 3. Experiment 2. The graph displays the average RT differences between right and left-dot presentations for each dot-stimulus interval as a function of the position in the WM sequence. Error bars indicate one standard error of the mean over all DPIs. Positive values correspond to faster responses after dot presentation on the left side of space. The regression line reflects the linear relationship as expressed by the polynomial contrast; where the black lines and data points display results across all DPIs and grey dashed line demonstrate this for each DPI separately.

GENERAL DISCUSSION

The current study demonstrates that performance on serial order WM retrieval can benefit from visuospatial priming: left and right exogenous cues facilitated the retrieval of begin and end elements of a WM sequence, respectively. Whereas in Experiment 1 such an effect of the spatial cues on WM retrieval was observed when these cues were task-relevant, in Experiment 2 this facilitation also occurred spontaneously, when task-irrelevant cues were presented around the time of WM retrieval. Furthermore, the effect was observed with both manual (Experiment 1) and vocal (Experiment 2) responses, suggesting that the effect is not driven by any spatial code associated with the used effector.

In complement to previous findings of van Dijck and colleagues (van Dijck et al., 2011; 2013; 2014) the current findings affirm the *bidirectional* relation between verbal serial order WM and spatial processing as is predicted in the mental whiteboard hypothesis – which assumes intrinsic and functional involvement of spatial processing in verbal serial order WM (Abrahamse et al., 2014). As such, it provides a viable candidate mechanism to substantiate the more abstract notion of serial position markers in verbal serial order WM. Such markers have been a core feature of prominent serial order models (see Marshuetz, 2005 for a review), but few specifications have been proposed as their cognitive and/or neural nature (but see Botvinick & Watanabe, 2007). The current observation that external spatial cues can modulate the retrieval performance on serial order WM tasks indicates that position markers can be understood as *specific coordinates within a spatially defined system*.

Importantly, although detailed modeling is needed to understand the exact nature of cognitive dynamics, conceptually this mechanism can easily account for various hallmark observations in the domain of serial order memory (Marshuetz, 2005). First, the typical serial position effect (gradual increases in response times for items further in the sequence; cf. Sternberg, 1967) can be directly related to the attentional search – from left to right – through the spatially defined WM representation. Second, the observation that it is more difficult to determine the serial order for nearby compared to more distant items (i.e., distance effect; Attout, Fias, Salmon & Majerus, 2014; Marshuetz, Smith, Jonides, DeGutis & Chenevert, 2000) may be explained by the fact that in space processing, discrimination between two stimuli is more difficult when they are positioned at nearby compared to further locations (e.g., Bahcall & Kowler, 1999; Cave & Zimmerman, 1997). Third, a similar (attentional) interference explanation may hold for the observation that errors in serial recall often involve switches between serially nearby items (i.e., transposition errors). Overall, the notion that serial order is spatially coded seems to provide a parsimonious account on the major serial order WM observations.

The perspective that verbal serial order WM is intrinsically linked to space also opens new questions to be explored. For example, it is currently unknown whether the observed involvement of space is limited to the verbal domain, or whether it reflects a property of serial order WM that is independent of the modality of the to-be-remembered items. Behaviorally, functional similarities have been observed between serial order WM for verbal and spatial items (Jones, Farrand, Stuart & Morris, 1995), suggesting domain-generality. This is further supported by a recent fMRI study where overlapping brain areas were recruited when processing serial order within verbal and visual WM (Majerus et al., 2010). Still, future research should directly address this question, for example by employing non-verbalizable items in paradigms such as the one used in the current study. Another outstanding question is whether the involvement of space is limited to the moment of retrieval, or whether the relation between serial order WM and space is already present during WM encoding and maintenance. Indirect evidence for the latter has recently been provided by Fischer-Baum and Benjamins (2014). They showed that the recall of serial order information was more accurate when, during the encoding phase, the WM items progressed from left to right compared to situations where they progressed in a right to left fashion.

More broadly, it may be interesting to note that our account corresponds with specific aspects of memory research in general. Most notably, the mnemonic tool referred to as the method of loci (Bower, 1970; Volkmann, 1929) builds on the idea that memory performance can be facilitated by visualizing to-be-remembered items in a familiar scene which you mentally walk through during item retrieval. Hence, like in our account, (working) memory performance is modulated by the use of spatial organization. Future work should explore the possibility of spatial coding of serial order WM as a determinant underlying the success of the method of loci, or whether this link merely involves an illustrative analogy.

In the current study we tested and confirmed a clear prediction from the mental whiteboard hypothesis. Yet, it may be argued that the observed link between serial order WM and spatial processing might be the *indirect* result of the well-established link between number and space processing. Specifically, serially presented items may be tagged to fixed number codes to maintain serial order – for example, a first item is tagged to the representation of "1" or "first' in, a second item to "2" or "second", etc (Botvinick & Watanabe, 2007; Marshuetz, 2005). These order tags, then, may subsequently drive spatial processing in line with the Spatial Numerical Association of Response Codes or SNARC effect (Dehaene et al., 1993). While we cannot entirely reject this alternative mechanism, the findings of van Dijck et al. (2011; 2014, see also Ginsburg et al. 2014) show that the spatial coding of serial order in WM occurs in the absence of any magnitude-based spatial priming (despite indications that the numerical magnitude was processed). These (and other) observations led us to claim in previous work that spatial effects of number magnitude may be driven by serial order WM (Fias, van Dijck & Gevers, 2011; van Dijck et al., 2014) – and not the other way around. Future research will need to further establish this primacy of serial order WM over number magnitude effects.

Finally, a closer look at the data of Experiment 2 learns that the spatial cueing effect for the fourth WM position is numerically smaller than would have been expected on the basis of the regression line. While we have no immediate and conclusive explanation for this observation, it should be noted that it is not the first time this observation is made (e.g., van Dijck et al., 2014). The diminished cueing effect could potentially be explained by the established 'special status' of the final item in a sequence, which is typically believed to remain (more) in the focus of attention (e.g. Nee and Jonides, 2008). As we argue that spatial attention is crucially involved in the retrieval of information from serial WM, it is not unlikely that this interacts with the previous location of the attentional focus. Further research is needed to understand the exact reason for the attenuated effect at position four, and why this is only observed in some studies.

Overall, the current findings indicate that verbal serial order WM and space are intrinsically related to each other by pointing to the existence of a bidirectional link. This observation is strong empirical evidence for the idea that, serial order coding occurs within a spatially defined coordinate system as proposed in our mental whiteboard hypothesis (Abrahamse et al., 2014; cf. Oberauer, 2009). Future studies will be needed to further explore exact underlying cognitive and brain processes and to further challenge verbal serial order coding theories to consider spatial processes as a core ingredient.

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CHAPTER 3

HOW SERIALLY ORGANIZED WORKING MEMORY INFORMATION INTERACTS WITH TIMING[1]

The temporary storage of serial order information in working memory (WM) has been demonstrated to be crucial to higher order cognition. Previous studies have shown that the maintenance of serial order can be a consequence of the construction of position markers to which to-be-remembered information will be bound. However, the nature of these position markers remains unclear. In the current study we demonstrate the crucial involvement of time in the construction of these markers by establishing a bidirectional relationship. Firstly, results of the first experiment show that initial items in WM result in faster responding after shorter time presentations, while we observe the opposite for items stored further in WM. Secondly, in the next experiment we observe an effect of temporal cueing on WM retrieval; longer time cues facilitate responding to later WM items compared to items stored at the beginning of WM. These findings are discussed in the context of position marker theories, reviewing

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[1] De Belder, M., van Dijck, J. P., Cappelletti, M., & Fias, W. (2016). How serially organized working memory information interacts with timing. *Psychological Research*, 1-9.

the functional involvement of time in the construction of these markers and its association with space.

INTRODUCTION

Working memory (WM) is used to temporarily store information, to keep it in an active and accessible state, and to manipulate, process and respond to it. The ability to process serial order information is fundamental to working memory and makes working memory vital to higher order cognition. This is the case for the verbal domain (for instance ranging from speech comprehension and perception to the acquisition of grammar and reasoning) as well as for the non-verbal domain (for instance to efficiently plan goal-directed behavior and motor actions (Baddeley, 2012; Hurlstone, Hitch & Baddeley, 2014).

Various theoretical models have been proposed regarding how serial order is encoded in and retrieved from working memory (see e.g., Henson & Burgess, 1998, for an overview). Chaining theories assume the storage of sequence order to be a consequence of associations between successive items. Stepping through the constructed chain allows the retrieval of order (Ebbinghaus, 1964; Slamecka, 1985). Ordinal approaches, such as the Primacy Model, argue order to be a consequence of attributing relative strengths to successive item representations in memory, with strength decreasing from the beginning towards the end of the sequence (Page & Norris, 1998). The most widely accepted models postulate that order is coded by binding information to specific position markers (e.g., start-end model; Henson, 1998). In principle, both space and time are dimensions that can be used to mark the occurrence of a certain item and situate it with respect to other marked items. We often consciously take grip on information in memory by storing to-be-remembered information within a timeframe or a mental spatial representation. Both time and space allow flexible manipulations and organization of information, supported by their inherent ordinal nature (Farrell, 2007; Henson & Burgess, 1998). While the fundamental role of space in serially ordered verbal WM has recently been confirmed (van Dijck & Fias, 2011), research that demonstrates a probable functional involvement of time in the construction of position markers is lacking.

Evidence that hints in the direction of the involvement of time as a position marker mainly derives from paradigms in which temporal aspects of encoding (e.g., presentation rate, list length) are manipulated and their effect on (free or serial) recall is examined. In these studies, serial order was defined temporally, and not spatially, by sequentially presenting each item in the center of the screen. It was assumed that during encoding, items are bound to their moment of occurrence in time, resulting in the formation of temporal position markers (e.g., Brown, Preece & Hulme, 2000; Burgess & Hitch, 1996; Henson & Burgess, 1998).

These theories however, remained controversial as the functional relationship between the manipulation of presentation rate and their effect on accuracy of recall remains unclear. The procedure of previously mentioned serial recall tasks make it hard to unequivocally assign the observed effects directly to the temporal characteristics of the presentation rate. For example, from the viewpoint of temporally constructed position markers, it would be expected that the presentation of to-be-remembered items would improve their memory if they were to be presented with increasing interitem intervals. A more distinctive temporal presentation would result in more unique and less overlapping temporal representations within WM. However, generally no advantages for this type of manipulation are observed (Baddeley & Lewis, 1984; Henson & Burgess, 1998; Neath & Crowder, 1990). Moreover, previous studies investigated serial order coding by the means of serial recall, causing also the recall effect to be characterized by a temporal component. The respective manipulations during encoding and the nature of the recall task make it hard to unequivocally assign temporal effects to any of these processes. Another potential threat regarding the validity of serial recall tasks relates to the fact that temporal reorganization may occur by rehearsal and current tasks cannot experimentally control for this. We designed two experiments to circumvent these problems, allowing us to examine the effect of time as a position marker in an unequivocal way.

Other research also touched upon a link between working memory and time, but does not consider the involvement of order and does not connect to the binding on temporal markers. For example, Fink and Neubauer (2005) showed that WM load affected perceived time, with increased WM load resulting in the perception of shortened time intervals. In a study of Pan and Luo (2012) participants had to memorize the color of a square and were subsequently shown two consecutively presented circles, of which one matched the memorized color. Participants reported longer presentation times for circles matching WM content, demonstrating an effect of non-temporal WM content on the perceptual experience of temporal duration.

In sum, despite the absence of conclusive evidence, previous research suggests the involvement of time in the construction of position markers to which information will be bound. However, the specific nature and involvement of time within the storage of sequential information has yet to be specified. To empirically investigate the involvement of time in the positional marking of information in WM and to unravel the nature of this involvement, we adapted an established paradigm, previously used to investigate spatial positional marking (De Belder, Abrahamse, Kerckhof, Fias & van Dijck, 2015). This particular paradigm proceeded in the following fashion; first, participants were presented a sequence of verbal stimuli to memorize and temporary maintain in WM. Secondly, whilst keeping these stimuli in WM, subjects performed a time processing task, involving the presentation of target stimuli which could either be part of the memorized sequence, or not. Items from the memorized sequence were considered to be located within WM, where these items are accordingly bound to position markers corresponding to the item's position within the sequence. Other verbal items, which were not part of the memorized sequence, are not considered to be available within WM and are therefore reasoned to be located 'outside' WM. Importantly, to ensure WM access during the time processing task, a go/ no-go instruction was included: the time processing task only had to be performed when the target was part of the memorized sequence. These manipulations would allow us to evaluate the effect of the serial position of the retrieved WM item on the processing of time.

In the first experiment, the task requiring time processing consisted of a go/no-go version of a foreperiod task (e.g., Vallesi, 2010). A foreperiod consists of the time interval between the initial stimulus presentation and the appearance of the target stimulus requiring a response. The foreperiod is argued to provide a temporal frame in which the participant is able to prepare his response; resulting in faster RTs when more preparation time was provided by a longer foreperiod (Cui, Stetson, Montague & Eagleman, 2009; Niemi & Näätänen, 1981; Vallesi, Shallice & Walsh, 2007). In the current study, the initial stimulus presentation involved the presentation of an item from inside/outside WM, followed by the actual target stimulus, which concerned the timed go-signal. This type of manipulation requires

WM access to precede the processing of time. Therefore, if serial order is coded by using temporal position markers, we hypothesize that the recognition of items occupying initial positions in the WM sequence will facilitate responses to short time presentations, while the opposite is expected for items located at the end of the WM sequence. In the second experiment, the opposite series of events occurred; a time manipulation was meant to prime positional information in WM. Participants first received a time interval of which the duration had to be evaluated followed by a target stimulus from in- or outside WM. In this way, we could investigate the effect of time perception on accessing information stored in WM. We hypothesized that the perception of a short temporal event would facilitate responding to items located in the beginning of the WM sequence, while the opposite would be expected for longer time events. The go/no-go phase in each experiment was followed by a memory test for the memorized WM sequence.

Across two experiments we tested the relationship between time and position in verbal WM in two directions; Experiment 1 focused on the effect of accessing information in WM on time perception; Experiment 2 investigated if prior time events affect the searching processes in WM. Establishment of the bidirectional effect is crucial for the unequivocal interpretation of the effects to position marking (De Belder et al., 2015). While the presence of a unidirectional link between time and serial WM would already indicate a strong relationship, only a reciprocal relationship would allow for the conclusion of an intrinsic involvement of time in serial WM and exclusion of the involvement of unrelated influencing processes, such as action preparation processes during variable intervals. More specifically, it was hypothesized that if positional markers are temporal in nature, the confrontation with WM information bound to these markers should facilitate responding to matching temporal information (Experiment 1). Initial items in WM were expected to be associated with short occurrences of time, while end items in sequential WM would be linked with prolonged time presentations. Similar findings were expected to be found when temporal processing preceded WM recognition; the introduction of a time event would activate matching position markers and facilitate responding to associated WM information.

EXPERIMENT 1

Participants

Twenty neurologically healthy participants provided written consent to participate in the study. Due to a technical failure (computer crashed after running the experiment) data from only sixteen participants could be analyzed (average age: 24,6; range: 18-46; 14 right-handed, 13 females). Participants received 10 EUR monetary reward for their participation. Participants were tested in groups of 1 to 5 people.

Materials

Participants were tested in a quiet room and sat in front of a 17-inch monitor at a viewing distance of approximately 50 cm. The task was administered with E-Prime 1.1, with all information on the screen presented against a black background. A QWERTY keyboard was used to register responses.

Procedure

The experiment consisted of 32 blocks, each consisting of the following three phases and each with a new sequence to be memorized: I) memorization of a WM sequence, II) go/no-go foreperiod task, and III) WM sequence verification (Fig. 1). During phase I participants were instructed to memorize a sequence of four letters in the correct order. Letters were individually presented in white on the center of the screen at a self-paced rate. The letters were randomly selected from the list: c, f, h, m, p, s, t and v (each 0.72° x 0.84°). Sequences were randomly constructed in such a way that across all blocks, all letters were presented and memorized equally often across all possible serial positions of the sequence. After memorizing the last letter, an interval of 2500 ms was provided before the start of the second phase to allow rehearsal.

The second phase consisted of a go/no-go foreperiod task (e.g., Vallesi, 2010). Each trial started with the presentation of a 500ms white fixation cross followed by a centrally presented stimulus, a time signal (a letter presented in colour red), followed by the imperative stimulus, the same letter stimulus turning green after a variable period of time, i.e., the foreperiod. The foreperiods were normally distributed around either 1100 ms or 3000 ms, with a maximum deviation of 250 ms, resulting in normal distributions between 850 ms and 1350 ms, and 2750 ms and 3250 ms. The lower limit of 850 ms for the short intervals was selected based on previous research (e.g., De Belder et al., 2015; van Dijck et al., 2011). These studies used a similar WM paradigm in which serially retained stimuli in WM required retrieval using a categorization task in a go/no-go setting. All averaged reported RTs for each condition of the categorization tasks were below 850 ms. Implementation of intervals of minimally 850 ms in our current design ensured that the search process in WM is finished within this interval, avoiding ongoing searching processes in WM to contaminate the processing of time. Participants responded to the imperative stimulus with a central response (pressing ‘b’ on the keyboard with the dominant hand) as fast as possible once the letter turned green AND the letter was part of the four-letter sequence they had to retain. No response was allowed when the presented letter was not part of the memorized sequence. In this latter case the letter was presented for 2000 ms, followed by an intertrial interval of

1500 ms, after which a new trial started. Participants completed 16 trials before the start of the third phase.

Before the start of the memory verification task (Phase III) the instructions for this task appeared on the screen. Participants were asked to indicate with a button press whether two letters were consecutively presented in the initial display in a given order (e.g.: "Was 'C' preceded by 'V'?"). Three trials of this fashion were completed during this phase. No time constraints were imposed. Within each block questions requiring a correct and incorrect response were presented randomly, with an equal amount of correct and incorrect order questions across blocks. After finishing Phase III, participants could take a short break of a self-determined duration, and then started the next block by pressing the spacebar.

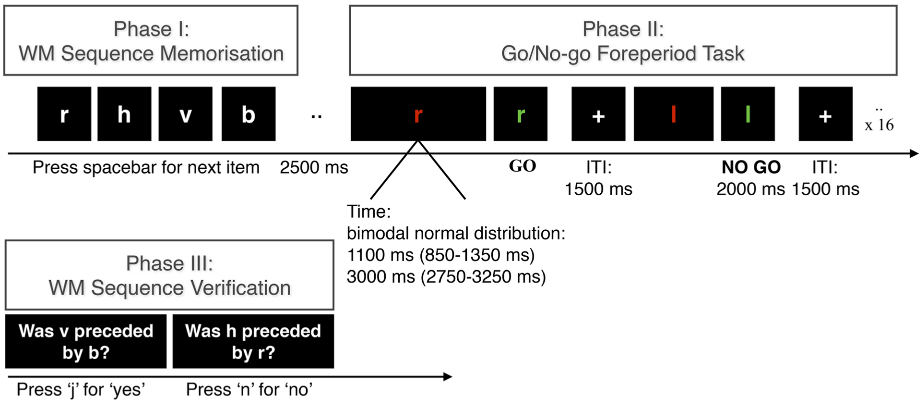

Figure 1. Experiment 1: Illustration of the three consecutive phases, repeated 32 times. Phase I consists of a self-paced presentation of four to-be-remembered items. During Phase II, red items turn green after a variable time interval. A central button press is required when the item turns green AND is part of the WM sequence. No response is required for items not part of the WM sequence. After 16 trials a

memory verification phase was initiated, testing memory of the order of memorized letters by yes/no-statements. Participants cycle through all of these phases 32 times.

Results and Discussion

Analyses were conducted on the go-trials of the foreperiod task of blocks whereby correct responses were recorded on the go-trials (overall accuracy: 98.06%, SD = .02; go-trials: 97.51%, SD = .02; no-go-trials: 98.61%, SD = .01), and the respective sequence was correctly remembered (i.e. all three sequences during the memory verification task had to be correctly answered; accuracy: 94,14%, SD = .08). The accuracy of no-go-trials (accuracy: 98.61%, SD = .01) was consistently high and therefore was not used as a criterion to include/exclude certain blocks. Mean reaction times (RTs) were computed per participant per condition for the foreperiod task, and submitted to a 4 x 2 Repeated Measures ANOVA with *WM position* (position 1 to 4) and *Time* (short: 850-1350 ms or long: 2750-3250 ms) as factors.

The analyses revealed a main effect of *WM position* [Wilks' lambda = .50, F(3,13) = 4.41, $p = .02$, $\eta_{p2} = .504$], with RTs for position 1 to position 4: 371 ms (SD = 54 ms), 369 ms (SD = 43 ms), 379 ms (SD = 53 ms) and 386 ms (SD = 53 ms). A main effect of *Time* was observed [Wilks' lambda = .20, F(1,15) = 59.01, $p < .001$, $\eta_{p2} = .797$], with a mean RT of 411 ms (SD = 63 ms) for short time presentations, and 342 ms (SD = 37 ms) for long time presentations. This latter main effect replicated the common finding that participants are faster when responding after longer foreperiods (Niemi & Näätänen, 1981; Vallesi, 2010). The *WM position* by *Time* interaction was significant [Wilks' lambda = .50, F(3,13) = 4.33, $p = .025$, $\eta_{p2} = .500$; Fig. 2A]. This interaction demonstrated to be in line with the hypothesis that WM retrieval influences the processing of time.

The nature of this interaction was further explored by calculating the slope for *WM position* on RT, separately for short and long durations (Lorch & Myers, 1990). The slope for short time presentations displayed a strongly positive trend [two-tailed t-test; t(15) = 3.86, *p* = .002, slope = 14.80], indicating slower reaction times after retrieving an item towards the end of the working memory sequence. The slope for long time presentations revealed a negative slope [two-tailed t-test; t(15) = -2.12, *p* = .05, slope = -3.56], indicating faster reaction times after retrieving items towards the end of the WM sequence (Fig. 2A). Moreover, differences in RTs (dRTs) for long versus short timing delays were calculated for each WM position. There was a negative and linear slope [t(15) = 3.29, *p* = .002, slope = -18.45; Fig. 2B]. In line with previously reported regression lines, it was observed that relatively faster RTs are observed for later WM items when responding after a longer delay, while the opposite conclusion could be made for initial WM items. These reported patterns indicated that retrieval of initial items of the sequence is preferentially associated with short durations and the retrieval of end items of the sequence is preferentially associated with long durations.

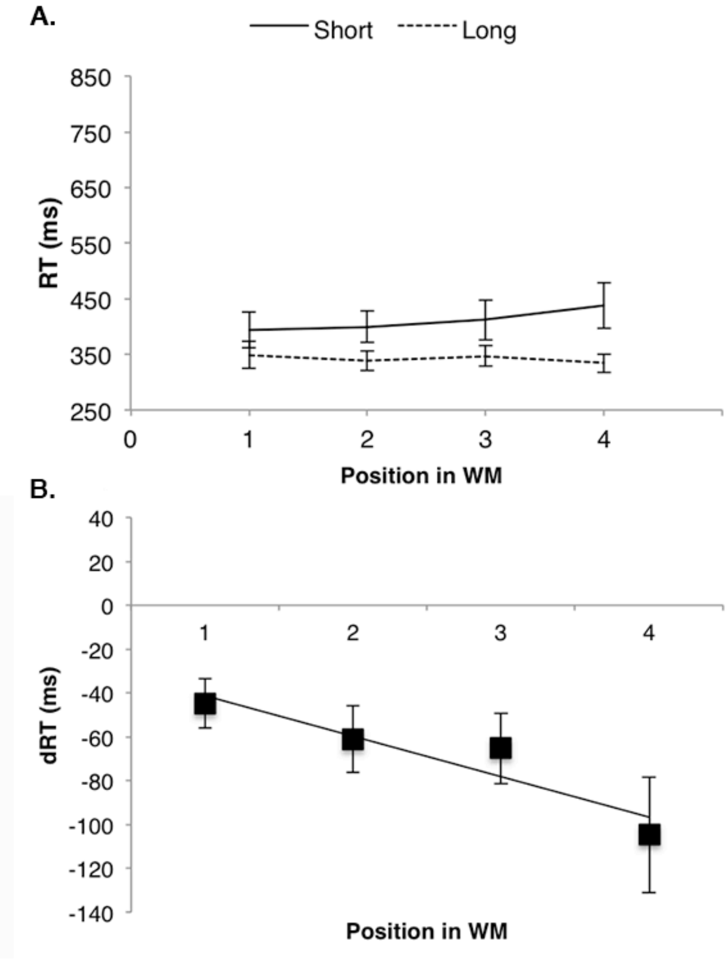

Figure 2. A. Results Experiment 1: Observed data, representing mean RTs for responses to the (short or long) timing signal for each position in WM. B. Observed data and regression line represented by RT differences between long and short time intervals. Smaller values indicate faster responses after long time intervals. Error bars reflect the standard error of the mean; standard deviation divided by the square root of the sample size.

EXPERIMENT 2

Participants

Twenty-four students (average age: 22.25 years, age range: 18-28; 22 right-handed; 17 females) participated in the study after signing an informed consent. In exchange for one hour of participation they were paid 10 EUR. Participants were tested in groups of 1 to 5 people.

Materials

Participants were seated in front of a 17-inch monitor at a viewing distance of approximately 50 cm in a quiet room. All information on the screen was presented against a black background. A QWERTY keyboard was used to register responses. Participants wore headphones throughout the entire experiment.

Procedure

The experiment again consisted of three phases, repeated 32 times, every time requiring the memorization of a different WM sequence: I) WM sequence memorization, II) time discrimination task and III) WM sequence verification (Fig 3). Phase I and III were exactly the same as in Experiment 1.

The durations to be discriminated were 300, 450, 600 or 750 ms and consisted of a time signal being presented for that duration (i.e., the presentation of *Time*). The time signal consisted of the combined presentation of a green dot (2.29° x 2.29°) and a sound, consisting of grey noise Participants were familiarized with these stimuli and durations before the actual start of the experiment. Familiarization occurred in the following fashion: a fixation cross (1000 ms) was followed by the time signal, the simultaneous presentation of the dot and sound. This time signal was sequentially presented twice for all four possible presentation times, starting with the shortest presentation time (i.e., the first time signal occurred for 300 ms, followed by a fixation cross of 1000 ms, a second time signal was presented for 450 ms, followed by a fixation cross, the next time signal of 600 ms, fixation cross, time signal of 700 ms… this procedure was repeated twice). The familiarization with these signals was followed by the instructions for the actual experiment. Ìn the actual experiment, in each trial of phase 2 a fixation cross (1000 ms) was followed by 150 ms ISI and by the time signal. A 150 ms black screen preceded the presentation of a 1000 ms probe (retrieval from *WM*). Participants responded as fast as possible with a central button press (the key ‘b’) if the previously presented duration was shortest or longest (300 or 750 ms) AND the probe was part of the WM sequence. However, they were instructed to refrain from responding if the time presentation was intermediate (450 or 600 ms) OR if the probe was not part of the memorized WM sequence. Participants completed 16 trials of the combined time and WM task before proceeding to the third phase, WM sequence verification. This phase was identical to Phase III of Experiment 1. The WM sequence verification task was followed by a break of a self-determined duration. A press on the spacebar initiated the start of the next cycle, starting with the memorization of the next WM sequence. During the complete experiment 32 blocks were administered, each with a different WM sequence.

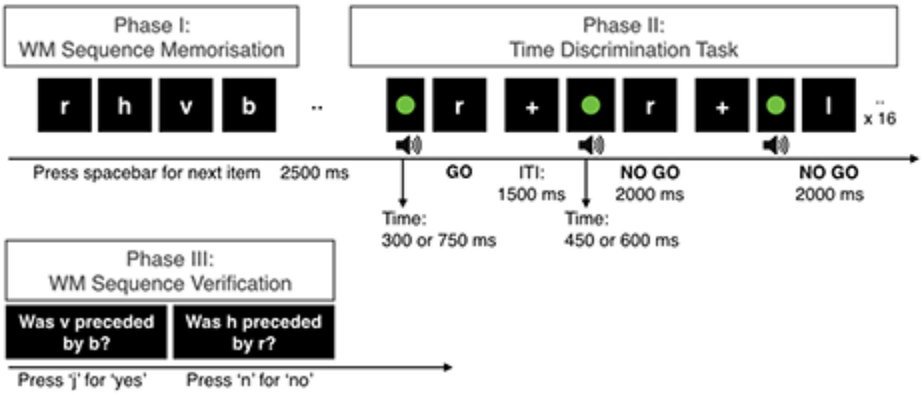

Figure 3. Experiment 2: Illustration of the three consecutive phases, repeated 32 times. Phase I consists of a self-paced presentation of four to-be-remembered items, memorized in the correct order. During Phase II, a green dot and sound are presented for 1 out of 4 possible time lengths, followed by the appearance of a letter. A central button press is required when the time event was extremely short/long (300/750 ms) AND the subsequently presented letter is part of the WM sequence. No response is required for intermediate time events or items not part of the WM sequence.

Results and Discussion

Analyses were only conducted on trials of the probe detection task whereby the entire sequence was correctly remembered during the memory verification task (accuracy: 92.71%, SD = .15). Moreover, only correct go-trials of the probe detection task were included (overall accuracy: 86.32%, SD = .04). The accuracy on no-go-trials (accuracy: 86.46%, SD = .04) was consistently high and comparable to the performance on the go-trials (accuracy: 86.09%, SD = .06), and was therefore not used as a criterion to include/exclude certain blocks. Mean RT for the probe detection task was 683 ms (SD = 111 ms). A 4 x 2 Repeated Measures ANOVA with *WM* *position* (position 1 to 4) and *Time* (short: 300 ms or long: 750 ms) as factors was conducted on the mean RTs, calculated for the probe detection task for each participant per condition. Again, multivariate results are reported.

A main effect of position in WM was observed [Wilks' lambda = .69, F(3,21) = 3.17, p = .046, $^{\eta}p2$ = .31], with RTs for position 1 to position 4: 547 ms (SD = 88 ms), 566 ms (SD = 90 ms), 578 ms (SD = 94 ms) and 585 ms (SD = 85 ms). This is taken to reflect a continuous scanning process in serial WM. The analysis revealed a trend towards a main effect of time [Wilks' lambda = .87, F(1,23) = 3.46, p = .076, $^{\eta}p2$ = .13], suggesting a possible advantage to responding to longer durations (mean RT for long times = 313 ms, SD = 41 ms; short times = 330 ms, SD = 46 ms). This effect demonstrated to be in line with the common observation that longer durations are often observed in combination with faster RTs (e.g., Cui, Stetson, Montague & Eagleman, 2009, Niemi & Näätänen, 1981; Vallesi, Shallice, Walsh; 2007). As predicted, the interaction between *Time* and *WM position* was significant [Wilks' lambda = .58, F(3,21) = 5.35, p = .007, $^{\eta}p2$ = .43] (Fig. 4A). Compared to longer presentation times, participants became significantly slower in responding to short durations when having to retrieve an item located further in serial WM.

To further investigate the nature of the interaction between *Time* and *WM position* we calculated the difference between the long and short timing durations for each position and computed the slope of WM position related to this difference measure (Lorch & Myers, 1990; Fias; Brysbaert, Geypens & d'Ydewalle, 1996). Differences in RTs (dRT) for long versus short time presentations were calculated for each WM position. There was a negative and linear slope [t(23) = 3.78, p = .001, slope = -17.09; Fig. 4B], revealing following pattern; the further items were located within WM, the larger the advantage towards responding after long time durations, as observed in larger negative difference scores. Taken together, this latter RT pattern supported the notion that items stored within WM are more easily accessed when either a short time durations is followed by an item at the beginning of WM or a when a longer duration is followed by a later WM.

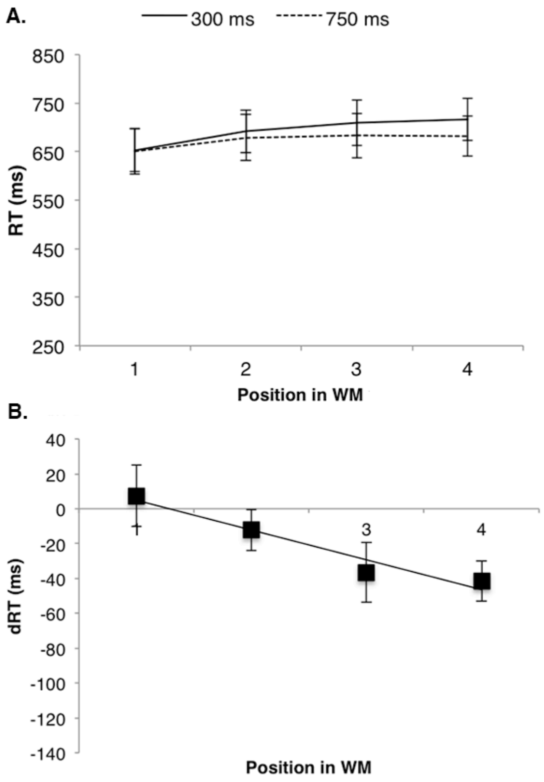

Figure 4. A. Experiment 2: Observed data, representing mean RTs for responses to WM items after a short or long time cue. B. Observed data and regression line represented by RT differences between long and short time presentations. Positive values indicate faster responses after short time cues. Error bars reflect the standard error of the mean; standard deviation divided by the square root of the sample size.

GENERAL DISCUSSION

In the current study we attempted to demonstrate the functional involvement of time in serial verbal WM. It has been argued that time could be used to construct position markers in WM, which brought us to the prediction that time-matched position markers could affect the processing of information bound to these markers and vice versa. Our findings emphasized the bidirectional nature of the relationship between time processing and sequential verbal WM. Results of Experiment 1 demonstrated that positional information of items accessed in WM influences time-related preparatory processes, as reflected in the observed interaction between time and WM order, and the reported negative linear regression line. More specifically, relatively faster RTs were observed for short foreperiods combined with the presentation of initial serial position WM items, while those RTs were longer for initial serial position WM items and long foreperiods. To the contrary, for end items of the WM sequence we observed relatively faster RTs for longer time presentations compared to shorter time presentations. Unexpectedly, the observation of this latter pattern emphasized the robustness of this effect, as it could be observed apart from very dominant serial scanning processes (De Belder et al., 2015; van Dijck et al., 2011). Moreover, the strong interaction between time and WM positions even overwrote the typically strong foreperiod effect. Namely, the foreperiod is argued to provide a temporal reference in which the participant strategically prepares his response (Cui, Stetson, Montague & Eagleman, 2009; Niemi & Näätänen, 1981; Vallesi, Shallice & Walsh, 2007). Generally, shorter RTs were observed after longer foreperiods, as longer intervals provide participants with more time to prepare their response. However, our data showed that this foreperiod effect could be modulated by WM position, as observed in the shorter RTs for items located further in WM. Additionally, the overall interaction pattern was similarly reflected in the linear regression performed on RT differences between short and long timing intervals; begin items from the WM sequence were responded to slower after a long time delay compared to a short delay, while participants became increasingly faster at responding to end items from WM after longer delays, emphasizing the effect of the activation of positional WM information on time processing.

Experiment 2 specifically explored how time perception influences verbal WM retrieval processes. We observed an interaction between the presentation of time (by the time signal) and speed of WM retrieval. Compared to initial items positioned in WM, RTs became increasingly larger when progressing through the WM sequence to later WM positions, with a larger deceleration when having to respond after shorter timing stimuli compared to longer timing stimuli. Importantly, this interaction was further clarified by the linear regression, which demonstrated that the process of memory retrieval is fastest when a short time stimulus if followed by an initial WM item or when a longer duration is followed by a WM item located further in WM. This regression pattern was similar to the pattern observed in Experiment 1, but the effect for long time signals was more evident in Experiment 1. However, note that previous studies already demonstrated how dominant serial scanning processes in WM overrule obvious observable interaction patterns, as observed in overall increasing RTs for increasing WM positions (De Belder al., 2015; van Dijck et al., 2011; van Dijck et al., 2013), making findings of Experiment 1 rather striking.

Moreover, our study addressed limitations of previous research concerning the interpretation of the effect of time manipulations. For instance, previous studies were limited to the manipulation of presentation rate in serial recall tasks in order to investigate WM position-time relationships. However, it remained unclear whether the mere manipulation of presentation rate could suffice to provide conclusive evidence concerning the construction of temporal position markers. For example, serial recall studies were confronted with the issue that memory performance did not improve when mental representations of WM items spread out in time were constructed, compared to items represented more proximate (or overlapping) in time (Baddeley & Lewis, 1984; Henson & Burgess, 1998; Neath & Crowder, 1990), contradicting the idea of temporally constructed position markers. Moreover, previous methods were not able to control for a possible temporal reorganization of stored items after the encoding phase. Therefore, firstly, we implemented a memorization phase only containing a positional encoding process of items in WM. Time events occurred independently of the encoding phase (Phase I), but took place in the subsequent test phase (Phase II), during the maintenance of WM information. Secondly, time was directly manipulated to specific durations and required a deliberate assessment in order to produce accurate responses (in Experiment 2). Moreover, time events were presented closely in time with the stimuli requiring WM access. This proximate time-WM item presentation allowed facilitated interpretation and assignment of effects of temporal features on recall accuracy to WM items and vice versa. Lastly, participants were allowed to memorize WM elements in a self-paced fashion, allowing the formation of an optimal memory trace. Participants were also requested to retain all items in the presented order and analysis was only conducted on correctly retrieved sequences, controlling for memory reorganization during memory repetition. Note that it can be argued that the implementation of this self-paced memorization phase allowed participants to create a mental representation in which time is one of the features distinguishing multiple items. However, as previously mentioned, other studies did not manage to find an effect on accuracy as a result of item proximity in time (Baddeley & Lewis, 1984; Henson & Burgess, 1998; Neath & Crowder, 1990). Moreover, if this event would occur during our experiment this would not alter our conclusions made with regard to the involvement of time in the construction of position markers.

Furthermore, while our findings suggest the crucial functional involvement of time in serial verbal WM, these results do not allow a definite conclusion about the specific nature of position markers. We do not know whether the effect of time is direct or relates to the mapping of time in space. In other words, our results pointing to time being associated to serial position does not exclude the involvement of space. In fact, it might be expected that a spatial coordinate system is inherent to WM, as the crucial involvement of space in WM has already been established (e.g., Abrahamse, van Dijck, Majerus & Fias, 2014; De Belder et al., 2015; van Dijck & Fias, 2011; van Dijck, Abrahamse, Majerus & Fias, 2013). Firstly, it has been shown that serial order in verbal WM is coded within a spatial coordinate system and that spatial attention is recruited to search through this system. (van Dijck et al., 2011; van Dijck, Abrahamse, Majerus & Fias, 2013; van Dijck, Abrahamse, Acar, Ketels & Fias, 2014). Secondly, recent findings of Hale, Thompson, Morgan, Cappelletti & Kadosh (2014) demonstrated the dominance of the spatial component in the context of synaesthesia for time, numbers and space. Synesthesia is a neurological phenomenon in which one sense, such as vision or mental perception, is experienced as it was simultaneously perceived with other senses, such as hearing or perception of colors. Compared to non-synaesthetes, synaesthetes showed an advantage towards responding to spatial information stimuli when an ordinal judgment was required. These latter findings matched the sequence account (Eagleman, 2009; Hale et al., 2014; Tang, Ward & Butterworth, 2008), in which the relationship between the three types of information is explained by the ordinal nature of their representations, characterized by the mapping on spatial coordinates. Thirdly, while the origin of the position markers in the start-end model of Henson focuses on the temporal representation of items, it also leaves room for the role of relative spatial positions. As briefly mentioned by Henson (1998, p. 81) "… such [start and end] markers may also apply for the coding of spatial position (e.g., Nelson & Chaiklin, 1980). For example, the relative distance from two of the ends of a horizontal array might provide an approximate code for an item's position within that array". Overall, our findings do not allow a definite conclusion concerning the involvement of space in the relationship between time and serial verbal WM, but did establish a strong interplay between time and serial WM processes.

In sum, our study demonstrates the engagement of time in the construction of position markers in serial verbal WM. Establishing the reciprocity of their relationship validates the crucial and fundamental involvement of time within serially ordered WM. Further research is needed to establish the involvement of spatial coding in this relationship.

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CHAPTER 4

INTENTIONAL AND INCIDENTAL ORDER PROCESSING IN WORKING MEMORY AS SPATIAL COORDINATE SYSTEM[1]

Previous research repeatedly acknowledged the crucial role of order processing in efficient working memory functioning (WM). However, mechanisms related to the processing of order were mainly studied in the context of intentional order memorization, where the task specifically included an order memorization instruction. As the representation of order in WM demonstrates to be so fundamental to daily life functioning, one might expect that order would be automatically processed within WM. However, up till now the occurrence of order processing in incidental conditions remains unknown. Therefore we designed an experiment to address following questions; first, is order information automatically processed within WM? Furthermore, when we intentionally memorize serial order, this information is spatially represented within WM (e.g., Abrahamse, van Dijck, Majerus & Fias, 2014). This observation leads to the second question; if the handling of serial order information automatically occurs, is the information also spatially coded in WM? Four hundred participants were submitted to a short experiment, instructing the memorization of a single sequence of five letters (in correct order or in any order). The

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[1] De Belder, M., van Dijck, J-P., & Fias, W.

memorization of these letters was followed by a task requiring the participants to categorize memorized letters according to font style (printed in italic or regular print), finishing the task by instructed full recall of the memorized letters. Results demonstrated I) automatic order memorization, II) spatial order coding, independent of order instruction and III) occurrence of spatial coding within WM, demonstrating that spatial coding is not a results of strategic behavior or long-term memory processes.

INTRODUCTION

Working memory (WM) allows information to be maintained in an accessible and processable state for a brief period, so that the stored information can quickly be retrieved and manipulated. One of the essential components supported by the WM is the storage of serial order, which is crucial for efficient everyday functioning, for example when using language, interpret auditory stimuli, learn new skills, cook a recipe etc (e.g., Baddeley, 2012).

Many theoretical approaches have been proposed to address the mechanisms underlying the construction of order representations during encoding and the use of these representations during retrieval (see Henson & Burgess, 1998 for a review). One of the most supported accounts argues that the construction of order is a consequence of binding information to position markers (e.g., start-end-model; Henson, 1998). This general theoretical account has recently been further specified in the mental whiteboard hypothesis (Abrahamse, van Dijck, Majerus & Fias, 2014). This model states that to-be-memorized information is bound to position markers, which are defined in spatial coordinates, and that mechanisms of spatial attention are employed to search for and retrieve information from the WM system. Importantly, the spatial coding of serial position is hypothesized not only to apply to visuospatially presented information (as in visual memory) but also to information that does not intrinsically have any spatial information, nor in content neither in the way it is presented, as is the case for verbal information (as in verbal working memory like remembering a phone number). Empirical support in favor of a spatially organized verbal WM system has recently accumulated by the demonstration that sequentially presented information receives position-specific spatial coding (e.g., van Dijck & Fias, 2011; De Belder, Abrahamse, Kerckhof, Fias & van Dijck, 2015). More specifically, when instructing participants to respond to memorized information with a left- or right-handed response, items from the beginning of the sequence are associated with the left side of space, as observed in faster left- than right-hand responses, while items towards the end of the sequence resulted in faster right- than left-hand responses, reflecting a right-sided association with space.

It is clear that the ability to represent order and to store information in an ordered fashion is a crucial function and is a process that is supported within WM. Up to date it is only understood how serially ordered WM traces are constructed in situations where we consciously focus on the memorization of serial order because it is necessary to successfully perform the task. However, the processing of order is also important when not being a requirement of the task at hand. For example, while no one asks you to remember the items on your shopping list in as specific order, it is most likely that while walking to the shop, you mentally repeat the list of items in a specific order. However, until now it remains unknown whether spatial coding of serial information in verbal WM occurs spontaneously or, alternatively, whether an explicit and controlled focus on serial ordering is necessary.

To our knowledge, the automaticity of spatial order coding has never been investigated. Even studies looking at automaticity of order coding irrespective of the spatial component, are rare, and their results were inconclusive (Jackson, Michon, Boonstra, De Jonge, De Velder Hasenhorst, 1986; Nairne, 1990; Naveh-Benjamin, 1990; Zacks, Hasher, Alba, Sanft &

Rose, 1984). For example, in a study of Naveh-Benjamin (1990), participants were submitted to an item categorization task (indicating the value of the presented item; cheap or expensive). Half of the participants were informed about an upcoming temporal order memory test, requiring the participant to put the twenty items they had previously categorized in the correct presentation order. The half of the participants who were unaware of the memory task performed worse than the informed participants. This observation was interpreted as evidence against the occurrence of automatic temporal order encoding. However, this study and others deal with a few issues, which might explain why previous studies were not able to establish the presence of automatic order processing tendencies. For example, it is observed that even in the absence of information about an upcoming ordered memory test, uninformed participants still perform quite well (Naveh-Benjamin, 1990). Differences between informed and uninformed participants could thus be the result of the informative instructions boosting memory and attention for the processed items. Furthermore, the couple of studies that investigated the existence of automatic (temporal) order coding often utilized a paradigm consisting of a multiple-trial setting, requiring the participants to repeatedly learn and recall sequences of items (e.g., Nairne, 1990; Zacks, Hasher, Alba, Sanft & Rose, 1984). One could argue that the repeated exposure to the same task would allow the participants to develop a strategy adapted to the task. While the memorization of order may not seem to be necessary to perform the task, after a couple of trials, one could still decide to employ a strategy involving serial memorization of items, helping to more efficiently perform the task. In other words, one might argue that due to the multiple-trial setting one cannot distinguish between automatic or non-automatic order processing.

In order to disambiguate reported findings in literature, the proposed research question in this paper is twofold. First, we are interested whether spontaneous order processing occurs in a context where order memorization is not necessary to successfully perform the task. In other words, do we only observe intentional order processing (instruction encompasses order memorization), or does incidental order processing additionally occur (no instruction to memorize order)? Second, if incidental order processing takes place, does its encoding process proceed in the same fashion as intentionally memorized order information, i.e., can we observe spatial mapping for the memorized items in WM?

The employed paradigm, based on the experimental procedure developed by van Dijck et al. (2011), consisted of three phases: I) memorization, II) go/no-go categorization and III) memory retrieval. During the memorization phase, participants were instructed to memorize five letters. Half of the participants additionally received the instruction to remember them in the correct order. During the go/no-go categorization phase, participants had to indicate with a left- or right-handed response whether the presented letter on the screen was printed in an italic font or not. The no-go instruction entailed that participants were only allowed to respond to letters they memorized in the first phase of the experiment. After the completion of the go/no-go categorization task, the phase for memory retrieval was initiated, requiring full recall of the memorized letters. While previous studies were characterized by repeating the entire paradigm multiple times, the current study required the memorization of only a single sequence. The experiment was set up in this way to hinder the development of strategic behavior. The reasoning was as follows: in the current study we were interested to observe whether spatial coding of serial order occurs both in the presence and absence of an order instruction. Important when considering this question is that we have to make sure that the presence of spatial coding observed in the experiment of the current study (and in previous studies, e.g., De Belder et al., 2015; van Dijck, 2011, 2013) is not a result of retrieval strategies developed by the participant over the course of the experiment. In the absence of any strategic behavior, we expected to observe that spatial coding would occur when participants were instructed to memorize serial order, but importantly, we expected to observe the same spatial coding tendency when the memorization of order is redundant to the task. Even more, we hypothesized that the tendency to spatially organize information in WM is an early process and therefore, would already be observed at the very first trial.

METHOD

As the entire experiment took 2 minutes to conduct, the experiment was added to the beginning or end of the protocol of several studies on unrelated topics that were run in the department. The data of 406 students was collected. Students could participate in exchange for a course credit or payment (depending on the duration of the entire experiment; 10 EUR/hour). All participants provided written consent prior to participation.

Materials

Participants were tested in a quite room and sat in front of a 17-inch monitor at a viewing distance of approximately 50 cm. The task was administered with E-prime 1.1, with all information on the screen presented against a black background. A QWERTY keyboard was used to register responses.

Procedure

First, participants were randomly assigned to one of four experimental groups. The experimental groups were determined by response mapping and by the presence or absence of an explicit order-instruction. Prior to the start of the experiment, participants were informed about the fact that they would have to memorize five letters (in any order / correct order), which would be followed by a go/no-go categorization task and a memory test. For the go/no-go categorization task of the experiment, response mapping 1 required left-hand response to italic printed items, right-hand responses to letters in a regular, straight print. Response mapping 2 required the opposite hand response to italic and regular printed items.

The experiment was based on the paradigm of van Dijck et al. (2011) and consisted of three phases: I) memorization of the WM sequence, II) go/no-go categorization task, and III) full recall. During phase I, participants were instructed to memorize five letters. Participants were randomly assigned to one of the following conditions: half of the participants received the instruction to memorize the five letters in correct order, the other half was simply asked to memorize the five letters (no further order-instruction was provided). The five to-be-memorized letters were presented one by one in the center of the screen (with a size of 0.72° x 0.84°) at a self-paced rate. The letters were randomly selected from the list: c, d, f, h, j, k, m, p, q, s, w, z. After the memorization of the last letter, an interval of 2500ms preceded the start of the second phase.

The second phase consisted of a go/no-go categorization task. Every trial was initiated by the presentation of a central fixation cross (500ms), followed by the presentation of a centrally presented stimulus, a letter (2000ms). This letter could be printed in a regular or italic print and be part of the WM sequence or not. Participants responded to the letter with a left- or right keyboard response (pressing ’s’ for left; ‘l’ for right) as fast as possible to categorize the print of the letter as being ‘italic’ or ‘not italic’. However, participants only performed this categorization task if the presented letter was part of the memorized WM sequence. No response was allowed for any other letter (no-go). This go/no-go instruction was included in order to ensure WM access during the go-trials of the categorization task. Thirty trials were completed (consisting of 50% go-trials) before the start of the third phase.

During the third phase, full recall of the sequence was required; for which the following instruction appeared on the screen “What was the series of letters you had to memorize?”. Participants, who were instructed to memorize the correct order, received the additional note “Type the letters in correct order”. With the use of the keyboard, participants had to provide the memorized letters. The entered letters simultaneously appeared on the screen, errors could be corrected by using backspace. No time constraints were imposed. Finishing the full recall phase, participants were paid, received their course credit or participated in a different experiment.

Importantly, the to-be-memorized sequences were randomly constructed, but in such a way that the participants in all groups memorized the same sequences (i.e., the first participant of group one had to memorize the same sequence as the first participant of group two, three and four; the second participant had to learn a sequence that was different from the sequence from participant one, but this sequence was the same for every second participant of each group).

Because our experiment consisted only of a small number of trials, it could be expected to be sensitive to noise. In an effort to reduce the noise as much as possible, participants performed a short practice block before the actual experiment, which we hoped would absorb much of the surprise reactions, task learning, uncertainty about the protocol etc. The practice block consisted of only 10 go/no-go categorization trials. During the practice phase, feedback was provided for the categorization and full recall phase. A single experimental block immediately followed the practice block. The entire experiment took no longer than 2-3 minutes to complete.

RESULTS

The data of 338 students (average age: 20.73; SD = 3.49; 251 females; 296 right-handed) were analyzed after exclusion of participant data in case of incomplete sequence recall (in any order; 8.78% of the participants), a performance accuracy below chance level (< 55%; 7.40% of the participants), use of incorrect response buttons, incomplete data sets (early disruption of the experiment).

Analyses of the experimental phase

Analyses were conducted on the correct go-trials of the categorization task (overall average accuracy: 76.17%, SD = .14; go-trials: 67.27%, SD = .19; no-go-trials: 85.08%, SD = .16), if the respective sequence was correctly remembered (i.e., for the order-instruction; a correct sequential recall was required; for the no-order instruction: five correctly recalled letters, in any order; accuracy: 94.31%, SD = .22). Errors made on go-trials consisted of 73.64% errors made due to pressing the incorrect response button and 23.36% no response errors. The accuracy of no-go-trials was consistently high and therefore was not used as a criterion to include/exclude certain blocks (no-go-trials: 85.08%, SD = .16). The mean reaction times (RTs) were computed for each participant for each of the 10 conditions of the categorization task determined by *WM position* (position 1 to 5) and *response hand* (left or right). For participants who did not receive order instructions, WM position was coded with respect to the sequence as they reported it (and not the original sequence). Actually, 93.80% of the participants recalled the original sequence, 8.78% recalled an incorrect sequence (i.e., incomplete sequence or incorrect letters; these participants were excluded), only .01% of the participants remembered the WM items in an order different from the original one. This observation provided a first indication of the spontaneous use of order-coding.

Due to the limited number of trials collected for each participant, there were no data for all conditions for each participant (27% empty cells, determined at random). The presence of missing data was anticipated and compensated by the large number of included participants. A linear mixed models approach was used for analysis, as LMM does not require a fully balanced design and adequately deals with at random missing data (Brown & Prescott, 1999; Van den Noortgate & Onghena, 2006).

The analysis was conducted on the mean RTs for all conditions with following variables: *order instruction* (yes or no), *WM position* (position 1 to 5), *response hand* (left or right). First, no main effect of *order instruction* was observed [F(1,308) = 1.74, p = .19], showing that participants are equally fast when they are instructed to memorize sequence order compared to memorizing items without the order instruction (order = 449ms, SD = 107ms; no order = 463ms, SD = 88ms). Also no main effect of *response hand* was observed [F(1,3610) = 1.38; p = .24], indicating equally fast responses for the right and left hand (left hand = 1002ms, SD = 217; right hand = 981ms, SD = 223ms). Importantly, a main effect was observed for *WM position* [F(4,3424) = 10.06, p < .001], demonstrating a general increase in RTs when responding to items located further in the memorized sequence of items, with RTs of 930ms (SD = 225ms), 951ms (SD = 240ms), 981ms (SD = 239ms) and 1009ms (SD = 264ms) for respectively position 1 to position 5. The observation of an effect of *WM position* is generally associated with a serial scanning process occurring in WM (De Belder et al., 2015; van Dijck et al., 2011), suggesting the serial scanning of memorized items. The absence of an interaction indicated that serial scanning occurred independent of the *order instruction.* This latter claim is further supported by the absence of an interaction between *WM position* and *order instruction* [F(3,3425) = .74, *p* = .57]. Crucially, the analysis also revealed an interaction between *response hand* and *WM position* [F(4, 3472) = 3.13, *p* = .01, Fig. 1A & B]. This interaction showed that initial WM items are associated with relatively faster left hand responses compared to right hand responses, while pattern switches and the difference between left- and right hand responses increases for further WM positions (Position 1: left= 931ms, SD = 284ms; right = 976ms, SD = 265ms; Position 2: left = 988ms, SD = 282ms; right = 965ms, SD = 287ms; Position 3: left = 1009ms, SD = 293ms; right = 969ms, SD = 275ms; Position 4: left = 1048ms, SD = 303ms; right = 1002ms, SD = 271ms; Position 5: left = 1028ms, SD = 260ms; right = 998ms, SD = 301ms). Interestingly, this two-way interaction did not seem to depend on the *order instruction*, as indicated by an non-significant three-way interaction [F(4,3472) = 1.60, *p* = .17]. Additionally, no two-way interaction between *hand response* and *order instruction* was observed [F(1,3609) = .49, *p* = .48].

The presence of the interaction observed between *WM position* and *response hand* is indicative for the presence of spatial coding of item information within WM. In order to evaluate this relationship, the presence of a linear relationship was investigated by means of a regression analysis on polynomial contrasts (e.g., Fias, Brysbaert, Geypens & d'Ydewalle, 1996). A linear relationship was found in the interaction between *WM position* and *response hand* [slope = -16.43, t(3490) = 2.73, *p* = .006; Fig. 1C]. This linear relationship demonstrated that participants were initially faster when responding with a left hand to initial WM items, but that they became gradually faster at responding with the right hand to items located further in the WM sequence.

Results of the linear mixed model analyses did not reveal any two-way or three-way interactions that would suggest differences due to the presence or absence of order instructions. However, in order to further strengthen our claim, a regression analysis for *WM position* and *response hand* was performed for *order* and *no order instructions* separately. These analysis revealed a significant negative linear trend when participants were instructed to memorize order [slope = -16.89, t(2062) = 2.12, *p* = .03]. This negative linear trend was also observed in the absence of any order instruction [slope = -19.06, t(1542) = 2.07, *p* = .04]. These analyses provided additional support for spatial mapping of item sequences in WM, independent of order instruction.

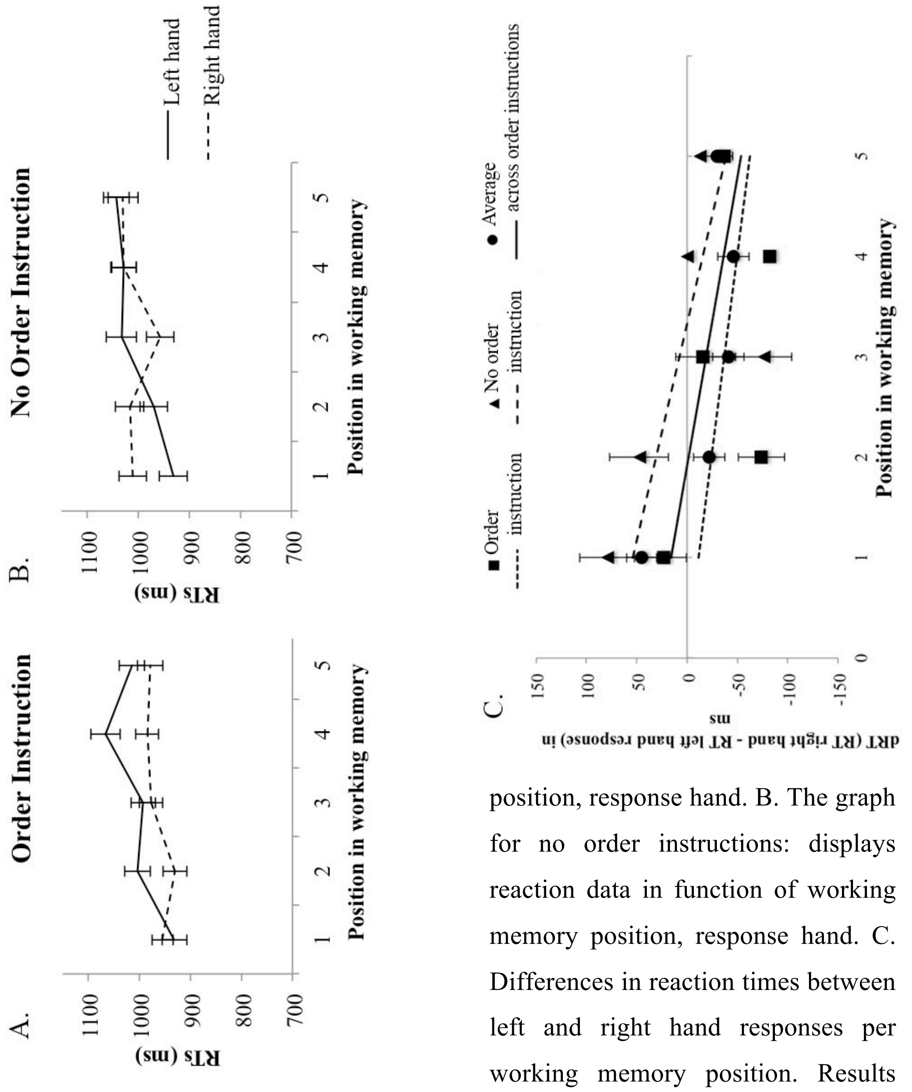

Figure 1. Results of the analysis on the experimental phase of the experiment. A. The graph for order instructions: displays reaction data in function of working memory position, response hand. B. The graph for no order instructions: displays reaction data in function of working memory position, response hand. C. Differences in reaction times between left and right hand responses per working memory position. Results are displayed for the conditions 'order instruction'/ 'no order instruction' and the average result across order instructions.

Analyses of the practice phase

Strategy development was constrained by running the experimental phase of the experiment only once. The previous experiment demonstrated that performances on the go/no-go categorization task are not driven by order instruction. However, in order to strengthen the claim that spatially constructed serial order traces are fast and automatically constructed, one might argue that previously presented results are not completely convincing. Prior to the execution of the experimental phase, participants performed a short practice trial. Despite the short length of the practice sequence and the lack of task repetition, it might be possible that participants developed a specific strategy that was adapted to this specific task based on their experience in the practice phase. Therefore, the same analyses as described in the previous section were performed on the practice trials; a linear mixed model analysis on *order instruction* (yes or no), *WM position* (position 1 to 5), *response hand* (left or right), followed by a regression analysis. Importantly, even more so than in the experimental phase, the practice phase is characterized by missing data. The data consisted for each subject of maximum one response (left or right) for each position in the sequence to query. Participants performing below chance level (accuracy < 50%) were removed. As analyses were performed on unaveraged single data points per subject, the results are very sensitive to outliers. Therefore, we removed outliers (i.e., participants with a deviation of more than 2SDs from the average). Results of the linear mixed models demonstrated a main effect of *WM position* [F(4,778) = 3.53, *p* = .007], with increasing RTs for responses to items located further in the WM sequence (average RTs and SDs: position

1 = 1018, SD = 280ms, position 2 = 1145ms, SD = 316ms, position 3 = 1137ms, SD = 345ms, position 4 = 1141ms, SD = 337ms, position 5 = 1137ms, SD = 309ms). We also observed a main effect of order instruction [F(1,778) = 5.31, *p* = .02], with generally faster RTs when participants were not instructed to memorize order (order instruction: mean RT = 1137ms, SD = 329ms; no order instruction: mean RT = 1063ms, SD = 311ms). All other main effects and interactions were non-significant (p > .10).

Similar to the analysis performed on the experimental phase, a more sensitive linear regression analysis was performed in order to assess the presence of spatial coding. A linear relationship was found between *WM position* and the differences in RTs between right hand and left hand responses [slope = -43.29; t(764) = 2.78, *p* = .006]. Despite the fact that there was a substantial amount of missing of data, these results indicated that spatial coding of the memorized sequence already occurred in the practice phase. However, amount of missing did not allow us to calculate the slopes independent of order instructions, as was done analyzing the experimental data. Note that the absence of any interactions with *order instruction* on the linear mixed model analysis already indicate that no differences are expected to be present for the negativity of the slopes depending on the presence/absence of an order instruction.

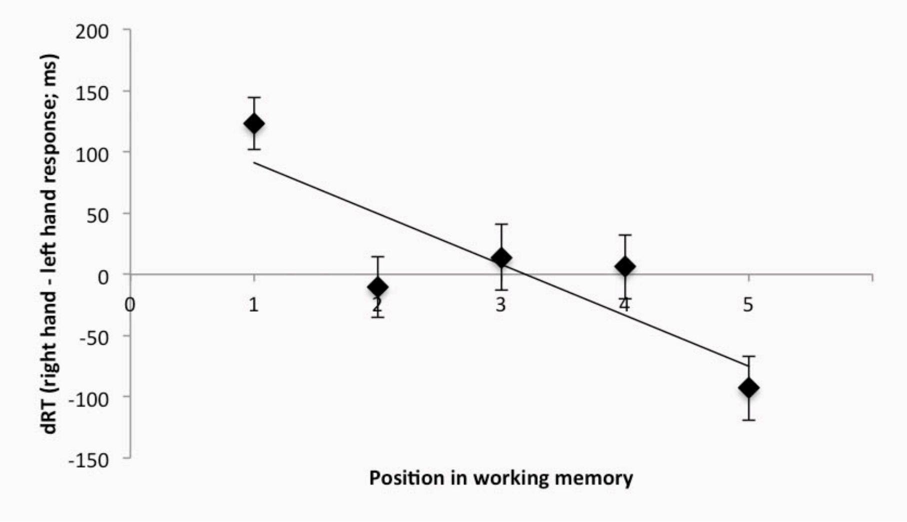

Figure 2. Results for the analysis of the practice phase: differences in reaction times between left and right hand responses per working memory position across order instructions.

Analyses of the first practice trial

In order to further substantiate our claim of automatic spatial coding of WM traces we further limited the focus of our analysis to the very first trial that the participant responded to. If the processing of serial order and construction of spatial memory trace is an automatic process, we should already observe effects of serial order encoding during the very first test trial of the go/no-go categorization task. As participants already completed a very short practice phase before being submitted to the longer experimental phase, the very first trial occurs in the practice phase.

In the following analyses we extracted the RTs for all participants for the first trial of the go/no-go categorization task they completed during the practice phase. Participants starting with a no-go trial were left out of the analysis (i.e., 219 or 54.94% of the participants). Furthermore, RTs of the participant were only analyzed if the participant responded correctly to the first trial (i.e., 187 or 45.06% of the participants). As a consequence of extracting a single data point per participant and the loss of participants starting with a no-go trial, a limited number of data was taken into account, of course leading to noise and limiting power. We therefore performed a very simple independent samples t-test on *congruency*. Congruency was determined as follows; the response of the participants was categorized as 'congruent' if the participant responded with a left-hand response to the first or second letter of the memorized sequence or when he/she responded with a right-hand response to the forth or fifth letter of the memorized sequence. A response to a trial was categorized as 'incongruent' if the participant had to respond with a left-hand response to the fourth or fifth letter of the sequence, or when he responded with a right-hand response to the first or second letter of the memorized sequence. Trials where the participant had to respond to the third letter of the memorized sequence were discarded as the central item of five elements could not unambiguously be assigned to the left or right side of (mental) space. The independent samples t-test showed that congruent items were responded to faster than incongruent [t(60) = -2.02, one-sided p = .02]. These results demonstrated that from the first trial on, participants tended to respond faster when the mental location of the WM item within the memorized sequence matched the spatial location of the response-hand, illustrating early-stage spatial organization of memorized information.

DISCUSSION

The current study was designed to investigate I) spontaneous order processing, and II) in the case of spontaneous order coding, the occurrence of item binding to spatial position markers, resulting in a spatial memory trace.

In contrast to previous studies the experimental task was limited to the memorization of a single sequence (De Belder et al., 2015, De Belder, van Dijck, Cappelletti & Fias, 2016; Nairne, 1990; van Dijck, 2011,2013; Zacks et al., 1984). By running a brief experiment in which only one sequence had to be memorized, we aimed at creating conditions for unequivocally evaluating spontaneous order processing, while reducing the possibility for participants to develop specific strategic behavior.

With respect to the occurrence of spontaneous order processing, the following observations were made. First, we observed that independent of whether the task instructed the memorization of order or not, only 0.8% of the participants recalled the memorized letters in an order differing from the original sequence, providing a first indication of spontaneous order memorization. Second, generally increasing RTs for responses to items located further in the memorized sequence were observed, again independent of an order instruction. This effect is generally interpreted to be a result of a serial scanning process, where the memorized WM sequence is scanned from start to end (De Belder et al., 2015; van Dijck et al., 2011). These two observations thus provide support for the idea that serial order coding in WM doesn't only happen in an intentional context, but also spontaneously when order is not mentioned in the task instructions.

For the second question, we investigated whether spatial coding of serial position happens spontaneously. With respect to this question, the following observation was made for the experimental phase: analysis revealed an interaction between WM position and a left- and right hand response. More specifically, during the categorization task participants responded relatively faster with the left hand to initial WM items, while they became faster at responding with the right hand to WM items located further in the WM sequence, suggesting item information to be spatially organized within WM. Moreover, it was demonstrated that this observation occurred independent of the order instruction. These results indicate that spatial mapping also occurs in incidental conditions, when the participant is not intentionally focusing on the memorization of order.

A follow-up analysis clarifying the interaction by evaluating the linear relationship between hand response and WM position, confirmed this initial observation. A strong linear trend showed that initial WM items were associated with the left side of space, while end items of WM are represented at the right side of WM space. These findings demonstrate spontaneous order processing, which in addition is supported by the process of item binding to spatial position markers, as it generally occurs in the context of intentional order processing (De Belder, 2014; van Dijck et al., 2011).

Importantly, the development of strategic behavior on the experimental phase was limited by a very short practice phase and the absence of any additional experimental blocks. However, it was reasoned that our allegations concerning the absence of strategic behavior and automaticity of order coding processes would be stronger when additionally analyzing the practice phase. Analysis of the practice phase replicated the observations made in the experimental phase.

Even more, in order to further strengthen our claim we investigated whether the memorization of order is an early process. Two main concerns are proposed to emphasize the importance of this question. First, in order to perform the go/no-go categorization task and limit memory decay, the memorized sequence has to be continuously repeated within the mind. One could argue that the repetition of this sequence leads to the development of retrieval strategies. These strategies would then lead to the spatial coding of the memorized information. In other words, spatial mapping of the memorized information might not be an early process, but could be developed over the course of sequence maintenance as a result of strategic behavior. This indirectly relates to the second point; the go/no-go categorization task can be considered to be a relatively long retention interval preceding sequence recall. The continuous mental repetition of the WM sequence during maintenance could qualitatively change the representations for this sequence. More specifically, during the course of the maintenance of the WM sequence, memorized information could (partially) be transferred to long-term memory. Therefore, it would remain unknown whether the spatial organization of the WM sequence would occur in long-term memory rather than in WM. Therefore, in order to investigate whether spatial coding is an early and automatic process located in WM, we proposed that the effect of spatial position binding of item information would already be observed in the very first trial of the go/no-go categorization task. A simple analysis on the first trial of the practice phase was performed to investigate whether congruent trials (left-hand response to the first or second item of the WM sequence; right-hand response to the third or fourth item of the sequence) were responded to more quickly than to incongruent trials (left-hand response to the third or fourth item of the WM sequence; left-hand response to the first or second item of the sequence). Indeed, this is what we observed. Similarly, while the experiment of Guida, Leroux, Lavielle-Guida & Noël (2015) required the memorization of many WM sequences, in an order-instructed experiment they also reported memory specialization for every first trial conducted after sequence memorization. These observations demonstrate that a spatial memory trace for a memory sequence is not constructed during the maintenance and retrieval of item information, but that the construction of position markers occurs early on in the WM.

Previous studies already addressed the crucial involvement of space within WM and suggested the existence of a spatial coordinate WM system used to temporary store verbal serial information (Abrahamse et al., 2014; De Belder et al., 2015; van Dijck et al., 2013). The observation of the spontaneous tendency to store presented information in an orderly fashion, resulting in a strong spatial representation, serves as another support highlighting the crucial involvement of position markers and space in information encoding within WM.

Moreover, previous studies reported that in the context of incidental compared to intentional learning, the encoding of positional information only occurred in the intentional condition (Naveh-Benjamin, 1990; Tzeng, Lee & Wetzel, 1979; Zacks et al., 1984). These latter studies all argued that the encoding of serial order is part of a non-automatic process. In contrast, the currently reported findings do suggest the presence of an automated order coding process. A few methodological differences may underlie the inability of observing automatic order coding events in older studies; the main difference between the current study and the previously reported studies concerned the employment of longer to-be-memorized wordlists, greatly exceeding WM capacity (e.g., 20 items). Moreover, most older studies worked with considerably long interval delays (with distraction) before recall, leading to a significant fading of the ordered memory trace. Additionally, the design of the current study mainly hindered the development of adapted task-oriented strategies as participants were submitted to a single test trial.

In sum, the current study demonstrated that serial order processing within WM occurs in a spontaneous fashion. Moreover, incidental and deliberate order coding are both supported by spatial memory traces, resulting from item binding to spatially localized position markers in WM.

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CHAPTER 5

IMPAIRED PROCESSING OF SERIAL ORDER DETERMINES WORKING MEMORY IMPAIRMENTS IN ALZHEIMER'S DISEASE[1]

Background: Working memory (WM) problems are commonly observed in Alzheimer's disease, but the affected mechanisms leading to impaired WM are still insufficiently understood. The ability to efficiently process serial order in WM has been demonstrated to be fundamental to fluent daily life functioning. The decreased capability to mentally process serial position in WM has been put forward as underlying explanation for generally compromised WM performances.

Method: A group of Alzheimer's patients (n = 32) and their partners (n = 25), assigned to the control group, were submitted to an extensive battery of neuropsychological and experimental tasks, assessing general cognitive state and functioning of several aspects related to serial order WM.

Results: The results revealed an impaired ability to bind item information to serial position within WM in Alzheimer's patients compared to controls. It was additionally observed that Alzheimer's patients experienced specific difficulties with directing spatial attention when searching for item

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[1] De Belder, M., Santens, P., Sieben, A., & Fias, W. (submitted). Impaired processing of serial order determines working memory impairments in Alzheimer's disease. *Journal of Alzheimer's Disease*.

information stored in WM.

Conclusion: The processing of serial order and the allocation of attentional resources are both disrupted, explaining generally reduced WM functioning in Alzheimer's patients. Further studies should clarify whether this observation could explain disease-related problems for other cognitive functions such as verbal expression, auditory comprehension or planning.

INTRODUCTION

Alzheimer's disease (AD) is typically characterized by cognitive impairments, and particularly memory deficits. Difficulties with episodic memory appear to be more profound, but memory impairments also include compromised functioning of working memory (WM) and/or semantic memory (Baddeley, Logie, Bressi, Della Sala & Spinnler, 1986; Baddeley, Bressi, Della Sala, Logie & Spinler, 1991; Baudic et al., 2006; Hodges, Salmon & Butters, 1992; Miller, 1973; Perry, Watson & Hodges, 2000; Stopford, Thompson, Neary, Richardson & Snowden, 2012; Welsh, Butters, Hughes, Mohs & Heyman, 1991). Current treatments are limited to the deceleration of this degenerative disease to improve the quality of life of patients and their family. This requires early diagnosis and goal-directed treatment strategies, such as cognitive training (for a review see; Baddeley & Hitch, 1974). To make progress in the development of these methods, it is crucial to understand the mechanisms underlying the dysfunction not only of episodic memory, but also of WM.

One possible mechanism for a deficient WM in AD is that WM problems are related to the dysfunctional employment of executive control, steered by the central executive (Baddeley et al., 1986, 1991; Baudic et al., 2006). According to the classic model of Baddeley and Hitch (1974), WM can be dissociated in three components; the central executive and two slave-systems that serve to temporarily store domain-specific information (the phonological loop and the visuospatial sketchpath). The central executive is the attentional control center and is taken to be responsible for the allocation of attention resources to the phonological loop and the visuospatial sketchpath, and thus plays a crucial role in the division of labor between tasks (Baddeley et al., 1986, 1991). A first argument suggesting a declined functioning of the central executive in AD is provided by performances of AD patients in dual-task settings, where the attentional resources have to be divided between two demanding and simultaneous tasks. In comparison to a single-task setting, AD patients typically experience serious problems performing dual tasks, this being independent on task-difficulty (Baddeley et al., 1986, 1991). This disadvantage for dual-task settings is significantly less pronounced in healthy elderly (Baddeley et al., 1986, 1991). Second, AD patients generally perform worse on a variety of executive tasks (e.g., verbal fluency test, Wisconsin Card Sorting Test, the Modified Card Sorting Test, delayed alternation, trail making test) compared to controls, tasks that are often related to the functioning of the central executive component (Baudic et al., 2006, Bhutani, Montaldi, Brooks & McCulloch, 1992). Based on these observations, the central executive is designated to be the component of the WM system that is compromised in AD. However, this explanation has difficulty reconciling the fact that central executive functions are supported by frontal brain areas, while degenerative processes in the early-AD brain are typically observed within more posteriorly located regions, mainly temporoparietal regions (e.g., Stopford et al., 2012; Chase, Foster & Mansi, 1983; Burton, McKeith, Burn, Williams & O’Brien, 2004; Foster et al., 1983; Neary et al., 1987).

Moreover, an executive function account is not easily reconciled with the fact that WM deficits have also been reported in studies that focus on WM capacity as the critical reason for WM impairments in AD (Stopford et al., 2010, 2012). In a study of Stopford et al. (2012) patients with frontotemporal dementia were compared to patients suffering from Alzheimer’s disease in their performance on attentional, executive and WM tasks. Both patient groups expressed a different pattern of impaired performance on the variety of tasks. Patients suffering from frontotemporal dementia expressed clear difficulties on the attentional and executive tasks. AD patients performed worse on the WM tasks and expressed specific difficulties with short-term memory, as reflected in quick information overload and difficulty holding information in WM. Based on these observations, it has been argued that WM problems in AD can be assessed in terms of a reduced WM capacity (Stopford et al., 2010, 2012).

In sum, two different accounts have been put forward to approach WM impairments in patients with AD. On the one hand, AD patients are thought to suffer from impaired executive functioning, hindering the central executive to efficiently distribute targeted attentional resources within WM (Baddeley et al., 1986, 1991; Baudic et al., 2006). On the other hand, empirical findings also supported the simple notion of a reduced WM capacity (Stopford et al., 2012, 2012). The inability to keep a sufficient amount of information online in WM would suffice to hinder patients in everyday functioning. Currently there is no consensus as to which mechanisms are responsible for unsuccessful employment of WM in AD. However, in the next section we will propose and substantiate the idea that the ability to order information in WM might be the crucial component that could reconcile the seemingly opposing ideas of a malfunctioning central executive and of reduced WM capacity underlying WM problems in AD.

Importantly, almost anything we do in daily life requires the temporary (in WM) or permanent (in long-term memory) storage of serial information, as if it was only to memorize a grocery list, to perform a daily routine, to cook a recipe, to learn a new skill or to formulate sentences. The functioning of the central executive encompasses many attentional tasks, such as task switching, updating the WM content, inhibition of task-irrelevant information, strategy selection etc. Importantly, all of these tasks at least partially rely on the processing of serial order (Baddeley, 2000, 2003; Bull & Scerif, 2001; Burgess & Hitch, 1999; Logan & Gordon, 2001). Also WM capacity is generally measured and evaluated by means of tasks inherently containing a serial order component; forward and backward digit span tasks, complex span tasks… (Baddeley, 1992; Richardson, 2007; Wilhelm, Hildebrandt & Oberauer, 2013). The performance of the participant is evaluated based on the successful serially ordered recall of the items. When the participant recalls the correct items, but in incorrect order, it is generally concluded that the number of to-be-memorized items exceeded WM capacity (Baddeley, 1992; Richardson, 2007). While WM capacity has been demonstrated to correlate with other WM measures evaluating the construction, maintenance and updating of memory traces (Wilhelm, Hildebrandt & Oberauer, 2013), only span tasks have previously been used to compute the size of WM capacity. In other words, the methods used to assess WM capacity and central executive functioning contain a component of serial order. In other words, the question rises whether the impaired use and processing of serial order could be the common underlying cause of impaired WM functioning in AD, which is then reflected in the impaired functioning of the central executive and a reduced WM capacity.

When attempting to understand impaired WM functioning in AD, little research has been done attempting to combine the two seemingly diverging perspectives on WM problems. Lamar and colleagues (2007) are one of the few that reported order-specific WM problems. They implemented an extended version of a backward digit span task, requiring ordered item recall. They reported that the order-specific recall performances in AD patients negatively correlated with the global degree of white matter hyperintensities observed in the brain, while this correlation with white matter alterations was not observed for the AD patients' performance when recalling digits in any order. The difference between performances on serial order recall versus unordered item recall in AD emphasized that AD patients experienced more trouble with the ordered storage of item information compared to a non-ordered global memorization of the item itself. The discrepancy between the memory for item identity and memory for order information was the first important step towards the identification of the exact mechanism underlying WM problems. More specifically, previous studies already highlighted the fact that memory for order and item information is dissociable (for a review see Majerus, 2008; Majerus, Glaser, Van der Linden & Eliez, 2006; Marshuetz, 2005; for imaging studies see Henson, Burgess & Frith, 2000; Majerus, Poncelet, Elsen & Van der Linden, 2006; Marshuetz, Smith, Jonides, DeGutis & Chenevert, 2006; Zhang et al., 2004). In order to conclude that order processing in AD is affected, it is crucial that we can ascertain that poor performances are only the results of impaired order processes and not of a generally compromised memory trace.

In sum, previous studies suggest that WM problems in AD are generally a result of impaired functioning of the central executive (Baddeley et al., 1986, 1991; Baudic et al., 2006) or of a reduced WM capacity (Stopford et al., 2010, 2012). In the current study we propose that the processing of serial order might be the larger underlying problem causing WM malfunctioning. Only one study suggested a disadvantage for the memory of order compared to unordered item identity (Lamar et al., 2007). Therefore, in the current study we investigated the specificity of impairments observed in verbal and visuospatial serial WM, by administering an extensive battery consisting of a variety of WM tests on AD patients and their partners. We hypothesized that when comparing AD patients to their partners, the processing of order will be more strongly affected than the memory trace for identity. Furthermore, the findings of the various conducted tasks should clarify whether malfunctioning of the central executive and/or reduced WM capacity can be assigned to be the main explanation to WM problems in AD – or whether the affected processing of order could explain both accounts. Three types of digit span tasks were executed, requiring forward or backward recall of item sequences. It was expected that the control group would outperform AD patients on these tasks. However, in order to answer our research question concerning impaired order processing in AD, a more fine-grained order measure had to be derived from the performances on the span tasks. This order measure was designed to mainly reflect the participants' ability to efficiently process order while filtering out any effects due to generally worse performances. This order measure was then addressed to test the following hypothesis: if a reduced WM capacity would be the only problem underlying difficulties in recalling memorized items in patients, AD patients would demonstrate performances similar to the performances of the control group. However, if patients experience specific problems with the mental processing of order within WM, the loss of order representations will be more pronounced, while the mere representation of digits (in any order) would remain relatively preserved.

Standardized tests were implemented to assess the comparability between the AD patients and the control group (their partners). AD patients were hypothesized to perform worse on measures evaluating general cognitive functioning and a simple math task (containing a minor component of order processing), but had to perform equally well on tasks assessing frontal cognitive functioning and pre-morbid intelligence.

DATA COLLECTION

The study was approved by the ethical committee of the Faculty of Psychology and Educational Sciences of Ghent University and in agreement with the Declaration of Helsinki.

All participating patients were recruited from the memory consultation of University Hospital of Ghent. Patients were selected by clinical diagnosis. The diagnosis was made on the basis of a combination of results of the following measures: performance on the Mini Mental State Examination test, neurological examination, detailed neuropsychological testing, MRI of the brain displaying temporal atrophy and biomarker analysis in cerebrospinal fluid (presence of bèta amyloid and tau protein). Table 1 displays which measures were obtained for each patient contributing to the diagnosis of Alzheimer's dementia.

The control group was composed by the partners of AD patients willing to participate. Control participants had no history of severe psychiatric conditions, never suffered from any neurological condition, cardiovascular problems or diabetes. However, note that the final control group cannot be considered to be a 'normal healthy aging' group as partners of AD patients are known to be at risk for depression or anxiety disorders (Cooper, Katona, Orrell & Livingston, 2008; Mahoney, Regan, Katona & Livingston, 2005).

All participants provided written consent prior to participation.

The data of 32 AD patients (average age 74.35 years, SD = 9.85; 21 females) were collected. Of these patients, 25 of their partners were additionally tested as control participants (average age = 72.50, SD = 9.22;

13 females; see Table 2 for analysis on demographics). All participants were tested at home at a table. The administration of the full test battery took 60 to 95 minutes. In order to avoid the participant to suffer from exhaustion and information overload, the full battery was administered during two separate home visits and if necessary, additional pauses in between the tests were implemented. Incomplete data collection occurred for the majority of the patients for various reasons like task complexity, fear for computerized tasks, time constraints, no re-test possibility, condition of the patient during the testing.

AD patient n°	Available score on Mini Mental State Examination	Neuroimaging	Neuropsychological Assessment Battery	Presence of familial history of AD	Biomarker analysis in cerebrospinal fluid
1	24/30	CT			
2	22/30		x	x	
3	23/30	MR			
4	24/30		x		
5	23/30		x	x	
6		PET	x		x
7	24/30				
8	23/30	MR			
9			x	x	
10	21/30	SPECT, MR	x		x
11	23/30	MR	x	x	x
12	14/30		x		
13	28/30		x		
14	23/30	MR	x		
15	17/30				x
16			x	x	
17	19/30			x	
18	18/30		x		
19	28/30	PET, MR	x		x
20	22/30	MR	x		
21	25/30	MR	x	x	
22	25/30	MR			x
23	23/30		x		
24	22/30	MR			
25	23/30		x	x	
26		MR	x		x

27		CT	x		
28			x		x
29	24/30		x		
30	25/30	PET			
31	24/30		x		
32	24/30		x		

Table 1. The table displays all the types of information collected for each AD patient that contributed to the diagnosis of Alzheimer's disease. The reported score on the Mini Mental State Examination reflects the score of the AD patient achieving during the most recent visit of the patient to the hospital prior to research participation. 'X's mark the availability of information provided by detailed neuropsychological assessment, known familial history in AD disease and/or the execution of biomarker analysis on cerebrospinal fluid.

		AD patients	Control group
Age	average	74.37	52.00
	t	.38	
	p	.71	
	n	32	25
Gender	% females	65.62	72.50
	t	1.16	
	p	.26	
	n	32	25
School leaving age	average	19.03	18.92
	t	.44	
	p	.67	
	n	32	25

Table 2. Data displaying the demographic variables for the AD patients and control group. Results of paired t-tests are reported, indicating the absence of any group differences on following variables; average age at testing, proportion of female/male participants in each group, the average each of leaving school.

METHOD

Neuropsychological tests

Several standardized neuropsychological tests were used to assess the level of functionality of specific psychological functions. Overall cognitive performance, the integrity of frontal lobe functionality, pre-morbid intelligence and math ability were tested. Analysis should reveal to what extent AD patients' performances differed from the controls.

Montreal Cognitive Assessment (MoCA)

A brief cognitive screening test evaluating the general cognitive status and severity of cognitive decline (Nassreddine et al., 2005).

Frontal Assessment Battery (FAB)

A short screening test to assess frontal dysfunction and meant to serve differential diagnosis of frontotemporal dementia. The test measures different aspects of frontal lobe functions in 6 subtests. These subtests cover conceptualisation, fluency, sequential movements, opposing movements, a go/no-go paradigm and utilisation (van Loo, Wiebrands, van Laar, 2007).

The Dutch Reading Test for Adults (or Nederlandse Leestest voor Volwassenen; NLV)

This test consists of a 50-item list of Dutch words that are derived from foreign languages (English and French). The participant's pronunciation of the words is scored and used as a measure of pre-morbid intelligence level. This task is often used to assess pre-morbid intelligence as it has been shown to highly correlate with verbal intelligence and has demonstrated to be relatively insensitive to cerebral damage (Schmand, Lindeboom & Van Harskamp, 1992).

Math task

A simple paper and pencil test consisting of 32 items; 8 summations, 8 subtractions, 8 divisions and 8 multiplications, each printed in a separate column, with an integer as outcome. This brief test was used to assess remaining math ability in patients and order processing for a simply daily task.

Experimental tasks

A variety of experimental tasks were designed with the aim to evaluate various aspects of WM functioning and serial order coding in the participants. Along with the described experimental tasks, participants also performed a magnitude task (Dehaene, Bossini & Giraux, 1993; ca. 10 min), a number interval bisection task (Zorzi, Priftis & Umiltà, 1993; ca. 7-10 min) and line bisection task (van Dijck, Gevers, Lafosse, Doricchi & Fias, 2011; ca. 2-3 min). These data were collected with respect to a different research question and are therefore not further discussed within this paper.

Long forward digit span

WM was assessed using a long forward digit task. Compared to the standardised digit span task, requiring the completion of 3 trials per span length, the current task consists of five more trials for each span length and does not employ a discontinuation rule, hence the ‘long’ digit span task. The experimenter read out a series of numbers at a rate of 1 digit per second. The participant was instructed to immediately verbally recall the numbers in correct order. The task was constructed in such a way that 8 trials of 3-, 4-, 5- and 6-digit span lengths had to be performed, for a total of 32 trials. All 4-

and 5-span trials were constructed according to a selection procedure proposed by Lamar et al. (2007).

The following dependent variables were collected for this task:

(1) Accuracy score for *serial order* – This score reflected the amount of correctly recalled numbers in their correct serial position, divided by the total possible recalled digits for each span length (e.g., from the original sequence "5942" the participant recalled "52". Only one item is recalled in the correct position, i.e., "5", the accuracy score for this sequence is thus 1 divided by 4, the original sequence length, i.e., 25%). These accuracy scores were calculated separately for each span length.

(2) Accuracy score for *any order* – This score reflected the amount of correctly recalled numbers of the sequence, independent of the correct recall position, divided by the total possible recalled digits for each span length. (e.g., in line with the previous example; if the participant recalled "52", he now received an accuracy score of (2/4)x100 = 50% on the *any order* measure). These accuracy scores were calculated separately for each span length.

(3) The *order ratio* - This order measure was used to measure to what extent memory for order was lost compared to the general (non-ordered) memory trace. The *order ratio* simply consisted of the ratio *serial order/any order.* Crucially, this order measure preserved the difference between the two measures, i.e., the processing of order, but filtered out other effects, e.g., resulting from overall bad performance. For example, imagine a patient would achieve a very low accuracy score of 20% on the *serial order* measure and 25% on

the *any order* measure, while a control subject achieved a score of 80% on the *serial order* measure and 100% on the *any order* measure. It is clear that we would conclude that the patient's memory for order is inferior compared to that of the control. However, taking into account the amount of items that were correctly remembered, we would conclude on the basis of the *order ratio* that the processing of order reached the same level in both participants: 20/25 is equal to 80/100.

(4) Working memory capacity – WM capacity was determined by evaluating accuracy scores on the *serial order* measure. WM capacity was determined by the largest span length with a >80% accuracy score. On average this means that the participant was allowed to incorrectly recall more than 1 but less than 2 out of the eight trials. As the task was quite demanding in terms of sustained attention, implementing this small buffer would allow for mistakes circumventing errors made due to fatigue.

(5) Error types – Similar to the analyses performed by Lamar & Price (2007) four types of errors were calculated; capture errors, transposition errors, perseverations and intrusion errors. Capture errors reflected the sum of two types of errors; 'within trial capture errors' and 'between trial capture errors'. 'Within trial capture errors' were recorded on 4-, 5- and 6- digit span trials when participants grouped numbers to create a contiguous series of numbers e.g., '361729' – recall of '612379'. 'Between trial capture errors' were coded on 3-, 4-, 5- and 6- digit span trials, when participants inserted a number from the previous trial creating a contiguous series of numbers, e.g., '5196' – recall of '5126'.

Transposition errors occurred when the participant misplaced a recalled number in the sequence, without creating a contiguous series of numbers, e.g., ‘8492’ – recall of ‘8294’. Perseveration errors were made when the participant recalled a specific number more than once during a single trial, e.g., ‘482’ – recall of ‘484’. Intrusion errors were made when the participant reported a digit that was not part of the current trial or the previous trial.

Long backward digit span

This task was designed and administered in the same fashion as the forward digit span. Participants were now instructed to recall the verbally presented sequences in backward order. The backward digit span task consisted of different sequences than the forward digit span task. The same five measures were collected as in the forward digit span task, but now assessing correct backward ordered recall.

Corsi block task

The Corsi block task assessed visuospatial WM. This task is very similar to the forward digit span task, but now participants had to recall the position of visuospatially presented blocks on a screen.

The task was administered on a 12” touch-screen of a convertible Acer laptop. The screen was put in a position of thirty degrees relative to the table. Nine grey 2x2 cm squares were presented against a white background at fixed positions. At a 1 square/second rate one of these squares lighted up in black. After 1 second, this square turned back to grey, with the next square turning black. Participants were instructed to memorise the correct order in which these squares turned black. After the presentation of the last black square, all squares turned back to grey and two black lines were displayed on the left and right side of the screen. The two black lines indicated that the participant could initiate full recall. At this point the participant was asked to indicate the correct order in which the grey blocks had turned black, by pressing with their finger on the correct squares. The experimenter manually initiated the next trial when the participant indicated to be ready. Series of 3 trials of 3-, 4-, 5- and 6-digit span lengths had to be performed. Block positions could not be repeated within a single sequence. Every participant had to complete all twelve trials. A short practice phase was implemented before the start of the actual experiment, presenting an example of a single trial of a 3-block span length.

For this task, the same measures were calculated as for the forward span task, except for the evaluation of error scores. Moreover, scores were now calculated for three trials per span length (instead of eight).

Verbal working memory position task

This WM task assessed position-specific problems located in WM representations and was based on the paradigm described by van Dijck, Gevers, Lafosse, Doricchi & Fias (2011). A full trial proceeded as follows: the experimenter read out a series of letters, which had to be memorised in correct order by the participant. Finishing the sequence, the experimenter queried the participant's memory for a specific position by posing a question in following format: "What was the second letter?". The verbal response of the participants was then recorded by the experimenter before reading the next to-be-memorised letter sequence.

Before the start of the experimental trials, the number of letters to-be-memorised by the participant was determined by a preceding practice phase using a step-by-step selection procedure. At the beginning of the practice phase, three trials of three letters had to be completed by the participant. If the participant made no errors on any of these trials, the next sequence length was assessed by means of three trials (i.e., 4 letters to-be-memorised). The sequence increased in length until the participant reached a sequence length where he made one or two errors out of the three trials. Only if the participant made an error during the first or second trial of the three-letter trial, a practice phase for two-digit length trials was initiated. If one or two errors were made on the three trials of the two-letter sequences, this digit span length was selected for the experimental task. If the participant responded correctly to all three test items of the two-letter sequences, the participant's understanding of the task was reassessed and the three trials of the three-digit length were repeated.

During the experimental task all positions of the letter sequences were queried equally often. All positions were tested 8 times for the 2-, 3-, 4- and 5-digit length sequences (i.e., resulting in a total of 16, 24, 32 and 40 trials for each digit span length respectively). If a participant was assigned to perform the task on a 6-digit sequence length, each position was queried 7 times, in case of a 7-digit sequence length only 6 times. This latter adjustment was necessary to limit the duration of the task and effects of exhaustion.

The following dependent variables were collected for the verbal WM position task:

(1) Accuracy scores – For each participant the percentage of correctly completed trials was calculated. Data for this simple measure were collected to assure that performances of AD patients equalled performances of the control group, showing that the appropriate sequence length was selected for each participant.

(2) Error types – Three types of errors were evaluated; distance errors, intrusion errors and no-response errors. Of all incorrectly completed trials the percentage of occurrence of each type of error was calculated. Responses were categorised to be a 'distance error' if the participant recalled a letter that was part of the memorised sequence, but which was not the correct answer. Intrusion errors reflected the recall of a letter by the participant that was not part of the memorised sequence. If the participant did not provide a response to a specific trial, this trial was categorised as a 'no-response' error. Note that distance errors reflect mistakes made to the recall of serial order. Performance patterns related to this type of error are further investigated by means of 'distance scores'.

(3) Distance scores – Distance scores were computed by calculating the distance from the recalled letter to the position of the correct letter. If the recalled number was positioned before the correct position, negative distances were counted; if the recalled letter was located further in the sequence than the correct position, positive distances were counted. Because each digit span length allowed for different possible deviation distances from the correct answer, the actual number of positions between the recalled position and correct answer was then divided by the maximum distance length for that particular digit span length. For example, the participant is asked to

recall the fourth letter of the presented series “BCDFG”, but answers with “C”. The distance of C from the correct answer (F) is -2, which is then divided by 4 (5-1). The averaged distance score was calculated to investigate whether participants deviated to the beginning or the end of the WM sequence when recalling an incorrect letter. The standard deviation provided an indication of incorrectly recalled letters being located closer or further away from the correct answer. For all participants the averaged distance score and the standard deviation were calculated and submitted to a paired t-test, comparing performances between the control group and AD patients.

RESULTS

Neuropsychological tests

For the MoCA test, which assesses general cognitive functioning, AD patients had an average score of 17.07, while their partners scored significantly higher, with an average score of 25.90 (Table 3). The cut-off score for normal cognitive functioning is 26 or higher, while a score of 22 to 25 would indicate mild cognitive impairment (Nasreddine et al., 2005). The average score for the control group equalled the cut-off score for healthy functioning, indicating that this group might already experience some cognitive decline. The large difference in MoCA-scores between the two groups validated further comparison of the AD patients to the control group; diagnosed patients clearly exhibited stronger cognitive decline compared to the control group.

Scores on the FAB did not differ between both groups, indicating that there are no group differences in terms of frontal (dys)function (Table 3).

Pre-morbid IQ was determined using the NLV task, for which no significant difference was observed between the two groups (Table 3)

Lastly, general remaining math ability was assessed using a simple math task. Patients made significantly more errors than controls (Table 3).

In sum, the MoCA test demonstrated the two groups to be significantly different from each other in terms of cognitive functioning, a crucial indicator for MCI or AD, and in terms of preserved math and order processing in a simple math task. Important for the interpretation of further results, both groups were comparable in terms of frontal functioning and pre-morbid intelligence level.

		AD patients	Control group
MoCA	average	17.07	25.90
	SD	4.58	2.83
	t	7.18	
	p	<.001	
	n	31	21
FAB	average	14.77	17.22
	SD	8.36	1.11
	t	1.94	
	p	.08	
	n	18	18
NLV	average	42.02	43.38
	SD	8.26	8.08
	t	.42	
	p	.68	
	n	26	21
Math task	average # errors	5.25	1.29
	SD	7.02	2.40
	t	2.63	
	p	.03	
	n	28	24

Table 3. Data of the neuropsychological tasks, performance scores, statistical results of paired t-tests and sample sizes are reported for Alzheimer's patients and control participants separately.

Long forward digit span task

27 AD patients and 24 controls successfully completed the forward digit span task.

First, differences in the size of the WM capacity between AD patients and the control group were assessed. On average, the patient group had a WM capacity allowing for the storage of 4.41 (SD = .84) elements. The control group had a WM capacity of 4.79 (SD = .78), which was not significantly different from the patients WM capacity [t(23) = 1.75, *p* = .10].

A repeated measures analysis was executed to investigate whether the AD patient group made different types of errors compared to the control group. The execution of a repeated measures ANOVA demonstrated that AD patients and the control group made the same type of errors [F(3,21) = .86, *p* = .11, ηp2 = .11]. In proportion to all errors made, transposition errors represented 82.55% (SD = .07) of all errors, capture errors were made in 11.37% (SD = .10) of the cases, 2.09% (SD = .03) were perseveration errors and 3.99% (SD = .08) were intrusion errors.

A repeated measures on span length (3, 4, 5 or 6) and between-subjects factor group (AD patient or control) ANOVA was conducted for *serial order* and *any order*, followed by the same analysis for the *order ratio*.

For *serial order*, a main effect of group was observed [F(1,49) = 7.01, *p* = .01, ηp2 = .13], indicating an overall worse performance for AD patients (accuracy scores: AD patients = 75.62%, SD = .14; controls = 83.61%, SD = .08). Also a main effect of span length was observed [F(1,49) = 218.94, *p* < .001, ηp2 = .82], reflecting decreasing accuracy scores with increasing span length for both groups (accuracy scores for digit spans of 3, 4, 5 or 6 digits respectively; 99.08%, SD = .03; 93.75%, SD = .12, 72.89%, SD = .19; 52.11%, SD = .24). The interaction between group and span length was significant [F(1,49) = 4.87, *p* = .03, ηp2 = .30], demonstrating that patient performance on the recall of order declined more strongly compared to controls as a function of digit span length (Figure 1A). Patients' serial order accuracy scores for span lengths of 3, 4, 5 and 6 digits spans were respectively 98.30% (SD = .04), 91.26% (SD = .16), 68.32% (SD = .21) and 44.81% (SD = .25). For controls the accuracy scores for *serial order* were the following: 100% (SD = 0.00), 96.29% (SD = .05), 77.22% (SD = .16) and 60.92% (SD = .21).

The analysis of the *any order* accuracy scores showed a main effect of group [F(1,49) = 4.80, *p* = .03, ηp2 = .09] and of digit span [F(1,49) = 93.81, *p* < .001, ηp2 = .66]. The more items to be recalled, the worse the performance was on the task. Again, an interaction between group and digit span length was observed [F(1,49) = 6.09, *p* = .02, ηp2 = .11, Figure 1B].

A repeated measures ANOVA on digit span length and between-subjects factor group was performed using the *order ratio* (accuracy *serial order* / accuracy *any order*). The results showed a main effect of group [F(1,49) = 5.411, *p* = .02, ηp2 = .10], demonstrating a lower *order ratio* of .82 (SD = .23) for patients, compared to the control group with a ratio of .88 (SD = .17). This main effect indicated that the specific memory for order is worse in AD patients compared to controls. There was also a main effect of digit span length [F(1,49) = 143.06, *p* < .001, ηp2 = .75], with scores on the *order ratio* of 1.00 (SD = .02), .96 (SD = .09), .82 (SD = .16) and .62 (SD = .23), for digit span lengths of 3, 4, 5 and 6 respectively. The interaction observed for group and digit span length displayed a trend towards increasing group differences with increasing span length [F(1,49) = 3.36, *p* = .07, ηp2 = .06; Figure 1C].

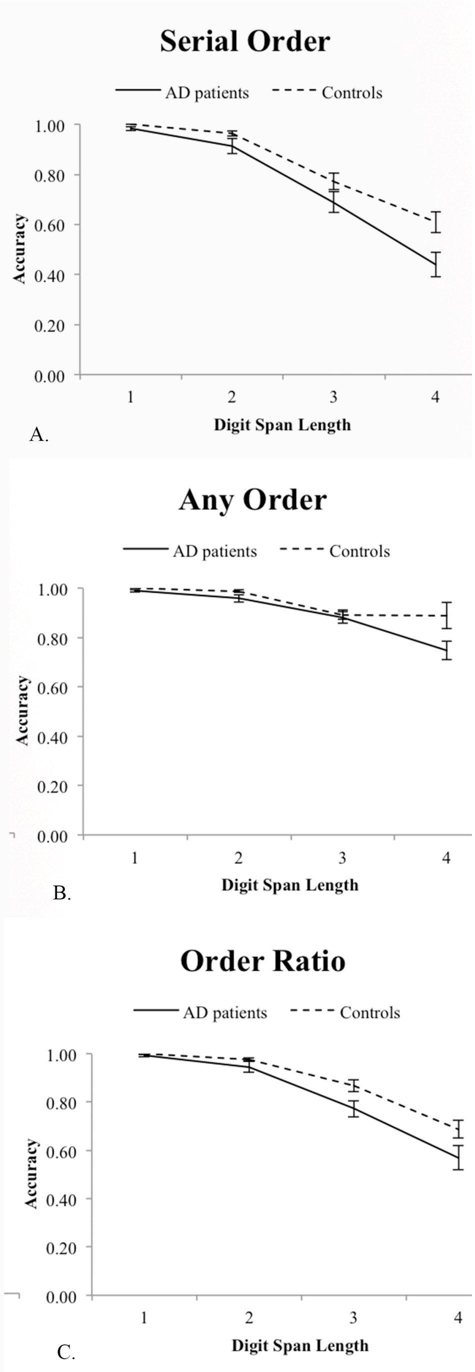

Figure 1. Visualization of accuracy scores on the forward digit span task, depending on the performed digit span length. A. Accuracy scores on the 'serial order' measure. B. Accuracy scores on the 'any order' measure. C. Scores on the 'order ratio', reflecting the accuracy scores for 'serial order' divided by 'any order'.

Long backward digit span task

Of all patients, 29 performed the long backward digit span task, along with 24 controls.

We first assessed differences in the size of the WM capacity between AD patients and the control. On average, the patient group had a WM capacity allowing for the storage of 3.12 (SD = .65) elements. The control group had a WM capacity of 3.75 (SD = .99), which was significantly different from the patients WM capacity [t(21) = 2.34, *p* = .04].

A repeated measures analysis was executed to investigate whether the AD patient group made different types of errors compared to the control group. The execution of a repeated measures ANOVA demonstrated that AD patients and the control group make the same type of errors [F(3,21) = 1.83, *p* = .17, ηp2 = .21]. In proportion to all errors made, transposition errors represented 81.90% (SD = .08) of all errors, capture errors were made in 9.31% (SD = .08) of the trials, 2.74% (SD = .05) were perseveration errors and 6.05% (SD = .11) were intrusion errors.

The same measures as in the forward digit span task were collected: accuracy on *serial order* and *any order*, the *order ratio* and *WM span*. A repeated measures ANOVA for *serial order* was performed with digit span as a within-subjects factor (4 lengths) and group as between-subjects factor. Analyses revealed a main effect of group [F(1,51) = 10.61, *p* = .002, ηp2 = .17], with lower accuracy scores for the patient group (accuracy *serial order* = 52.97%, SD = .17), compared to the control group (accuracy *serial order* = 68.21%, SD = .15). Also a main effect of digit span length was observed

[F(1,51) = 253.03, *p* < .001, ηp2 = .83], with decreasing accuracy scores for increasing digit span lengths of 83.09% (SD = .21), 61.82% (SD = .25), 48.29% (SD = .20) and 42.17% (SD = .20), for the span lengths of 3, 4, 5 and 6 digits respectively. No interaction was observed [F(1,51) = 2.67, *p* = .11, ηp2 = .05; Figure 2A].

Analyses for the *any order* measure revealed a main effect of group [F(1,51) = 8.53, *p* = .005, ηp2 = .14], with an accuracy score on *any order* of 79.01% (SD = .09) and 88.95% (SD = .06) for patients and controls respectively. A main effect of digit span length was also observed [F(1,51) = 80.07, *p* < .001, ηp2 = .61], with accuracy scores of 97.38% (SD = .05), 87.81% (SD = .12), 76.00% (SD = .15) and 71.46% (SD = .17) for all four digit span lengths respectively. Furthermore, no interaction was observed [F(1,51) = 1.77, *p* = .17, ηp2 = .10; Figure 2B].

The analysis of *order ratio* revealed a main effect of group [F(1,51) = 8.69, *p* = .005, ηp2 = .15], with a ratio of .63 (SD = .30) for patients, and .76 (SD = .22) for controls. In accordance to observations made for the forward digit span task, these results indicated a deterioration of order representational memory traces in patients compared to the controls. A main effect of digit span length was also observed [F(1,51) = 107.25, *p* < .001, ηp2 = .68], with decreasing *order ratios* for increasing digit span lengths of .85 (SD = .19), .69 (SD = .24), .58 (SD = .24) and .48 (SD = .28) for digits spans of 3, 4, 5 and 6 respectively. Also an interaction was observed [F(1,51) = 4.23, *p* = .04, ηp2 = .08; Figure 2C]. Not only were patients worse at processing order than controls, the deterioration of order processing was proportionally much stronger than in controls when WM became increasingly loaded. Patients displayed an *order ratio* of .83 (SD = .22), .61

(SD = .26), .55 (SD = .25) and .49 (SD = .30) for span lengths of 3, 4, 5 and 6 digits respectively. The ratios for the control group were the following: .88 (SD = .16), .79 (SD = .18), .70 (SD = .21) and .61 (SD = .21).

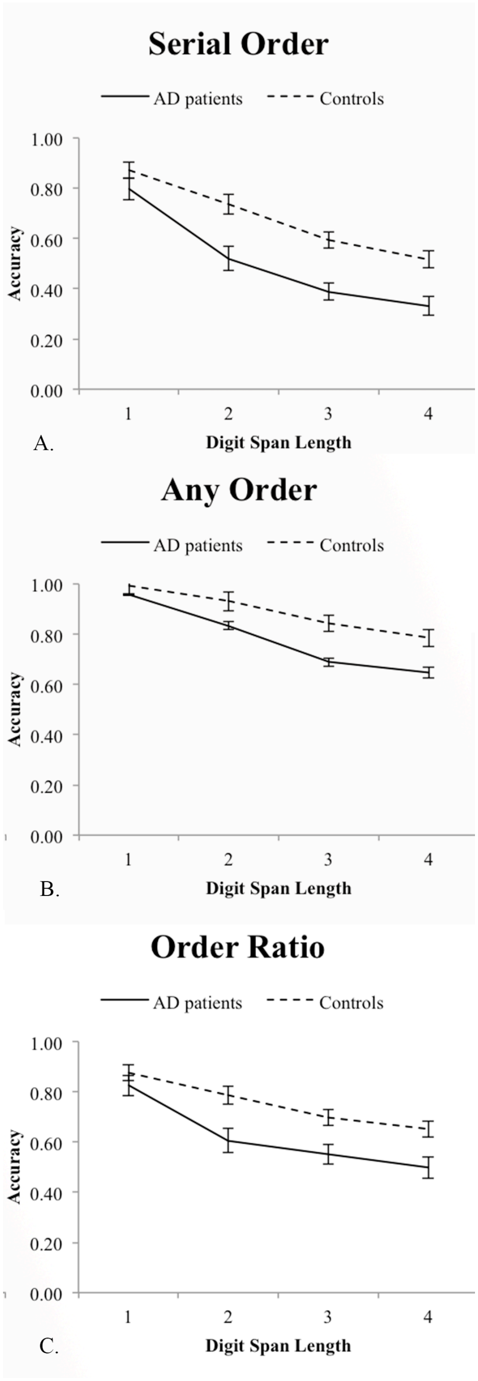

Figure 2. Visualization of accuracy scores on the backward digit span task, depending on the performed digit span length. A. Accuracy scores on the ‘serial order’ measure. B. Accuracy scores on the ‘any order’ measure. C. Scores on the ‘order ratio’, reflecting the accuracy scores for ‘serial order’ divided by ‘any order’.

Corsi block test

This computerized visuospatial WM test was completed by 21 AD patients and 18 controls.

First, visuospatial WM capacity was computed for each subject. As only three trials per digit span size had to be completed, visuospatial WM capacity was assigned to the last digit span size for which a 100% performance was observed on all three trials. The average visuospatial WM span for patients resulted in the average storage of 2.91 (SD = .53) spatial items, while healthy controls were able to memorize about 3.89 (SD = .83) items [t(17) = 3.92, *p* = .001].

A repeated measures ANOVA was performed on block span length (memorization of 3, 4, 5 or 6 block positions), with group as between subject factor on *serial order*. The analyses revealed a main effect of group [F(1,35) = 26.77, *p* < .001, ηp2 = .43], indicating a general worse performance for AD patients (accuracy *serial order* = 58.34%, SD = .22) compared to controls (accuracy *serial order* = 81.51%, SD = .14). Also a main effect of block span length was observed [F(1,35) = 149.64, *p* < .001, ηp2 = .81], as well as an interaction between group and block span length [F(1,35) = 4.75, *p* = .04, ηp2 = .12; Figure 3A]. Performance decreased with increasing block span length, but the AD patient's decline with increasing block length was much more expressed than for the control group. Accuracy scores on *serial order* for the AD patient group were 80.05% (SD = .26), 66.67% (SD = .19), 52.00% (SD = .22) and 34.65% (SD = .20), respectively for block span size of 3, 4, 5 and 6 elements. For the control group these accuracy scores were 94.44% (SD = 11.59), 94.44% (SD = .09), 76.67% (SD = .17) and 60.49% (SD = .17).

The same analysis for the *any order* measure revealed a main effect of group [F(1,35) = 24.52, *p* < .001, ηp2 = .41] and main effect of block span size [F(1,35) = 48.43, *p* < .001, ηp2 = .58], but no interaction [F(1,35) = .78, *p* = .38, ηp2 = .02; Figure 3B]. The main effect of group again indicated a worse performance for AD patients (83.81%, SD = .14) compared to controls (94.45%, SD = .06).

Analysis of the *order ratio* also demonstrated a main effect of group [F(1,35) = 16.46, *p* < .001, ηp2 = .32], showing a lower score on the measure for AD patients (*order ratio* = .69, SD = .27) than for controls (*order ratio* = .86, SD = .17). Again, a main effect of block span length [F(1,35) = 102.60, *p* < .001, ηp2 = .75] and interaction [F(1,35) = 6.67, *p* = .01, ηp2 = .16; Figure 3C] were observed. The *order ratio* scores for the AD patient group for the digit spans of 3, 4, 5 and 6 blocks respectively were .93 (SD = .15), .75 (SD = .20), .59 (SD = .23) and .46 (SD = .25). For the control group these *order ratio* scores were respectively .96 (SD = .10), .96 (SD = .08), .82 (SD = .16) and .69 (SD = .15). The larger the to-be-recalled block span was, the worse both groups became at accurately recalling order relative to the recall of specific block items. Performance on order recollection decreased even more strongly in AD patients compared to controls, indicating the quick and specific loss of supportive order representations.

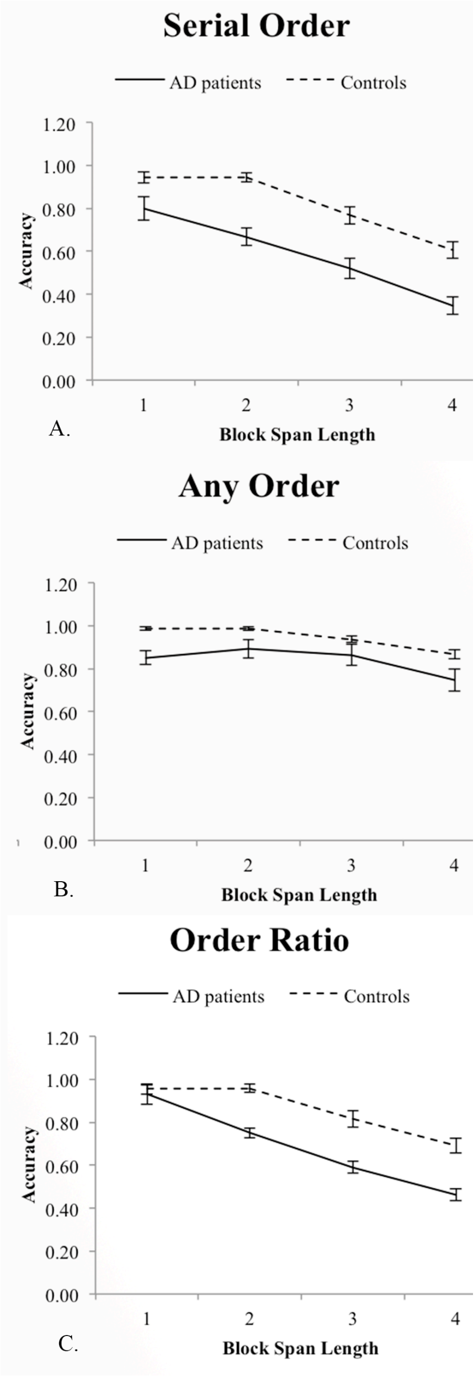

Figure 3. Visualization of accuracy scores on the Corsi block task, depending on the performed digit span length. A. Accuracy scores on the ‘serial order’ measure. B. Accuracy scores on the ‘any order’ measure. C. Scores on the ‘order ratio’, reflecting the accuracy scores for ‘serial order’ divided by ‘any order’.

Verbal working memory position task

The verbal WM position task was successfully completed by 30 patients and 25 controls.

This task was meant to investigate the role of directed positional search of information stored within WM. For each participant an adjusted digit span length was selected, in such a way that the to-be-memorized information did not exceed the participants' WM capacity. On average, patients reached a digit span length level of 4.20 (SD = .76) elements, while controls had an average digit span length of 5.02 elements [SD = .77; t(25) = 4.87, *p* < .001]. Importantly, patients and controls made the same amount of errors for their selected digit span length [t(25) = .30, *p* = .77], making further analysis of performances between the groups comparable. The average accuracy score for the AD patient group was 69.92% (SD = .15), for controls an average accuracy score of 68.45% (SD = .10) was reported. Three types of errors were reported: distance errors, intrusion errors and no-response errors. A repeated measures ANOVA demonstrated that patients and controls made equally often the same types of errors [F(2,22) = 1.39, *p* = .27]. On average, participants made 17.28% (SD = .10) distance errors, 8.57% (SD = .06) intrusion errors and 5.02% (SD = .06) no-response errors.

For further analyses, paired t-test was performed to investigate the effect of group on the averaged distance scores. The results for the averaged difference scores revealed no effect of group [t(24) = .49, *p* = .63], with an average distance score of -.07 (SD = .30) for patients and -.11 (SD = 20) for controls.

Next, we investigated the consistency of the averaged deviation scores in AD patients and controls. First, a paired t-test was performed in order to assess a left- or rightsided mental deviation. Indeed, on average participants tended to report more earlier WM items, located before the position of the correct letter [t(54) = 2.10, p = .04], with a average difference score of -.07 (SD = .26). Second, analyses of the averaged standard deviations observed for the distance scores demonstrated a significant difference between both groups [t(24) = 2.46, p = .02], with a standard deviation of .50 for the AD patient group and .37 of the control group.

DISCUSSION

This study was designed to shed a light on the mechanisms underlying WM deficits observed in AD patients. A wide variety of tests was conducted to investigate (1) the role of an affected central executive attentional system or reduced WM capacity in impaired WM functioning and (2) to what extent impaired order processing could be the underlying process explaining impairments in the functioning of the central executive/WM capacity.

First, it appeared that the simple reduction of WM capacity as a consequence of AD did not demonstrate to be the core problem located within the WM system, but that the central executive fundamentally contributes to the capacity limit of WM. The WM capacity, as determined by the long forward digit span task, was equal for AD patients and the control group. Interestingly, a reduced WM capacity in AD patients was observed once additional WM operations were required, i.e. during the backward digit span task. Furthermore, a similar observation was made for the verbal WM position task, where an adjusted digit span length was selected for each participant. The selected digit span lengths for AD patients were smaller than for the control group. As the verbal WM position task specifically relied on the allocation of attention to search through WM, one might argue that the hindered allocation of additional cognitive resources led to a reduced WM capacity. Overall, these findings suggest an intact WM capacity in a non-demanding task setting. However, the increase of cognitive load requires the recruitment of additional (attentional) resources, resulting in a reduction of WM span. In other words, these findings indicate that WM capacity and the central executive are functions that are at least partially dependent on each other. More specifically, their interdependency is observed in the fact that a reduced WM capacity is associated with the employment of additional cognitive resources by the central executive (e.g., by performing transformational processes or direct internal attention within WM).

Second, and crucially, compromised order processing marks the functioning of the WM system in AD patients. The *serial order* measure and *order ratio* of the forward and backward digit span tasks demonstrated that AD patients' order performances were worse than those of controls. The order ratio specifically demonstrated that the impairment observed for the processing of order was not in proportion to the ability to store a general (non-orderly) memory trace of digits within WM. These tasks show that in AD patients memory for item order is proportionally more impaired than memory for item identity, especially when WM load increases. Moreover, it was observed that AD patients and controls make the same type of errors. This observation suggests that differences in performances between AD patients and controls are indeed driven by differences in order processing, and not by other problems, such as difficulties with disengaging from automatic and procedural memories (Lamar et al., 2007; Stuss, Shallice, Alexander & Picton, 1995).

Third, and importantly, not only do AD patients experience trouble with the processing of order, they clearly express difficulties with directing their attention in a goal-directed way to a specific position in the working memory sequence. When AD patients had to recall the item at a cued location in the sequence, they demonstrated larger deviations with respect to the position of the correct answer compared to controls.

Interestingly, serial order problems were not restricted to the verbal domain but also affected visuospatial material. A reduced WM capacity was assessed using the Corsi block task. Results of the forward and backward digit span task clearly indicated problems with the successful serial processing of information within WM, an observation that was replicated in the Corsi block test. Not only were AD patients worse at the recall of order information, memory for order suffered more strongly than the general memory trace for the visuospatial stimuli, as observed in smaller order ratios for AD patients compared to control subjects. Moreover, the deterioration of these order representations increased when WM load was increased.

Importantly, note that all observations were made based on the comparison of performances between AD patients and their partners, serving as control group. While screening the medical history of the partners didn't reveal any pronounced neurological deficits, partners still represent a particular group that cannot simply be approached as a normal ageing and healthy group. It has repeatedly been shown that partners of AD patients are known to be at higher risk for depression or anxiety disorders (Cooper et al., 2008; Mahoney et al., 2005). Also, the average MoCA score of 25.90 in AD patients' partners indicate that we are not dealing with an entirely healthy group (cut-off for healthy functioning is 26/30). Therefore, it could be the case that the control group of this study already experienced initial stages of cognitive decline. In other words, the group of AD patients and the control group are not necessarily as different as would be the case when comparing to a healthy aging control group. Nevertheless, the study managed to capture compelling differences between the two groups.

A topic that should be addressed in future research starts from the following observation: a better integrity and level of functioning of WM processes is often associated with the observation of slower functional decline in AD patients (Pillai, Bonner-Jackson, Walker, Mourany & Cummings, 2014). Cognitive training is regularly used to stimulate the development of restorative or compensatory strategies by AD patients, a method that has been shown to be effective for many, but not all, patients (Bahar-Fuchs, Clare & Woods, 2013; Ball et al., 2002; for a review see; Sitzer, Twamley & Jeste, 2006). In light of these observations, combined with the results of the current study, the effectiveness of cognitive training, focusing on order-specific processing problems and the directing of internal attention, should be addressed as a possible avenue in the development of cognitive training programs.

Based on the findings of the current study, we should be aware of the overarching impact of impaired order processing on other cognitive functions. For example, AD patients are also known to express reduced language functioning, a cognitive ability that crucially relies on the serial organization of informative components. It has previously been shown that AD patients experience trouble with verbal expression and auditory comprehension, reading and writing (Murdoch, Chenery, Wilks & Boyle, 1987). Moreover, when describing a target picture, AD patients needed more words to communicate a similar amount of information compared to controls (Smith, Murdoch & Chenery, 1989) and expressed difficulties in the processing of syntactic complexities (Emery, 1999, 2000), issues that all might reflect difficulties with the organization of information within WM. Indeed, previous studies investigated the link between WM and language impairments in AD (MacDonald, Almor, Henderson, Kempler & Andersen, 2001). However, the explanation for the observed link between the two has been hindered by a lack of clarity concerning the underlying affected WM mechanisms. Therefore, insights provided by the present study might be implemented to investigate their immediate effect on other impaired cognitive domains, such as language processing. Moreover, if the processing of serial order turns out be a determinant of the integrity of other cognitive functions, research should investigate whether the assessment of order processing could facility early AD diagnosis or serve as a predictor for future cognitive decline in healthy people of patients diagnosed with mild cognitive impairment.

In sum, the current study clarified the mechanisms that underlie deficient WM functioning in AD patients. It is concluded that the reduced size of WM capacity in AD patients is not the core problem, but that the functioning of the central executive plays a more important role in WM problems. Observations of reduced WM capacity were only observed when additional WM (order-related processing) operations were required. Moreover, the goal-directed control of attention showed to be seriously affected, and matched more closely the viewpoint of a dysfunctional central executive. Second, impaired performances in AD demonstrated to be related to the impaired processing of serial order within a spatial coordinate WM system, both for verbal and visuospatial information. Note that future research should investigate at what level of information processing order processing comes into play. Serial order processing seems to be related to the functioning of the central executive. However, we cannot exclude the fact that order might be so fundamental to behavior that order processing might occur beyond the central executive, but serves to bind the central executive to short-term storage systems.

Overall, in the context of serially organized WM, AD patients demonstrate two crucially compromised WM components; (I) difficulty with the representation and processing of order and (II) an impaired employment of internal spatial attention, marking the role of an affected central executive.

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CHAPTER 6

COMPROMISED ORDER PROCESSING IN ALZHEIMER'S DEMENTIA DEMONSTRATED BY CORTICAL THICKNESS, DTI AND RSFMRI[1]

Executive dysfunction observed in patients with Alzheimer's dementia is commonly attributed to higher order working memory (WM) processes. The mental representation of serial order is one of the essential components represented in serial verbal WM and is crucial for smooth daily life functioning (e.g., cooking, memorizing a phone number). A recent study demonstrated that WM impairments in Alzheimer's disease can be attributed to impaired order processing and affected attentional processes. However, the neural substrates underlying order processing remain unspecified. Data was collected for 18 patients diagnosed with Alzheimer's dementia and 14 of their partners, serving as control group. They were submitted to a neuropsychological test battery, having to perform a Backward Digit Span (BDS) task, Forward Digit span (FDS) and Corsi Block (CB) test, from which an order-measure was calculated to investigate order-specific

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[1] De Belder, M., van Dijck, J-P., Santens, P., Doricchi, F., Sieben, A., Aerts, H., & Fias, W. (submitted) Compromised order processing in Alzheimer's dementia demonstrated by cortical thickness, DTI and rsfMRI. *Neuroimage: Clinical*.

regional alterations in the brain. The order-measure was associated with following subjects' brain data; anatomical information by T1, white matter integrity using the fractional anisotropy (FA) maps of diffusion tensor images and connectivity measures derived from resting state networks. The results demonstrate that order-problems within WM are associated with specific alterations in the brain; mainly localized in frontal and parietal regions, as observed by cortical thinning and reduced functional connectivity and the integrity of fronto-parietal and fronto-temporal white matter tracts.

INTRODUCTION

Alzheimer's dementia (AD) is typically characterized by long-term memory impairments, but also a diminished functioning of working memory (WM) has consistently been described (Baddeley, Logie, Bressi, Della Sala & Spinnler, 1986; Baddeley, Bressi, Della Sala, Logie & Spinnler, 1991; Baudic et al., 2006; Hodges, Salmon & Butters, 1992; Miller, 1973; Perry, Watson & Hodges, 2000; Stopford, Thompson, Richardson, Neary & Snowden, 2012; Welsh, Butters, Hughes, Mohs & Heyman, 1991). WM problems in AD patients are expressed in detrimentally impaired performances in dual-task settings (Baddeley et al., 1986,1991) or in rapid information overload, even for simplified message content and basic task instructions (Stopford et al., 2010). The exact mechanisms underlying impaired WM functioning have long been unclear. The limited understanding of the nature of WM problems in AD hindered the diagnosis of AD, the assessment of AD-related problems, goal-directed treatment and the comprehension of the impact of WM problems on daily life functioning.

A recent study (De Belder, Santens, Sieben & Fias, submitted) showed that the ability to mentally represent the order of items in memory was the crucial determinant of WM deficits in AD. Results from that study revealed that AD patients experienced problems with the maintenance of information in an ordered fashion and that this could explain the co-occurrence of a reduced WM capacity and central executive problems. In particular, it was found that while AD patients experienced few problems with the maintenance of (unordered) item information, severe difficulties were detected with the retention of ordered information within WM. Furthermore, AD patients exhibited specific difficulties with allocating attention in a goal-directed fashion to search for position-specific item information within WM, which is a crucial process that has been attributed to efficient functioning of serial verbal WM (Abrahamse et al., 2014).

While many studies have recognised the presence of WM impairments in AD patients, the idea of an underlying problem with the processing of order in WM is fairly new. In the context of AD it is crucial to understand the affected neural substrates that are associated with behavioural changes. However, as described in the following section, knowledge of the affected brain structures and functional networks in AD in the context of WM functioning is limited and of a general nature, failing to relate brain states to functionally specific impairments. The current study therefore attempted to shed light on the neural substrates related to impaired order processing in WM.

Many studies addressed the general question as to what regions or connections are affected in AD dementia, as evaluated by studies focusing on brain anatomy, white matter structures and resting state networks.

Anatomical brain studies showed that early stages of the disease are generally associated with medial temporal lobe atrophy, with progressively increasing atrophy of the entire temporal lobe and global cerebral atrophy with advancing AD (e.g., Killiany et al., 1993; Fox et al., 1996). The functioning of WM has been associated with severity of atrophy (Kaszniak, Garron & Fox, 1979), but this correlation relates to general cerebral atrophy and is therefore non-localisable.

Analyses of white matter tract integrity using diffusion tensor imaging (DTI) data are typically performed in order to examine structural connectivity. By providing an indication of degree of anisotropy of water molecules in white matter tracts, fractional anisotropy (FA) values are typically being used to assess white matter integrity. The reduction of FA values reflects declining movement restrictions for water molecules in the fiber tracts and suggest the deterioration of the white matter tracts (Charlton et al., 2006). The reduction of these FA-values in AD was generally observed for temporal and parietal regions, including cingular tracts (Zhan et al., 2009). In addition, diffusion analyses demonstrated deterioration of white matter tracts in the splenium of the corpus callosum, superior longitudinal fasciculus and cingulum (Rose et al., 2000), as well as the fornix and inferior longitudinal fasciculus (Kantarci et al., 2010).

Furthermore, research on resting state functional magnetic resonance images (rsfMRI) also added some significant contributions to the assessment of brain changes associated with AD. RsfMRI studies repeatedly suggested that AD is a disconnection syndrome, in which connections between cognitive networks suffer more than sensory networks (Li, Wu, Fleisher, Reiman, Chen & Yao, 2012; Wang, Liang & Wang, 2007). Specifically, the default mode network (DMN) – a network that engages during rest and disengages during cognitive load – and the executive attention network appeared to show reduced functionality in AD (Buckner, Andrews-Hanna & Schacter, 2008; Mevel, Chételat, Eustache & Desgranges, 2011; Sorg & Riedl, 2007). Moreover, reduced connectivity between posterior cingulate cortical regions, the medial frontal gyrus and ventral anterior cingulate cortex has been associated with performances on cognitive and working memory tasks (Hampson, Driesen, Skudlarski, Gore & Constable, 2006;

Sambataro, 2010).

Despite the extensive literature describing AD-related brain changes in grey and white matter and in functional connectivity, many questions remain. While many studies recognized the association between brain alterations and cognitive decline in AD, the studies specifically focusing on the role of WM are quite limited, probably due to a lack of clarity regarding the underlying mechanisms. In the current study we therefore combine multiple imaging techniques to investigate variations of structural and functional brain measures and their relation with the ability to efficiently process order within WM.

As indicated before, the current study started from the observation that AD patients specifically experience problems with the processing of order information in WM. However, to our knowledge, only Lamar, Catani, Price, Hailman & Libon (2008) performed an imaging study addressing WM functioning in a context relying on order processing. Lamar et al. (2008) established an association between region-specific leukoaraiosis (i.e., nonspecific and diffuse hyperintense white matter changes observed with MRI) in AD and WM problems. In their study, a long digit backward span task required participants to recall presented series of numbers in backward order. For each subject it was then evaluated how well they recalled the numbers in the correct order or in any order. Compared to healthy controls, AD patients were worse at recalling item order than the item information itself. Moreover, the performance on ordered item recall was found to correlate with severe leukoaraiosis in the left-sided posterior horn and frontal centrum semiovale. In the present study, an extended version of the backward digit span task of Lamar et al. (2008) was implemented. A new fine-grained order measure was derived from the performances on this task by comparing memory for serial item recall to unordered recall of item identity.

In our previous study (De Belder et al., submitted) data were collected for verbal forward (FDT) and backward digit span (BDT) tasks and a visuospatial Corsi block test (CBT), from which an order-specific *order ratio* measure was derived. These tests required the memorization of items in the correct order and the immediate recall of these numbers in exactly the same or backward order. An order measure was developed to specifically capture the efficiency of order processing in WM. Importantly, previous studies argued that the ordered recall in a FDT differs from the mechanisms underlying recall in the BDT and CBT (Li & Lewandowsky, 1995). Successful forward recall is argued to rely simply on the construction of inter-item associations. In contrast, the BDT and the CBT require the construction of visuospatial representations and rely more on an executive recall process (Li & Lewandowsky, 1995; Hoshi et al., 2000). Based on these findings, behavioral results reported in De Belder et al. (submitted) were further analyzed to assess the extent to which FDT, BDT and CBT differ from each other. In the present study, the processing of order in WM, quantified by the order measure, was related to the imaging results derived from grey matter, white matter and functional connectivity images. The analysis of the measures for grey matter, white matter integrity and functional connectivity allowed for an assessment of brain alterations in AD associated with impaired order processing within WM.

METHODS

Participants

All participating patients were recruited from the memory consultation of the University Hospital of Ghent, and provided written consent. Patients were selected on the basis of a clinical diagnosis of AD, which took into account the following measures: clinical history, neurological examination, detailed neuropsychological testing, MRI of the brain displaying temporal atrophy and biomarker analysis in cerebrospinal fluid.

WM tasks were administered at participants' own home. The administration of the full battery took 60 to 95 minutes and was often performed in two sessions. Most of the tasks were discussed in detail in our previous report (De Belder et al., submitted). The tasks of interest for the current study involved the Long Forward and Backward digit task and the Corsi block test. After performing the behavioral testing, AD patients and their partners were invited to return to the Ghent University Hospital for an additional MRI-scan session. Data were collected from 18 AD patients (average age = 72.33 years, SD = 9.34; 11 females). Fourteen of their partners were tested as a control subject (average age = 72.00 years, SD = 10.10; 7 females). On average, there was a two-week interval between behavioral testing and the MRI-scan with a maximum interval length of one month.

Behavioral WM tasks

Long forward digit span task (FDT)

The experimenter read out a series of numbers at a 1 digit/second pace. Participants were instructed to perform an immediate recall of the numbers in correct order. For each span length (3, 4, 5 or 6 digits) 8 trials had to be completed resulting in a total of 32 trials. No discontinuation rule was implemented, which required the participant to complete all 32 trials. Further details addressing the construction of the number sequences are described in De Belder et al. (submitted).

Long backward digit span task (BDT)

This task was designed and administered in the same way as the FDT with the exception that the participants were instructed to recall the verbally presented sequences in backward order.

Corsi block task (CBT)

The exact procedure for this task is described in De Belder et al. (submitted). In this visuospatial WM task, participants are confronted with the visual presentation of grey colored squares at different positions on a 12" touch-screen Acer laptop. These squares turned black at a rate of 1 square per second. The participants were instructed to memorize the correct order in which the black squares appeared. The presentation of the last square was followed by immediate recall, whereby the participant had to indicate the order in which they memorized the black squares by touching the screen at the corresponding square locations. Three trials had to be completed for span lengths of 3, 4, 5 and 6 blocks. Again, no discontinuation rule was applied and all 12 trials had to be completed.

MRI data acquisition

MRI images were acquired with a 3T Siemens Magnetom TrioTim (Ghent University Hospital, Ghent), with a 32-channel head coil. Anatomical T1-weighted 3D images were acquired with an interleaved scanning order for the evaluation of anatomical structures, cortical thickness and coregistration with other MR-images (160 slices; TR = 2500 ms; TE = 2.84 ms; TI = 900 ms; field of view = 270 mm; slice thickness = 1.20 mm; flip angle = 9°; 256 x 256 matrix; voxel size = 1.1 x 1.1 x 1.2 mm). Functional resting state (fMRI) echo-planar imaging (EPI) data were acquired in an interleaved order (37 slices; time repetition = 2260 ms; time echo = 27 ms; field of view = 216 mm; slice thickness = 3.00 mm; flip angle = 90°; 72 x72 matrix; voxel size = 3.0 x x3.0 x 3.0 mm). Participants were instructed to close their eyes during the collection of resting state fMRI data. A 64-direction DTI data set was acquired using an EPI sequence with following parameters: 60 slices; time repetition = 10800 ms; time echo = 83 ms; field of view = 240 mm; slice thickness = 2.5 mm; 96 x 96 matrix; voxel size = 2.5 x 2.5 x 2.5 mm, interleaved image acquisition. Data acquisition took about 45 minutes.

Analysis of behavioral data

Calculation of the order measure for the BDT, FDT and CBT.

As a measure of efficiency of processing order information, an order ratio was derived from each task by collecting the following measures for each digit span length (3,4,5 or 6 digit or blocks to-be-recalled): 1) the percentage of accurately recalled numbers in correct *serial order* and 2) the percentage of accurately recalled numbers in *any order*. The desired order measure, i.e., *order ratio,* simply consisted of the ratio *serial order/any* *order*.

Analysis of brain imaging data

The reasoning behind the analyses described below was as follows: the goal was to relate the performance scores on the behavioral measure '*order ratio*' to changes observed in the brain. These analyses were performed to identify brain regions, white matter structures and functional activity related to order processing. We did not differentiate between groups, but mainly focused on the assessment of the linear relationships between brain and behavioral data

The data of two AD patients were removed due to excessive head motion (>2mm). For the analyses using the BDT and FDT task the analyses were performed on the data of 30 participants (16 AD patients; 14 control subjects). Due to incomplete behavioral data collection, the analyses using the measure of the CBT were performed on the data of 26 participants (13 AD patients; 13 control subjects). All analyses on brain data were corrected for gender. The rationale for including gender as covariate was that different brain morphology has been reported depending on the gender of patients suffering from Alzheimer's disease (Schmidt et al., 2007). Furthermore, previous research demonstrated systematic gender differences in resting state functional MRI (Biswal et al., 2010).

Anatomical image analyses

Volume measurements, such as cortical thickness, were calculated using the software FreeSurfer, version 5.3.0 (***http://surfer.nmr.mgh.harvard.edu***, Dale, Fischl & Sereno, 1999 and Fischl, Sereno & Dale, 1999). The full processing stream has been previously described in full detail (see Dale, Fischl & Sereno, 1999; Fischl, Sereno & Dale, 1999). In short, the procedure goes as follows; first, preprocessing is done, involving motion correction, removal of non-brain tissue, normalization, segmentation of white and grey matter and intensity normalization, tessellation of the grey matter white matter boundary, automated topology correction and surface deformation. Subsequently, data are registered to a spherical atlas, followed by surface extraction and gyral labeling. After completion of the automated processing stream, resulting brain volumes and surfaces for each subject were manually checked. Small inconsistencies observed in the skull stripping, segmentation, constructions of surfaces, topological defects and pial surface displacements were manually corrected. Depending on the error, a part of the processing stream was rerun based on the added correction. For further analysis of the data, each subject's data were resampled into a common space and subsequently smoothed with a 10 mm full-width/half-maximum Gaussian kernel. The order measure derived from the FDT, BDT and CBT was implemented in a separate general linear model for each task (i.e., three general linear model computations). A general linear model of cortical thickness was computed as a function of the order measure and sex. Parametric maps that were obtained from this analysis consisted of voxel-wise correlations between the order measure and cortical thickness, with the effect of sex regressed out. Results were then submitted to a cluster-wise correction for multiple comparisons, by means of a Monte Carlo simulation to determine clusters with a corrected significance of $p < .05$.

The hippocampus has been demonstrated to be specifically compromised in AD (e.g., Braak & Braak, 1991) and has been associated with the ability to keep track of the order of events (Davachi & DuBrow, 2015). To evaluate the potential contribution of the hippocampus to order processing in AD, some follow up analyses were executed. First, during the preprocessing of the original analyses, the volume of subcortical structures was calculated. These values for the hippocampal structures were extracted for each subject. The volumes of the left and right hippocampal region were averaged before being correlated with the order measure derived from the FDT, BDT and CBT. Second, significant regions resulting from the initial analysis of the general linear model of cortical thickness were selected as regions of interest. The relation between the cortical thickness of these regions and the intactness of the hippocampus was assessed by correlating the averaged cortical thickness of these regions of interest with the hippocampal volume. The same analyses were preformed for the volume of the left and right hippocampus separately.

Tract-Based Spatial Statistics (TBSS) and DTI

Voxelwise statistical analysis of the FA data was carried out using TBSS (Smith, 2006), which is a part of FSL (FMRIB Software Library v5.0; Woolrich et al., 2009; Smith, 2004). First, FA images were created by fitting a tensor model to the raw diffusion data using FDT (i.e., diffusion toolbox), and then brain-extracted using BET (Smith, 2002). All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT (Andersson, 2007a, 2007b), which used a b-spline representation of the registration warp field (Rueckert, 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics. Nonparametric permutation inference is performed using the FDT, BDT and CBT measures, regressing out the effect of sex. 500 permutations of the data were generated to build up the null distribution to test. Threshold-free cluster enhancement was applied, producing p-value images fully corrected for multiple comparisons across space.

fMRI data preprocessing and functional network construction

Preprocessing of each subject's functional MRI data was performed using the FMRIB Software Library v5.0 (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki, Woolrich et al., 2009) and AFNI (Cox, 1996). In particular, preprocessing encompassed the following steps: skull extraction using BET, motion correction, slice time correction, spatial smoothing using a 6 mm FWHM Gaussian kernel, temporal filtering with a band-pass frequency range from 0.009 Hz to 0.08 Hz, and detrending of the signal by removal of linear and quadratic trends. Functional images were then coregistered to the individual's structural space and normalized to the MNI standard template using the linear and non-linear registration algorithms provided by FSL (FLIRT and FNIRT; Jenkinson & Smith, 2001; Jenkinson et al., 2002; Andersson et al., 2007b; Woolrich et al., 2009). Next, segmentation of the anatomical data was performed using FAST (Zhang, Brady & Smith, 2001) and covariates, consisting of six head motion parameters, the white matter signal and cerebrospinal fluid signal, were regressed out of the fMRI signal.

In the next step, the GIFT software (*http://mialab.mrn.org/software/gift,* Correa et al., 2005) was used to perform independent component analysis (ICA) on the preprocessed fMRI signal in order to extract resting state networks. Specifically, the ICASSO method was used to run ICA with 20 predefined components, running the full ICA 100 times to assure component stability and obtaining the best estimate for each component. From the resulting 20 components, we were interested in subjects' default mode network and executive network. To automatically extract these components, the component labeler was used, which correlates each component with a standard template for the given network. The best component is then selected based on the maximum correlation value. The use of this labeler led to the extraction of five default mode networks (DMNs), one left executive and one right executive network on group-level. The most representative DMN was selected based on visual evaluation of the involved regions typically associated with the DMN, which involve the posterior cingulate, precuneus, anterior cingulate cortex, angular gyri, medial frontal cortex and medial temporal lobe (Garrity, Pearlson, McKiernan, Lloyd, Kiehl & Calhoun, 2007; Greicius, Srivastava, Reiss & Menon, 2004). Subsequently, a second-level analysis was performed using SPM8 (University College London, UK; *http://www.fil.ion.ucl.ac.uk/spm/software/spm8*). A linear voxel-wise regression was performed on each subject's component of interest (DMN, left or right executive network) as a function of BDT, FDT and CBT, regressing out the effect of sex. A correction for multiple comparisons was applied by means of a family wise error correction, with a corrected significance of $p < .05$.

RESULTS

Behavioral results

An ANOVA was performed on the averaged *order ratio* across all span lengths with the within-subjects variable *task* (forward, backward digit span task and Corsi block task) and the between-subjects variable group (AD patient or control). Results reveal a significant main effect of task [F(2,32) = 27.68, *p* < .001, np2 = .63]. Post-hoc paired *t*-tests assess the way in which the three tasks relate to each other. All three paired t-tests turn out to be significant, indicating that all three tasks significantly differed from each other; [t-test FDT and BDT: order ratio FDT = .86, SD = .09; order ratio BDT = .70, SD = .18; t(30) = 7.63, *p* < .001]; [t-test for FDT and CBT: order ratio CBT = .78, SD = .14; t(26) = .3.61, *p* = .004] and [t-test for BDT and CBT: t(26) = 3.68, *p* = .001; Figure 1]. The correlations for the performance scores on the three task reveal strong associations; a patient who performed bad on one task was also more likely to perform bad on the other two tasks (FDT and BDT: Pearson's *r* = .63, *p* <.001; FDT and CBT: Pearson's *r* = .55, *p* = .001; BDT and CBT: Pearson's *r* = .51, *p* = .002). Results of the ANOVA furthermore reveal an interaction between the task and participant group [F(2,32) = 4.04, *p* = .03, np2 = .20], demonstrating generally worse performances for the AD patients, especially strongly expressed for the BDT (Figure 1). The AD patients demonstrate an *order ratio* of .84 (SD = .10), .64 (SD = .19) and .71 (SD = .16) for the FDT, BDT and CBT respectively. The controls' *order ratio* scores for the FDT, BDT and CBT are respectively .89 (SD = .07), .76 (SD = .14) and .86 (SD = .05). Compared to the controls, AD patients only perform worse on the BDT [t(29) = 2.33, *p* = .03] and the CBT [t(25) = 2.38, *p* = .03], but not on the FDT, as revealed by post-hoc independent sample t-tests [t(29) = 1.18, *p* = .25]. These behavioral analyses show that the three tasks are clearly different. However, the high correlations between the performance on the three different tasks shows that bad performances on one task is more likely to co-occur with bad performances on the two other tasks, suggesting an underlying deficit in these three tasks.

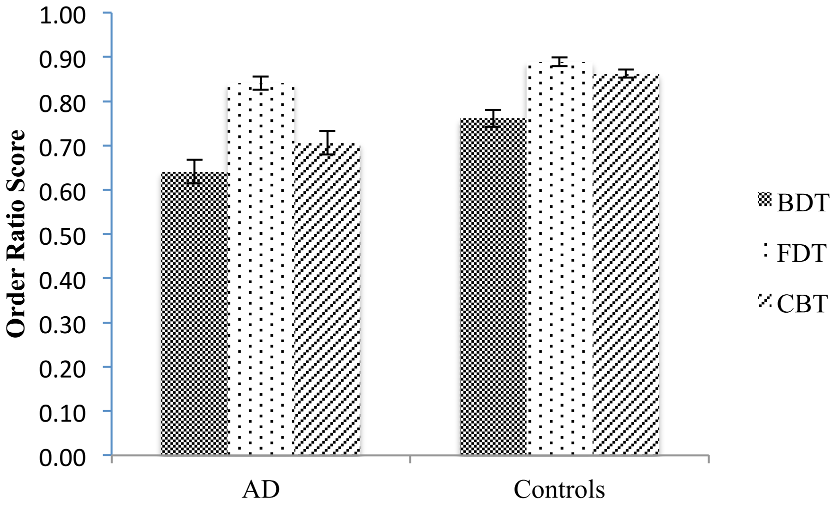


Figure 1. Visualization of the averaged scores on the order ratio for the BDT, FDT and CBT, for the AD patients and control group separately.

Cortical thickness and T1

Forward digit span

We observe no significant regional differences in cortical thickness in function of the order measure for the FDT.

Backward digit span

After multiple-comparison correction, the results demonstrate cortical thinning related to impaired order processing for two clusters in the left hemisphere; in pars opercularis (BA 44, cluster size = 746 mm², x-, y- and z-center location coordinates in MNI space are -60, 8, 16), the supramarginal gyrus (BA 40, cluster size = 511 mm²; center location = -54, -24, 31; Figure 2 and 3). For the right hemisphere, five clusters are identified: one cluster stretching from the pars opercularis and inferior frontal gyrus to the inferior parts of the precentral and postcentral gyri (the inferior frontal cluster, BA 40-43-44, cluster size = 2819 mm², center location = 63, -18, 20), a cluster in the inferior temporal gyrus (BA 20, cluster size = 722 mm², center location = 61, -23, -22), a cluster in the supramarginal gyrus (BA 39, cluster size = 1049 mm², center location = 53, -47, 28), a cluster the temporal pole (BA 38, cluster size = 570 mm², center location = 53, 10, -35) and finally, a cluster in the middle frontal gyrus, stretching over the rostral middle frontal and inferior orbitofrontal area (BA 11, cluster size = 1982 mm², center location = 17, 49, -19, Figure 2).

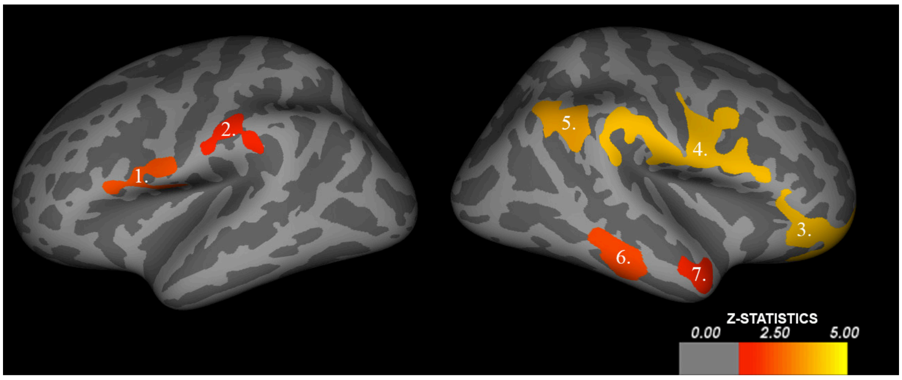
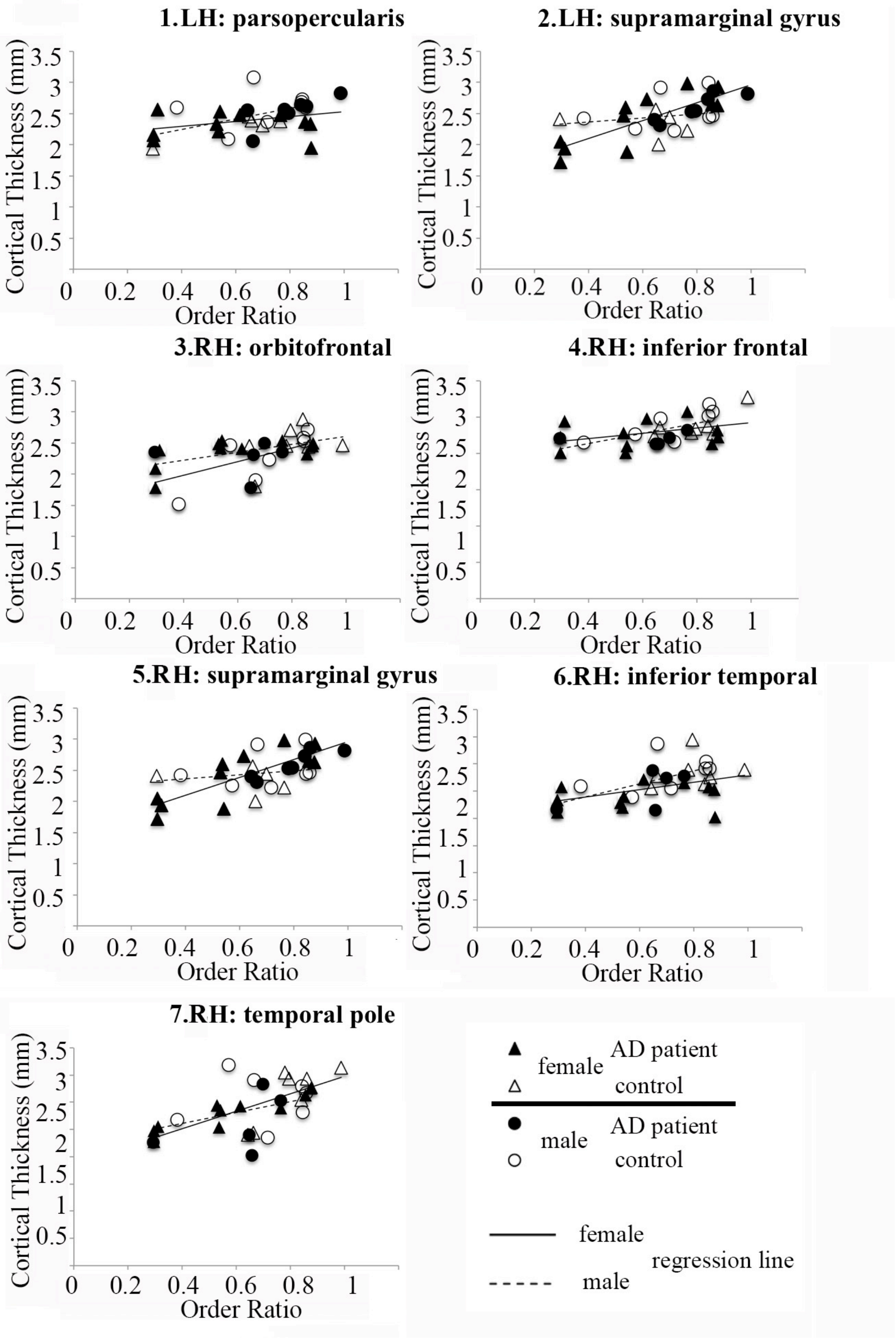


Figure 2. Shows the regions where cortical thickness is associated with the behavioral measure *order ratio* of the BDT. Monte Carlo cluster-wise simulation: the displayed clusters indicate where impaired order processing is simultaneously observed with significant region-specific cortical thinning. The left and right hemisphere are respectively visualized with the identified clusters. The regions are numbered according to their matching dot plots (see Figure 3).

Figure 3. (Next page) Results of the measured correlation between cortical thickness and the behavioral measure *order ratio* of the BDT for the identified clusters. The dot plots display the values observed for the order ratio score and corresponding cortical thickness. A distinction was made between the values recorded for AD patients compared to controls for illustrative purposes. Regression lines are drawn for males and females separately.


1.LH: parsopercularis
2.LH: supramarginal gyrus
3.RH: orbitofrontal
4.RH: inferior frontal
5.RH: supramarginal gyrus
6.RH: inferior temporal
7.RH: temporal pole
Cortical Thickness (mm)
3.5
3
2.5
2
1.5
1
0.5
0
0.2
0.4
0.6
0.8
1
Order Ratio
female
AD patient
control
male
AD patient
control
female
male
regression line

Corsi block task

For the left hemisphere, five separate clustered regions demonstrated cortical thinning related to decreased order representations according to the CBT ($p < .05$, corrected for multiple comparisons). The cluster for the right hemisphere shows a peak in the inferior frontal gyrus, with the cluster largely stretching over the rostral middle frontal gyrus and inferior orbitofrontal area (BA 57, cluster size = 1480 mm^2, center location = 30, 29, -23; Figure 4), demonstrating cortical thinning of the cortex related to worsening order processing. Repetition of the analysis with the exclusion of a possible outlier did not alter the initially observed results.

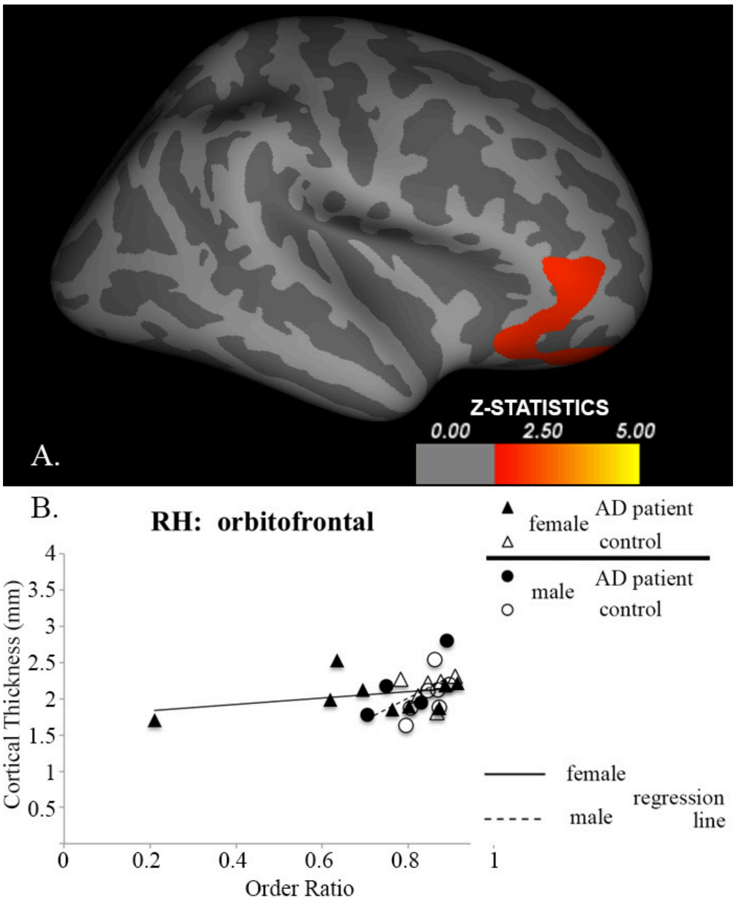


Figure 4. A. Shows the regions where cortical thickness is associated with the behavioral measure *order ratio* of the CBT, visualizing the right hemisphere. Monte Carlo cluster-wise simulation: the displayed cluster indicates where impaired order processing is simultaneously observed with region-specific cortical thinning. B. Results of the measured correlation between cortical thickness and the behavioral measure *order ratio* of the CBT for the identified orbitofrontal cluster. The dot plot displays the values observed for the order ratio score and the cortical thickness measure of that cluster/region for the corresponding participant. A distinction was made between the values recorded for AD patients compared to controls for illustrative purposes. Regression lines are drawn for the gender groups.

Analyses of hippocampal volume

Correlating hippocampal volume with the order measure of the FDT, BDT and CBT reveals no significant associations (FDT: *Pearson's r* = .-.10, *p* = .63; BDT: *Pearson's r* = .08, *p* = .72; CBT: *Pearson's r* = .29, *p* = .16), suggesting the absence of a relationship between hippocampal volume and order processing.

The regions resulting from the correlational analysis between the order measure and cortical thickness were selected as regions of interest for the following analysis. Hippocampal volume was then correlated with the cortical thickness of these regions. For the BDT and left hemisphere, these regions are the pars opercularis and supramarginal gyrus. For the right hemisphere the orbitofrontal region, inferior frontal cluster (cluster stretching from pars opercularis to the inferior frontal gyrus), supramarginal gyrus, inferior temporal region and temporal pole were included. Results reveal a significant correlation between the volume of the hippocampus and cortical thickness for the left pars opercularis (*Pearson's r* = .47, *p* = .009), but not for the supramarginal gyrus (*Pearson's r* = .13, *p* = .49). For the BDT and right hemisphere, the volume of the hippocampus correlates significantly with the thickness of the supramarginal gyrus (*Pearson's r* = .55, *p* = .005), the right inferior frontal cluster (*Pearson's r* = .53, *p* = .007), the inferior temporal region (*Pearson's r* = .59, *p* = .002) and temporal pole (*Pearson's r* = .50, *p* = .01), but not with the cortical thickness of the orbitofrontal region (*Pearson's r* = .008, *p* = .97).

The same analysis was executed for the right orbitofrontal region, resulting from the cortical analysis for the CBT. However, the correlation between hippocampal volume and thickness of the right orbitofrontal region from the CBT demonstrates to be non-significant (*Pearson's* = -.19, *p* = .37).

The execution of the same analyses for the left and right hippocampal volume separately results in the same observations, suggesting no lateralised contribution of the hippocampus to any of the earlier observed effects.

TBSS and DTI

Forward digit span

No significant regional differences in FA-values in function of the order measure for the FDT were found.

Backward digit span

The FA-maps on the BDT order measure correlated with the integrity of the left superior longitudinal fasciculus and corpus callosum. Moreover, results also reveal a relation with the integrity of bilateral occipitally and frontally located parts of the inferior fronto-occipital fasciculus, a tract that passes backward from the frontal lobe via the occipital lobe to the temporal lobe; and the left inferior longitudinal fasciculus, connecting the occipital and temporal lobes (Adel & Ronald, 2005). For these regions, lower FA-values associate with a lower order measure score, indicating an affected integrity of the WM structures related to order processing (Figure 5).

Corsi block task

Lower order ratio scores on the CBT associate with decreased FA-values for following regions: the posterior part of the left and right superior longitudinal fasciculus, the anterior part of the corpus callosum, including the forceps minor and a bilaterally small frontal part of the inferior fronto-occipital fasciculus (Figure 5).

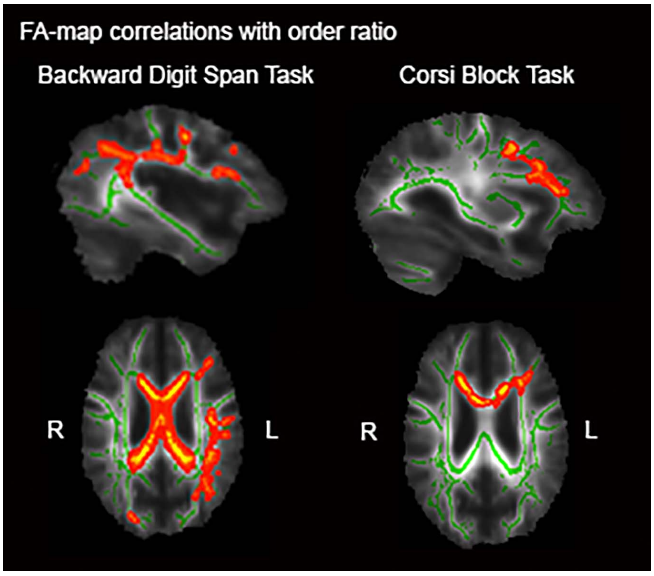


Figure 5. Results from the TBSS, showing the WM regions where FA-values correlated significantly with the behavioral order ratio of the BDT and CBT respectively. Slices are chosen to optimally visualize the identified tracts.

Functional networks and rsfMRI

Twenty independent components were estimated, from which the networks were visually identified to match typical left and right executive networks and the default mode network (as described by Beckmann, De Luca, Devlin & Smith, 2005; De Luca, Beckmann, De Stefano, Matthew & Smith, 2006; Figure 6). The remaining 17 components were related to different identifiable networks or displayed effects of head motion or other artifacts. The three selected networks were correlated with the *order ratio* of the FDT, BDT and CBT, while being controlled for sex.

Forward digit span

Performances on the FDT task do not relate to alterations in any of the three functional networks.

Backward digit span

Correlating the *order ratio* with the left executive network demonstrates reduced functional activity associated with lower *order ratio* scores in the left inferior frontal region (BA 45; x-, y- and z- of peak location = -51, 18, 15). For the right executive network the same relation can be observed in the right midfrontal areas (BA 10, peak location = 45, 51, 3). The DMN associates with altered functional activity in the vermis (BA 19, peak location = 6, -51, 6; Figure 6).

Corsi block task

Correlations with the *order ratio* and the left executive network reveal a positive correlation between functional activity in the left angular gyrus (peak location = -48, -66, 36) and the right temporal pole (BA 38, peak location = 60, 15, -18). The right executive network demonstrates reduced activity in the left and right parieto-occipital fissure and gyrus cinguli posterior (BA30, x-, y- and z- coordinates of peak locations are respectively 9, -57, 6 and -9, -60 6), the right precentral (BA 6, peak location = 42, 0, 45) and right superior frontal (BA 9, peak location = 18, 33, 42) areas. Reduced functional connectivity in following regions associates with lower order ratio scores for the DMN; the left and right parieto-occipital fissure and posterior cingulate gyri (BA 23,31, peak location = 9, -60, 6; -9, -57, 6), a right precentral (BA 6, peak location = 42, 0, 45) and a frontal superiorly located region (BA 9; peak location = 18, 33, 42; Figure 7).

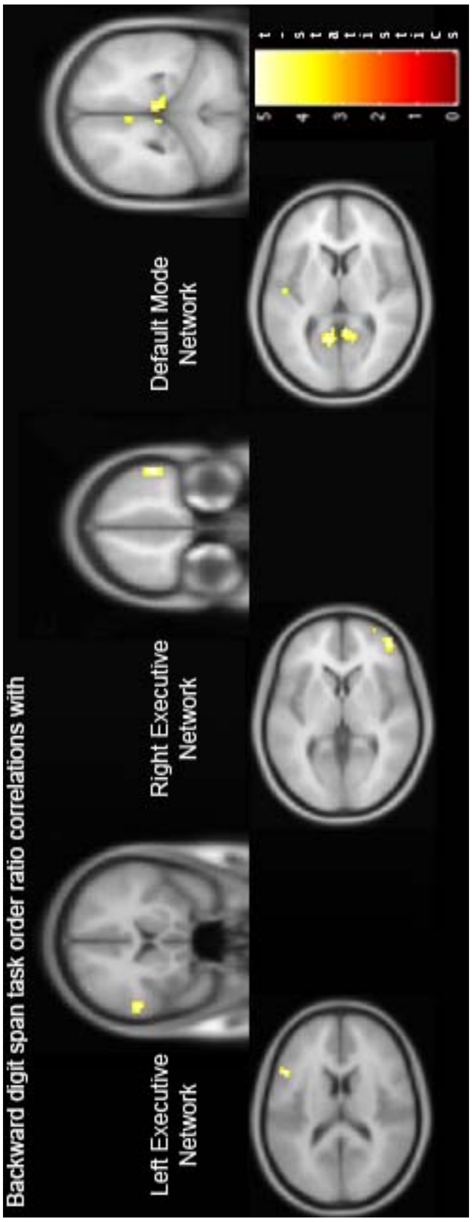


Figure 6. Results show the regions where the functional activity for three functional networks (left, right executive network and the default mode network respectively) correlate significantly with the behavioral measure *order ratio* for the BDT.

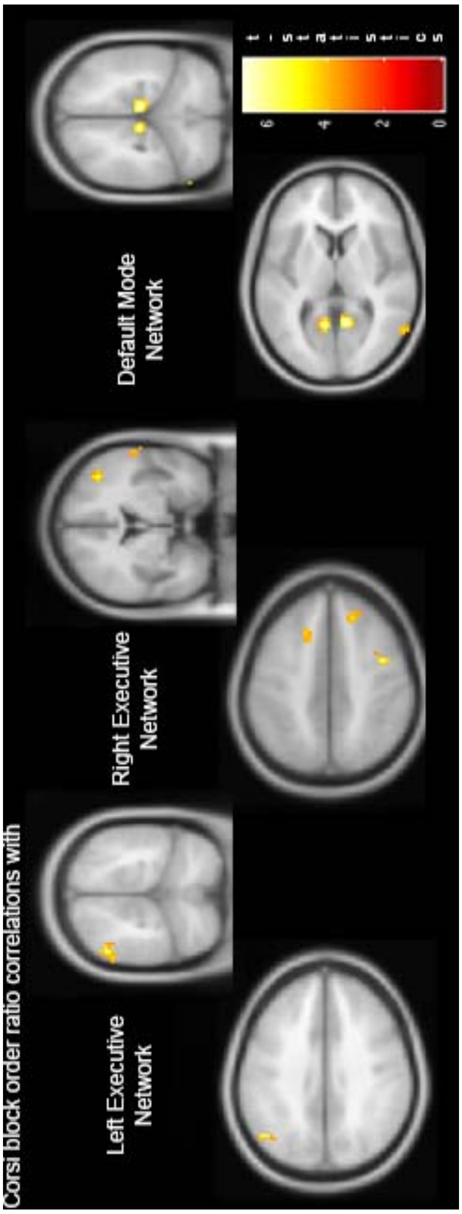


Figure 7. Results show the regions where functional activity for three functional networks (left, right executive network and the default mode network respectively) correlate with the behavioral measure *order ratio* for the CBT.

DISCUSSION

The central question of the current study concerned the localization of affected brain structures in AD related to the degradation of order processing in WM, which is crucial to make WM function optimally. An order-specific measure was derived from three different tasks; the FDT, BDT and CBT. The behavioral results confirmed that AD patients suffer more from a compromised ability to maintain information in an orderly fashion than control subjects. This observation was in line with the earlier observation that AD patients specifically suffer from impaired order processing compared to the memory trace for item identity (De Belder et al., submitted). Furthermore, when observing the scores for the *order ratio* measure, AD patients performed the worst on the BDT and the best on the FDT. This latter observation matches findings of previous studies (Li & Lewandowsky, 1995). The BDT and CBT task are generally considered to be more difficult to perform, as the execution of these tasks require the construction of complex visuospatial representation that are easily manipulated (Hoshi et al., 2000). Representations made for the FDT do not need to be manipulated for recall and can thus rely on the simple construction and recall of interitem associations (Li & Lewandowsky, 1995). When correlating the order measure of the three span tasks with available brain measures, the BDT and CBT correlated with several alterations in brain structures and functionality, while nothing was found for the FDT. The absence of any correlations between brain alterations and the FDT might reflect the difference in the mechanisms that are used to maintain order for the FDT versus the BDT and CBT.

Analysis of the brain images led to the following results. First, the decreased ability to process serial order (reflected in a reduced order ratio) was associated with cortical thinning in temporal and parietal regions for the BDT and CBT. In the early stages of Alzheimer's disease these are the main regions to be affected by atrophy (Killiany et al., 1993; Fox et al., 1996). Furthermore, the order measure also revealed an association with cortical thickness of frontal regions (orbitofrontal, rostral middle frontal). These latter regions are typically associated with executive functioning and would accommodate the observation that patients experience difficulties with directing internal attention to search through the WM system (Baddeley, 1986; De Belder et al., submitted; Shallice, 1988). However, the role of these regions could also reflect processes related to the integration of sensory information, goal-directed decision-making and multiple-task coordination (Bechara, Damasio, Damadio & Anderson, 1994; Gilbert, et al., 2006; Kringelbach, 2005; Rolls, 1996).

The hippocampus is one of the main structures affected in Alzheimer's disease and people at risk for AD (Braak & Braak, 1991; Convit et al., 1997; Jack et al., 1999; Schuff et al., 2009). Moreover, previous research described the role of the hippocampus in the processing of order (Davachi & DuBrow, 2015). We therefore investigated whether this relation between hippocampal volume and order processing could also be observed in the current data. However, analysis revealed no relation between hippocampal volume integrity and performances on the order measure of the FBT, BDT and CBT. These analyses were performed on a group consisting of only a limited number of AD patients, which has obviously led to restricted power. However, further analyses demonstrated clear correlations between hippocampal volume and regions that were associated with order processing; the bilateral pars opercularis, the right supramarginal gyrus, the right inferior temporal region and right temporal pole. Only the orbitofrontal regions did not correlate with hippocampal volume. These results indicated an association between the integrity of the hippocampus and the cortical thickness of specific cortical regions associated with order processing. Further research should clarify the nature of this relation and investigate whether this relationship could simultaneously occur with a correlation between hippocampal volume and the behavioral ability to process order.

Whole-brain analyses of the FA-maps correlating with the order measures suggested the essential involvement of frontal regions in the communication with other regions for proper WM functioning. More specifically, for the BDT and CBT, FA-values were significantly reduced for the superior longitudinal fasciculus, a tract that connects posterior regions with the frontal brain areas (Makris et al., 2005). Degradation of the longitudinal fasciculus disturbs the bidirectional transfer of information between the parietal and prefrontal cortex and could lead to several detrimental consequences. On the one hand, the deterioration of this track hinders the transfer of information concerning the perception of visual space. On the other hand, WM, which relies heavily on prefrontal functioning, will be hindered from sending signals to the parietal cortex to regulate and direct the focus of spatial attention (De Schotten, 2011; Makris et al., 2005). The regulation of spatial attention in WM has been argued to fundamentally contribute to efficient order processing (Abrahamse et al., 2014). Impaired order processing in WM may therefore result from the affected integrity of the superior longitudinal fasciculus. Moreover, impaired order processing in WM for both the BDT and CBT were associated with reduced interhemispheric structural connectivity, which is crucial for the intra-hemispheric transfer between frontal, occipital and temporal regions.

Furthermore, scores on the order ratio for the BDT and CBT positively correlated with the integrity of parts of the inferior fronto-occipital fasciculus, essential to the integration of auditory and visuospatial input from the sensory areas in the prefrontal cortex.

Finally, while the results for the resting state networks turned out to be less pronounced than for the previously mentioned measures, small alterations were revealed in the functional connectivity of the DMN and executive networks. Scores on the order measure of the BDT positively correlated with functional connectivity for small frontal areas in the left- and right hemisphere for the left and right executive network. Also for the CBT task, left and right frontal areas demonstrated functional alterations for the right executive network. The left executive network revealed alterations in the left temporal pole and angular gyrus when correlated with the order measure. For the BDT and CBT, the DMN only demonstrated alterations in the left and right parieto-occipital fissure and gyrus cinguli, and a small change in the functionality of the right precentral and superior frontal region for the CBT.

The observed deterioration of white matter tracts connecting frontal, occipital and temporal regions are generally reported in the context of cognitive decline and dementia (Charlton et al., 2007). Moreover, a network that encompasses inferior parietal and occipito-temporal regions is also know to be essential to mental visualization and spatial manipulations, strategies that are argued to be applied when performing the BDT or CBT (Hoshi et al., 2000; Lamar et al., 2008). In addition to the observed disruption of these white matter tracts, cortical thinning was localized in frontal and temporal areas, combined with altered functional network activity. Moreover, the main involvement of frontal and temporal areas and frontal to temporal connections in the processing of order within WM does match earlier findings in healthy controls, lesion studies and animal studies (Majerus et al., 2008; Marshuetz, 2005). More specifically, previous research highlighted the fact that memory for order and item information is dissociable and that distinctive regions are responsible for the processing of either order or item identity (for a review see Majerus, 2008; Marshuetz, 2005). Order information is supported by prefrontal and parietal regions (Henson, Rugg, Shallice & Dolan, 2000; Marshuetz, Smith, Jonides, DeGutis & Chenevert, 2006; Zhang et al., 2009), item identity is argued to recruit temporal brain areas (Majerus, Poncelet, Elsen & Van der Linden, 2006). In our study we attempted to correlate brain alterations with a pure order measure, largely removing other interplaying effects occurring in WM. However, developing a measure that entirely excludes effects of memory for item identity is probably not feasible as processes and networks involved in order and item identity memorization have to operate in strong interaction for WM to work efficiently (Majerus et al., 2008).

Additionally, further research should investigate to what extent efficient processing of order in WM supports information transfer and consolidation processes in long-term memory or how long-term memory affects the construction of ordered memory traces within WM. To be concrete, patients with dementia experienced disrupted primacy and recency effects in the immediate and delayed recall trials of the list learning task (e.g., RVLT & CERAD; Bruno et al., 2015; Howieson et al., 2011; Paul, Cohen, Moser, Zawacki & Gordon, 2002), suggesting impaired order processing in WM and long-term memory. Further research should clarify to what extent long-term memory is affected specifically due to impaired order processing in WM.

Overall, the results of the current study indicate that the impaired ability to successfully process order within WM is associated with the integrity of frontal, parietal and temporal regions. This is reflected in cortical thinning, but also the degradation of white matter structures, allowing for interhemispheric and parietal to frontal/frontal to parietal and fronto-temporal information transfer. Moreover, the functional involvement of frontal regions in order processing has been confirmed by the alterations observed in the executive resting state networks and the DMN.

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CHAPTER 7

GENERAL DISCUSSION

The investigational aims presented in the current dissertation were addressed to gain an understanding of processes involved in spatial order coding within working memory (WM). Experiments were executed to submit the fundamentality of order processing within WM to the test. We further assessed the nature of position markers, to which to-be-memorized information is bound. Moreover, we evaluated the automaticity of order coding processes and investigated the role of order in the context of impaired WM functioning. In the discussion of this dissertation we will summarize all findings in light of a better understanding of general WM functioning. We further discussed the theoretical implications, methodological limitations, practical contributions and remaining questions for the purpose of future research.

RESULTS: AN OVERVIEW

The basic model of serial order coding in working memory

Many models endorsed and described the role of serial order processing occurring in WM. While they all agreed on the fundamental ability to handle serial information, the proposed explanatory models diverged on many aspects. The most empirically supported model was put forward by Henson (1998), describing the start-end-model. Essential in this model was the role of position markers localized in WM, which are used to bind to-be-memorized information to. However, a missing piece in the start-end-model, and other serial order WM models, concerns the description of the nature of the specific position markers. The start-end-model leaves room for the spatial and temporal construction of position markers, but lacks further clarification by empirical findings.

The current dissertation builds upon the idea described in the mental whiteboard hypothesis (Abrahamse, van Dijck, Majerus & Fias, 2014) and evidence provided in CHAPTER 2 evidence that was used to substantiate this model. The mental whiteboard hypothesis found its origin in the idea of spatial position markers serving to construct an ordered memory trace in WM. The mental whiteboard hypothesis describes serial verbal WM as a system, which is localized in a spatially constructed attention system. Information to-be-stored within WM is bound to position markers, which are defined as coordinates in a spatially defined system. Spatial attention has to be allocated to search through the WM system and retrieve position-specific item information. The approach described by the mental whiteboard hypothesis was further advocated in the current dissertation, by assessing the nature of the position markers used to construct order within WM. CHAPTER 2 addressed the spatial construction of position coordinates, while CHAPTER 3 was designed to assess the possibility of sequences constructed by means of temporal information.

The idea that mainly spatial coordinates characterize the nature of position markers within WM was initially supported by findings of van Dijck et al. (2011; 2013). More specifically, van Dijck et al. (2013) observed the following; the presentation of a WM item localized at the beginning of the memorized sequence, facilitated the detection of targets on the left side of the screen. End items of the WM sequence facilitated detection of right-sided spatial targets. This observation provided a first indication that serial order in WM is associated with (external) space. Moreover, they further substantiated this idea by reporting instances in which items from serial WM could serve as a cue to direct attention to spatially located dots. The experiments conducted in CHAPTER 2 served to complement the findings of van Dijck et al. (2011; 2013), by establishing a bidirectional relationship between serial order position in WM and spatial processing. Two observations had to be made in order to assure that space is fundamental to the construction of position markers in WM. First, and established by van Dijck et al., (2013), if serial information is supported by position markers constructed in a spatial coordinate system, the recognition of spatial cues should be facilitated/hindered by the prior presentation of a memorized stimulus (van Dijck et al., 2013). Second, external spatial cues should in turn facilitate/hinder the retrieval of items located in serial verbal WM. We found further support for the intrinsic role of spatial processing in serial order by means of two conducted experiments. Both experiments demonstrated how spatial cues could serve as a prime to steer spatial attention and facilitate/hinder the recognition of items stored in WM. Initial sequence items in WM were recognized faster when primed by a left-sided cue than by a right-sided cue, while the opposite was observed for later sequence items. Interestingly, this effect was also found in the context of backward priming; where the overlap between serial order retrieval and spatial attention processing was maximized. Moreover, we observed that task-relevancy and the modality of responses (manual or vocal) did not alter the observed association between serial order in WM and external spatial cues.

While the essential role of space in serial order coding was established in CHAPTER 3, we were still interested whether other modalities of information could still be employed to support the construction of position markers. For example, the purely computational oscillator-based memory model for serial order was one of the few models expressing the clear nature of position markers, supporting the idea of temporal position coding (Brown, Preece & Hulme, 2000; Burgess & Hitch, 1996). Moreover, the influential theory proposing 'A Theory of Magnitude' (Walsh, 2003), described the close interplay between metrical types of information such as numbers, time and space. This theory proposed a common neural substrate, the common magnitude system, in which all metrical information is processed. This idea was generally well received as it provided an explanation for commonly observed overlap and interactions between the modalities of numbers, time and space. Despite the strong theoretical claim of this model, little direct empirical support is available. However, the fact that literature suggested a relation between time and space opened the following interesting scope to investigate: can time serve to construct serial position in WM? The execution of two time-WM-related experiments revealed the existence of a bidirectional relationship between the processing of time and serial order in verbal WM. The processing of timed events primed position-specific item retrieval; items at the beginning of the sequence were recognized faster when primed by short time events compared to longer time events, while the opposite was observed for items located at the end of the memorized sequence. Moreover, the retrieval of items from WM affected the processing of time; items located at the start of the memorized sequence facilitated responses to short time events compared to longer events. Again, the opposite was observed for end items of the sequence and long time events. The occurrence of this bidirectional interaction between time and serial verbal WM indicated a fundamental involvement of time in the construction of position markers. In other words, the results described in CHAPTER 2 and CHAPTER 3 indicate that serial order can be constructed in a spatial and/or temporal fashion. However, in the context of temporal order formation it remains unclear to what extent the effect of time is direct or relates to the mapping of time in space. It is possible that position markers can additionally benefit from binding to temporal information, but this does not exclude the involvement of space, which very likely serves the entire serially order WM system. This is one of the issues that remain lingering concerning the understanding of serial order construction in WM. Other concerns and remaining questions are discussed later on in this chapter.

The basic model of serial working memory: an extension

Various aspects of a serially ordered WM were established by previous research and supported by empirical observations (e.g., Abrahamse et al., 2014; De Belder et al., 2015). First, serial order coding is a fundamental part of WM processes. Second, the coding of order happens through information binding to position markers. Third, these position markers can be spatial and/or temporal in nature. Fourth, the goal-directed steering of spatial attention serves to localize and retrieve information stored in WM. However, importantly, the identification of processes related to serial order coding in WM always occurred in the setting of memorized serially ordered item sequences. In other words, we know that the previously described components are involved in the coding of serial order in intentional conditions; the task at hand specifically requires the processing and coding of order in WM. Thus, what will happen if serial order is not a fundamental part of the given task setting? Are the mechanisms described to be involved in serial order coding so fundamental to WM functioning that they are automatically recruited and employed in contexts where serial order is redundant to the task?

In literature we observed that the automatic memorization of serial order of items is often assumed. For example, in the context of list-learning paradigms, such as the RVLT or CERAD-task, participants have to recall a list of items, but are free to recite them in any order (Bruno et al., 2015; Howieson et al., 2011; Paul, Cohen, Moser, Zawacki & Gordon, 2002). However, results are generally interpreted by means of a serial position curve, evaluating the accuracy scores for each item with respect to its position in the original list. The early recall of start and end items of the list often reflect the occurrence of primacy and recency effects, but do not further substantiate the assumption of automatic order coding. Moreover, the automaticity of (temporal) order coding had already been challenged in a few studies, indicating that the assumption of the automatic tendency to encode order within WM is not as obvious as generally believed (Jackson, Michon, Boonstra, De Jonge, De Velder Hasenhorst, 1986; Nairne, 1990; Naveh-Benjamin, 1990; Zacks, Hasher, Alba, Sanft & Rose, 1984). For example, Naveh-Benjamin (1990) observed worse performances on a task requiring temporal reordering when participants were not aware of the upcoming task, compared to participants who were previously informed about this task. In CHAPTER 4 we thus addressed the following questions; first, does incidental order coding occur when the memorization of serial order is redundant to the task? Second, if serial order is automatically represented within WM, does this incidental memory trace receive the same spatial characteristics as intentionally memorized order?

In order to avoid strategy development, we performed a large-scale single-run experiment on hundreds of students. Half of these students were submitted to a paradigm forcing them to memorize the order of a presented sequence of items. The other half of the students were free to choose the way in which they memorized the presented items, as long as they could recall them at the end of the experiment. First, and interestingly, when recalling the memorized items, those who were free to report the memorized items in any order, almost always recalled the WM items in the order they had perceived the items during the memorization phase of the experiment. Only 0.8% of the participants recalled the correct items in a different order. Second, a clear serial position effect was observed in both groups. Whether order had to be memorize or not; slower responses were observed for items located further on in the sequence. These first two observations already indicated the occurrence of incidental and intentional order coding. The third observation revealed a spatial mapping pattern; not only do participants automatically tend to store to-be-memorized information in a serial fashion, this serial fashion receives the same spatial information as in the condition of intentional order memorization. Apparently, automatic serial order coding also leads to information binding to spatially located position markers, giving the stored information its spatial identity.

While automatic order coding is often inherently assumed, these findings are one of the first to convert this assumption into an empirically supported claim. Not only do we automatically tend to organize presented information in a serial fashion, this information is similarly treated to intentionally memorized order sequences and is bound to spatial position markers.

Alzheimer’s patients: a bigger underlying problem

The importance of order processing has been established in healthy participants. However, specific patient groups also suffer from WM impairments, such as patients with Alzheimer’s disease (AD). The reason to address WM impairments and serial order coding in this specific patient group encompasses two arguments. First, the cause of WM impairments in Alzheimer’s patients is insufficiently understood and supported by diverging viewpoints. A proper understanding of the processes causing patients to experience hinder in daily functioning is crucial to early diagnosis, improve quality of life of the patient (along with better empathy for the situation of the patient) and the development of goal-directed treatment strategies. Second, damage to specific processes involved in efficient WM functioning allows us to test hypotheses in situations that are impossible to recreate in a regular experimental setting. In other words, patients provide us with an unique opportunity to improve understanding about their disease and to make a theoretical contribution towards the development of comprehensive WM models.

CHAPTER 5 mainly focused on the behavioral changes resulting from AD, unraveling the role of serial order coding in observed WM impairments. CHAPTER 6 further elaborated on the identification of cortical areas, white matter networks and functional networks that are fundamental to efficient order processing in WM.

Two diverging accounts have previously been proposed to explain the commonly observed WM problems in AD. On the one hand, patients with

AD were argued to suffer from a dysfunctional central executive, a cognitive control center that deals with the division of attentional resources (Baddeley et al., 1986,1991; Baudic et al., 2006). On the other hand, it has been proposed that AD patients simply suffer from a reduced WM capacity (Stopford et al., 2012). These two approaches have been employed as opposing accounts, hindering any consensus concerning as to which mechanisms are truly responsible for unsuccessful employment of WM in AD. In the current dissertation we developed an extensive battery containing neuropsychological and experimental tasks to assess multiple aspects of WM functioning for verbal and visuospatial WM; the allocation of (spatial) attentional resources, WM capacity and the processing of order.

During the performance of general cognitive assessment, AD patients already demonstrated to experience difficulties with completing a math task, while their partners (controls) experienced none or little difficulty with this task. The math task required the execution of only very simple calculations (e.g., 7+5 or 18:2), as frequently performed in daily life. While this task requires little attention and unlikely overloads WM with information, it contains an element of order processing. More comprehensive experimental tasks were executed to test the hypothesis that AD patients specifically suffer from impaired order processing, which affects general WM functioning.

The neuropsychological tests revealed no frontal dysfunction or lower IQ-scores for AD patients compared to the control participants. However, the analysis of the AD patients' performances on the experimental tasks led to the following conclusions. First, WM capacity was not reduced unless the additional WM (order-related processing) operations were required. Second, the goal-directed allocation of attention was impaired, reflected in difficulties with the retrieval of position-specific information stored in WM. AD patients consistently tended to deviate more from the correct item position than control participants. Third, and most importantly, the interaction between those two mechanisms could probably be explained by following striking observation; generally impaired WM functioning in AD demonstrated to be related to the impaired processing of serial order within a spatial coordinate WM system, both for verbal and visuospatial information. AD patients thus specifically experience problems with (I) the information binding to position markers and (II) the employment of internal spatial attention, relating to an affected central executive system.

Alzheimer's patients: the neural landscape

Much empirical evidence is available describing AD-related brain changes in grey and white matter and functional networks. However, most studies employed only one neuroimaging parameter at a time and failed to capture co-occurring functional and structural brain alterations (e.g., Sorg et al., 2007). Moreover, few studies addressed the role of affected WM processes in the investigation of brain changes in AD. Also, while the role of anatomical brain areas in order processing has been established in healthy participants, the viewpoint of an affected mechanism supporting order processing in AD is very new, and thus limits the amount of support explaining the role of specific brain areas or connections that are fundamental to order coding. In extension to the behavioral experimental part of the study of AD, AD patients and their partners were requested to partake in the neuroimaging part of the study. The goal of this study was to relate the degree of integrity of the order processing mechanism with following neuroimaging measures: cortical thickness (T1), integrity of white matter structures (DTI) and functional connectivity (rsfMRI). An order-measure was developed based on the long backward (BDT) and forward digit span (FDT) task and the Corsi block (CBT) task, behavioral tasks that were conducted in the behavioral part of the study. This order measure was specifically developed to reflect the remaining ability to process ordered information.

When relating brain measures with the order measure of the FDT task, no associations were found with any type of alterations in the brain. By contrast, the order measure for the BDT and CBT clearly demonstrated associations with alterations in the brain. Importantly, previous studies already reported qualitative differences between the FDT and BDT/CBT; while the FDT is argued to simply rely on the construction of interitem associations, successful performances on the BDT task and CBT are a result of constructing visuospatial representation, located within the spatial coordinate system of WM (Li & Lewandowsky, 1995; Hoshi et al., 2000). The absence of any relation between the FDT and brain measures was thus reasoned to be a consequence of the different mechanism FDT relies on to represent order. Importantly, correlations between the order-measure of the BDT and CBT revealed strong associations with cortical thickness of frontal (orbitofrontal and rostralmiddlefrontal) regions. The BDT task also demonstrated the role of parietal and temporal regions (left temporal pole and inferior temporal gyrus). Moreover, these cortical changes co-occurred with deterioration of the superior longitudinal fasciculus and corpus callosum, for both the BDT and CBT. The superior longitudinal fasciculus connects posteriorly located regions with the frontal brain areas, the ‘control’ center (Makris et al., 2005). One of the implications of a disrupted superior longitudinal fasciculus is that the WM (relying on prefrontal functioning) is hindered in the transmission of signals to regulate and to direct the focus of attention (localized parietal; De Schotten et al., 2011; Makris et al., 2005). The CBT and BDT also demonstrated an association between order coding and integrity of the inferior fronto-occipital fasciculus, crucial for the intra-hemispheric transfer of information between frontal, occipital and temporal regions.

In order to investigate alterations in functional connectivity related to performances on the order-measure, the default mode network and executive network were selected as networks-of-interest. These two networks are known to typically suffer in AD (Buckner, Andrews-Hanna & Schacter, 2008; Mevel, Chételat, Eustache & Desgranges, 2011; Sorg et al., 2007) and are associated with performance on cognitive tasks (Hampson, Driesen, Skudlarski, Gore & Constable, 2006; Sambataro et al., 2010). While the relation between functional network alterations and order coding was less pronounced in the data presented in CHAPTER 6, small alterations could still be observed. For the executive networks, alterations were observed in the left inferior frontal region and right midfrontal area for the BDT task. Similarly, for the CBT, the executive network revealed reduced functional activity in the left and right parieto-occipital fissure, right precentral and right superior frontal areas, left angular gyrus and left temporal pole. The default mode network mainly revealed reduced functional activity in the left and parieto-occipital fissure and gyri cinguli for the BDT and CBT related to the declining ability to process order. The results for the default mode network for the CBT also revealed reduced activity located right precentral and superior frontal. In sum, these results emphasized the role of specific frontal, parietal and temporal regions associated with order processing in WM, reflected in cortical thinning, degradation of white matter tracts (indicating degradation of the communicating tracts between involved cortical areas). The results for functional activity, mainly for the executive network, also emphasized the involvement of frontal regions in order processing.

In other words, it was found that AD patients specifically suffer from difficulties with the processing of order in WM, which relate to specific brain changes, as observed in cortical thinning, affected integrity of white matter tracts and altered activity of functional networks.

THEORETICAL IMPLICATIONS AND FUTURE RESEARCH OPPORTUNITIES

The fundamentals of the mental whiteboard hypothesis were supported and extended by the findings reported in this dissertation, more specifically by specifying the nature of position markers and emphasizing the automaticity of the order coding process. In CHAPTER 2 it was demonstrated that spatial coordinates are essential to the serial order representation of item information. In CHAPTER 3 we observed that position markers could additionally be constructed by means of temporal information. As briefly mentioned earlier on, the functional involvement of time in serial verbal WM does not indicate whether time directly serves to construct position markers, or whether time is mapped in space. Along with the findings reported in CHAPTER 2, the strong relation between space and the allocation of spatial attention to search through WM is repeatedly reported (e.g., Abrahamse, van Dijck, Majerus & Fias, 2014; De Belder et al., 2015; van Dijck & Fias, 2011; 2013). Secondly, in the context of synesthesia for time, numbers and space, the spatial component has demonstrated to dominate (Hale, Thompson, Morgan, Cappelletti & Kadosh, 2014). These reports suggest that space will always underlie position coding and that other modalities of information could serve as additional support in the construction of ordered memory traces. Therefore, while the engagement of time in the construction of position markers has been established, further research should clarify whether temporal information would or would not suffice to maintain ordered information independent of space.

Moreover, the nature of position markers in the context of order coding has been mainly investigated in the context of verbal WM. In the current dissertation only one visuospatial WM task has been executed to investigated serially ordered WM processes. Patients in AD were instructed to perform a Corsi block task, assessing visuospatial WM processes. In parallel with the BDT and FDT task, an order measure was calculated for the CBT task. AD patients revealed impaired order coding performances for the BDT and FDT task, but also for the CBT task. As decline in performances on the order-measure for the CBT task paralleled the performances observed for the entire battery of verbal WM tasks, this suggests that little difference is expected to be found when investigating the nature of position coding for visuospatial stimuli compared to verbal stimuli. Moreover, similarities between the processing of serial verbal and visuospatial WM material has already been put forward by studies demonstrating the functional similarities between the two, suggesting domain-generality (Hurlston, Hitch & Baddeley, 2014; Majerus et al., 2010). However, as earlier mentioned, the conclusions put forward in CHAPTER 2 to CHAPTER 6 mainly address verbal WM and do not allow for an extension of conclusions towards visuospatial WM. Further research is required to clarify whether the observed involvement of space and/or time is limited to the verbal domain, or whether it reflects a property of ordered WM that is independent of the modality of the processed information (i.e., verbal or visuospatial).

Another important contribution of the research presented in the dissertation concerned the emphasis on the fundamentality of order coding in WM. Findings reported in CHAPTER 4 demonstrated the automatic tendency to memorize item in serial fashion, even if order was redundant to the task performance. Moreover, incidental order coding, similar to intentional order memorization, was accompanied by information binding to spatially located position markers. While the importance of serial order representations in WM has been repeatedly emphasized in literature (e.g., Baddeley, 2003; Henson, 1998; Marshuetz, 2005), the current dissertation provided one of the first bits of evidence supporting (I) the automaticity of serial order coding and (II) the automaticity of spatial binding to position markers in the context of incidental order coding. However, the current research took place in a context where the amount of inflow of information remained within the participants' WM capacity. This indirectly leads to two fundamental questions. What happens when information inflow maximally occupies the available storage space of the WM; what happens when information inflow puts WM to the test by exceeding its capacity limit?

Focusing on the first question: how is the automatic order coding process affected when the to-be-memorized stream of information exceeds WM capacity? A study of Naveh-Benjamin (1990) investigated the automaticity of temporal order coding where participants had to memorize a 30-item list, an amount of items greatly exceeding WM capacity. Half of the participants were informed about the fact that the upcoming recall task required the temporal re-ordering of items, the other half of the participants were only informed about a (unordered) memory test. The results showed that participants who received incomplete information about the temporal re-ordering memory test performed worse compared to participants who were informed about the full nature of the recall task. This observation was interpreted against the automatic encoding of temporal order. However, the study suffered from a couple of methodological limitations, possibly obscuring this automatic ordering process. For example, the instructions for the upcoming task could simply have boosted the construction of the memory trace, explaining the difference in performances between the group of participants who were and those who were not informed about the temporal re-ordering task. So far it thus remains unknown how serially ordered WM would deal with an excessive amount of incoming information.

Second, how is serial information processed when reaching the limits of WM capacity? The majority of research settled on the idea that the average WM capacity allows for the storage of four to six elements (Anderson, Bothell, Lebiere & Matessa, 1998; Cowan, 2001; Gobet & Clarkson, 2004; Mathy & Feldman, 2012; Miller, 1956). The compression of information into ‘chunks’ allows for the retention of larger amounts of information. For example, a phone number 037659305 is hard to be memorized in its original sequence-state, while it appears to be much easier to recall this phone numbers as 03 765 93 05. The basic process of chunking compromises a condensation of information by enhancement and creation of inter-item associations between items within chunks, which can be stimulated by contextual regularities or distinctiveness (e.g., Chekaf, Cowan & Mathy, 2016; Gallistel, 1990). As chunking encompasses a strategy frequently adopted in daily functioning, it is crucial to understand how condensed units of information are encoded and represented within WM.

Chunks consist of separate elements stored in a common unit. This leads to the obvious question; does each element in a single chunk remain its positional identity or is information so condensed that the entire chunk is bound to a single position marker in WM? Moreover, as chunks are more complex than single items, do sequences of chunks relate to each other in the same fashion as sequences of items? Initial research suggested that item identity is not lost when stored within a chunk, which means that each item within a chunk is bound to its own position marker (and not a common position marker for all elements within a common chunk). Moreover, it appeared that chunks are additionally treated as separate elements and a sequence of chunks is stored in the same serial and spatial fashion as item sequences (Abrahamse, et al., in preparation). However, this research is limited to the chunking of random sequences of letters and needs to be extended to the evaluation of existing chunks (e.g., abbreviations, words, phone numbers).

Lastly, by means of an Alzheimer patient study, the current dissertation attempted to extract the crucial brain structures and localized functional connectivity that are essential to order coding within WM. Specific areas in the frontal, parietal and temporal regions of the cortex, along with frontal functional activity in the default mode network and executive networks demonstrated to be associated with the ability to code order information within WM. Moreover, the integrity of large posterior-to-frontal tracts, such as the superior longitudinal fasciculus, and communication between the two hemispheres demonstrated their involvement in order coding in AD. The partaking of so many parts of the brain indicated that the processing of order in WM is a demanding process that relies on the integrity of the cortex, but also communicative white matter tracts and specific functional connectivity within the brain, which had already been partially shown in healthy subject studies (e.g., Majerus, 2008; Marshuetz, 2005). For example, distinctive brain areas have been associated with the processing of order versus item identity; while prefrontal and parietal regions demonstrated to be crucial to the processing of order information (Henson, Burgess & Frith, 2000; Marshuetz et al., 2000), the processing of item identity is supported by temporal brain areas (Majerus et al., 2006). Moreover, AD is also typically associated with impaired long-term memory processes, which are associated with damage to related areas, such as the temporal cortex (e.g., Simons & Spiers, 2003). In light of the observed brain alterations in the context of AD and impaired order processing, it would be interesting to investigate to what extent the information binding to position markers in WM supports information transfer and consolidation processes in long-term memory or how long-term memory affects the construction of ordered memory traces within WM.

Importantly, the idea of impaired serial order processing in AD underlying WM deficits is completely new. As a consequence, many questions remain concerning the consequence of this observation. It should be investigated whether the conduction of serial order tasks would facilitate early and a more comprehensive diagnosis of AD. Moreover, further research could add to the development of training tools or other treatment strategies designed to specifically improve the employment of WM and the application of WM strategies. Furthermore, the assessment of problems with order processing could be associated with other cognitive dysfunctions (e.g., issues observed with auditory comprehension and verbal expression), allowing for a development of domain-general treatment strategies. Moreover, as experienced in clinical practice, patients and their significant others experience an insufficient understanding of what the disease does with the brain, leading to feelings of defeat, frustration and uncertainty about how to react to specific situations. A better understanding of affected processes resulting from Alzheimer dementia might serve to improve the significant others' understanding and therefore improve the quality of life for both parties (e.g., improved empathy, providing information in a strictly structured fashion). In other words, the scope of the reported findings should be extended and further explored in many other areas relating to AD.

GENERAL CONCLUSION

The current dissertation emphasized the importance and the omnipresence of order processing in WM. Whether we are attending to the ordered structure of information or not, our mind seems to automatically process and structure this information. Actually, the processing of serial order seems to be so fundamental to behavior, that it is unsure whether order processing should be a part of the central executive system or whether it is independently processed and serves to bind the central executive to the short-term memory systems. Moreover, the serial organization of information in WM demonstrates that it is determined by space and time, but poses the question to what extent our way of thinking is generally limited by processing space and time. Overall, it is clear that serial order processing (at least partially) shapes our thinking, however, it is unknown how far this mind shaping goes.

Overall, the studies presented in the current dissertation demonstrated the automaticity of order processing, using space and time to construct serial order in WM. Furthermore, serial order processing demonstrated to be specifically affected in patients with Alzheimer's disease, which broadens the scope to investigate whether it could offer an explanation for other affected cognitive abilities (e.g., language processing). Also, comprehension of the neural image underlying order processing in Alzheimer's disease was substantiated by the observation of alterations in cortical thickness, white matter integrity and functional networks.

However, further research is needed to investigate the true effect of order coding in WM on our thinking. The automatic tendency to structure information in an orderly and organized fashion might shape and influence our thinking in a way that is currently severely underestimated and misunderstood, but provides an incredibly interesting field of research to further dig into.

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CHAPTER 8

NEDERLANDSTALIGE SAMENVATTING

In het dagelijkse leven worden we bijna continu geconfronteerd met noodzaak om informatie op een seriële manier te verwerken. Zo omvat het koken van een recept een chronologische doorloop van stappen om tot een lekker gerecht te komen. Wanneer we communiceren met anderen, zorgen onderliggende regels over de zinsbouw ervoor dat we elkaar kunnen begrijpen. Daarnaast omvat het doorlopen van de dagelijkse routine eveneens een chronologische structuur. Kortom, het kunnen verwerken van seriële informatie en het mentaal kunnen ordenen van informatie zijn essentieel om in het dagdagelijkse leven efficiënt te kunnen functioneren. Daar waar we langetermijn representaties van seriële orde hebben, zoals een specifieke herinnering waar alles geordend is in tijd, moeten we ook vaak informatie op een tijdelijke manier kunnen vasthouden. Dit laatste gebeurt in het werkgeheugen (WG), een flexibel cognitief systeem waar de tijdelijke opslag van informatie plaatsvindt en opgeslagen informatie makkelijk gemanipuleerd kan worden (Baddeley, 1996; Jonides, Lacy & Nee, 2005). Zoals afgeleid kan worden uit de gegeven voorbeelden, zijn vaardigheden zoals het gebruiken van taal, redeneren en leerprocessen grotendeels afhankelijk van het WG en orde verwerking (Baddeley, 2012; Martin & Gupta, 2004). Het achterhalen van hoe informatie in het WG gestructureerd wordt, is dus cruciaal om ons gedrag in het dagdagelijkse leven beter te begrijpen en vormt dus de focus van deze thesis.

Hoofdstuk 2 en 3 in dit proefschrift zoeken een antwoord op ‘hoe’ informatie op een seriële orde opgeslagen wordt in het WG. Hoofdstuk 4 gaat na in welke mate seriële orde op een automatische manier verwerkt wordt. Bovendien gaan we hier na of seriële orde op een kwalitatief gelijke manier voorgesteld wordt in het WG wanneer we enerzijds bewust focussen op het onthouden van seriële order versus wanneer we dit niet doen. Hoofdstuk 5 en 6 focussen we op patiënten met de ziekte van Alzheimer (ZvA), een patiëntengroep die gedeeltelijk gekarakteriseerd wordt door ernstige WG problemen (e.g., Baddeley, Logie, Bressi, Della Sala & Spinnler, 1986; Baddeley, Bressi, Della Sala, Logie & Spinnler, 1991; Baudic et al., 2006). Het is echter onvoldoende begrepen welke mechanismen precies aangetast zijn in het veroorzaken van WG problemen bij Alzheimer-patiënten. In Hoofdstuk 5 testen we de rol van een verkleinde werkgeheugencapaciteit, aangetaste aandachtsprocessen en een mogelijke grotere onderliggende factor: het niet efficiënt kunnen verwerken van orde informatie. In Hoofdstuk 6 worden gedragsmatige bevindingen uit Hoofdstuk 5 gecorreleerd met verschillende types beeldvorming van de hersenen. Hierbij wordt nagegaan welke corticale structuren, wittestofbanen en functionele netwerken er aangetast zijn in de ZvA, die leiden tot problemen met het verwerken van orde.

ORDE IN HET WERKGEHEUGEN: IN TIJD EN RUIMTE

Vele theoretische modellen werden reeds gepubliceerd die het belang van ordeverwerking benadrukken en de onderliggende mechanismen trachten te beschrijven. Zo zijn er ‘kettingmodellen’ die aangeven dat seriële orde in het WG gevormd wordt doordat opeenvolgende items in een reeks aan elkaar gebonden worden (Elman, 1990; Murdock, 1993; Richman & Simon, 1994). Hierdoor kan elk item dienen als cue voor het ophalen van het hierop volgende item. Deze modellen hebben echter verschillende tekortkomingen. Zo zou volgens kettingmodellen de prestatie verminderen wanneer er in een reeks twee keer hetzelfde item wordt aangeboden (e.g., 528623), hoewel dit in de praktijk geen problemen oplevert. Door dit soort eenvoudige tekortkomingen worden kettingmodellen doorgaans overstemd door de populairdere 'positionele modellen'. Het 'start-end' model van Henson (1998) is het meest bekende model. Hierbij wordt beargumenteerd dat sequentiële informatie op een seriële manier in het WG wordt opgeslagen doordat elk item van de reeks informatie krijgt over de sterkte van een begin- en eindmarker. De sterkte van de beginmarker is het sterkste voor het allereerste element uit de reeks en neemt af in sterkte naarmate items verder naar het einde van de reeks gelegen zijn. Het omgekeerde geldt voor de eindmarker, die het sterkste is voor het laatste element uit de reeks.

De literatuur beschrijft nog enkele andere positionele modellen, maar deze lijden grotendeels aan dezelfde tekortkomingen: I) de meeste modellen zijn weinig empirisch getest, maar berusten vooral op computationele berekeningen (Brown, Preece & Hulme, 1996; Burgess & Hitch, 1996), II) hoewel, o.a., het start-end model, spreekt over positie markers, worden er zelden uitspraken gedaan over de exacte natuur van deze positie markers en III) ook de onderliggende neurale natuur van positie markers is tot nu toe onbeschreven gebleven.

Deze theoretische tekorten gaven een kader waaruit het onderzoek van deze thesis vertrok. In onderzoek door van Dijck, Abrahamse, Majerus en Fias (2013) werd er reeds gevonden dat het verwerken van informatie opgeslagen in het WG invloed had op hoe efficiënt hierna gepresenteerde ruimtelijke targets werden verwerkt. Meer specifiek, proefpersonen werden gevraagd om een reeks getallen te onthouden in de juiste volgorde. Hierna voerden ze een taak uit waarbij eerst een getal werd aangeboden, gevolgd door een ruimtelijke cue, i.e., een bol aan de linker- of rechterkant van het scherm. Proefpersonen werden gevraagd om zo snel mogelijk aan te geven of de bol aan de linker- of rechterkant van het scherm verscheen, maar mochten enkel een antwoord geven wanneer het voorgaande getal deel uitmaakte van de reeks die ze moesten onthouden. Hierbij observeerden ze dat proefpersonen sneller een linkerbol detecteerden wanneer deze voorafgegaan werd door een item uit het begin van de WG reeks. De detectie van een rechterbol werd gefaciliteerd wanneer een einditem uit het WG vooraf ging aan de verschijning van de bol. Hiermee toonden ze reeds aan dat er een sterke link is tussen ruimte en seriële orde in het WG. In Hoofdstuk 2 gingen we na of deze rol essentieel en functioneel is. Om aan te tonen dat ruimtelijke informatie fundamenteel is om informatie in serieel verbaal WG te organiseren moest er aangetoond worden dat hun relatie op een bidirectionele manier werkt. Enerzijds toonden van Dijck et al. (2013) aan dat seriële informatie uit het WG het verwerken van ruimtelijke cues kan faciliteren. Wij trachtten deze bevinding aan te vullen met de observatie dat ruimtelijke cues eveneens het lokaliseren van informatie in het WG kunnen faciliteren. Twee experimenten werden uitgevoerd om deze hypothese te testen. De experimenten waren als volgt opgebouwd: proefpersonen werden gevraagd om een reeks van letters te onthouden in de correcte volgorde. Hierop volgend werden bollen aangeboden aan de linker- of rechterkant van het scherm, gevolgd door een letter. In Experiment 1 werden proefpersoon gevraagd om zo snel mogelijk te reageren met een druk op een centrale knop wanneer een volgende event zich voordeed: de bol verscheen extreem links of extreem rechts op het scherm (niet centraal) en de gepresenteerde letter kwam uit de reeks die ze moesten onthouden. In Experiment 2 mocht de proefpersoon de ruimtelijk aangeboden bollen volledig negeren, maar werd er gevraagd verbaal te reageren wanneer de aangeboden letter één uit de te onthouden reeks letters kwam. Observaties voor beide experimenten waren dezelfde; proefpersonen reageerden sneller op een item uit het begin van de WG reeks wanneer deze voorafgegaan werd door een links aangeboden cue, terwijl het omgekeerde werd geobserveerd voor letters uit het einde van de WG reeks en rechts aangeboden cues. Deze bevindingen onderbouwen de aanwezigheid van een bidirectionele link tussen ruimtelijke informatie en de seriële opslag van items in WG, aangevend dat informatie in het WG opgeslagen wordt binnen een ruimtelijk coördinatensystem. Deze bevinding droeg bij aan de uitwerking van de 'mental whiteboard hypothesis', beschreven door Abrahamse, van Dijck, Majerus & Fias (2014). Zij werkten een breder theoretisch kader uit om te beschrijven hoe seriële informatie gerepresenteerd wordt binnen het WG. De 'mental whiteboard hypothesis' vertrekt vanuit het idee dat opgeslagen informatie in het WG georganiseerd wordt binnen een ruimtelijk coördinatensysteem. Bovendien baseert het model zich op drie essentiële assumpties over de werking van dit coördinatensysteem: I) opgeslagen informatie in het WG wordt ruimtelijk georganiseerd doordat de items gebonden worden aan positie markers, II) om informatie op te zoeken in het WG moet intern ruimtelijke aandacht aangewend worden en III) het ophalen van WG informatie gebeurt door selectie via het sturen van deze ruimtelijke aandacht.

Een beperking van deze theorie is echter dat het de betrokkenheid van andere modaliteiten van informatie in het construeren positie markers niet verder bespreekt. Echter, het positionele ‘oscillator-based’ model suggereert dat de interne staat van neurale oscillators gebruikt wordt om seriële orde op te slaan in het WG. Hierbij wordt beargumenteerd dat ‘tijd’ cruciaal is om orde op te slaan en dat de staat van de oscillatoren bepaald wordt door het punt in de tijd waarop specifieke informatie binnen komt. In Hoofdstuk 3 gaan we hier verder op in en werden hiervoor twee experimenten afgenomen. Opnieuw werd de aan- of afwezigheid van een bidirectionele link tussen een opgeslagen WG reeks en de verwerking van tijdsinformatie nagegaan. Experiment 1 verliep als volgt: proefpersonen werden gevraagd om een reeks letters te onthouden in de correcte volgorde. Hierna moesten ze een taak uitvoeren waarbij een letter in het rood werd aangeboden. Deze letter veranderde na een korte (1100ms) of langere (3000ms) tijd naar groen. De taak van de proefpersoon was om zo snel mogelijk op een knop te duwen wanneer de letter groen werd, maar dit enkel te doen wanneer de letter uit de WG reeks kwam. De resultaten toonden aan dat proefpersonen sneller waren om te reageren na een kortere wachttijd wanneer ze een item uit het begin van de WG reeks zagen, terwijl het omgekeerde werd geobserveerd voor de langere wachttijd. Deze resultaten suggereerden al dat seriële positie van een item uit het WG een effect heeft op het verwerken van tijd. In Experiment 2 werd het omgekeerde verband getest. Opnieuw werden proefpersonen gevraagd om een reeks van letters in een bepaalde volgorde te onthouden. Hierna kregen ze telkens een geluid en een groene bol te zien, gevolgd door de aanbieding van een letter. De taak van de proefpersoon was om zo snel mogelijk op een knop te duwen wanneer het geluid heel kort of heel lang was en het item uit de WG reeks kwam. Een respons was niet toegelaten wanneer het aangeboden geluid slechts van middelmatige duur was of het item niet in de WG reeks voorkwam. De resultaten waren als volgt; een kort geluid faciliteerde het herkennen van een item uit het begin van de WG reeks, een lang geluid faciliteerde het herkennen van een einditem van de WG reeks. Deze twee experimenten bevestigden de bidirectionele link tussen seriële positie en het verwerken van tijd. Met andere woorden, temporele informatie kan dus gebruikt worden om seriële orde in het WG op te slagen.

Kortom, de bevindingen gerapporteerd in Hoofdstuk 2 en 3 geven aan de seriële orde in het WG gerepresenteerd kan worden aan de hand van ruimtelijke en/of temporele informatie. Voor de constructie van temporele positie markers kunnen we echter niet uitsluiten dat temporele informatie gedeeltelijk ruimtelijk ondersteund is. Met andere woorden, mogelijk kan tijd gebruikt worden om aanvullend op ruimtelijke informatie seriële orde te representeren in het WG, maar het is onduidelijk of temporele informatie ook gebruikt kan worden onafhankelijk van de aanwezigheid van ruimtelijke informatie. Het is aan toekomstig onderzoek om een antwoord op deze vraag te bieden.

DE ZIEKTE VAN ALZHEIMER: EEN UNIEK LANDSCHAP

De zieke van Alzheimer (ZvA) is vooral bekend om de opvallende problemen die patiënten vertonen met het langetermijngeheugen. Echter, hoewel werkgeheugenproblemen minder opvallen, omvatten zij een fundamenteel onderdeel van de ziekte en tastten zij de patiënt aan in het dagdagelijks functioneren (Baddeley et al., 1986, 1991; Baudic et al., 2006; Hodges, Salmon & Butters, 1992; Miller, 1973; Perry, Watson & Hodges, 2000; Stopford, Thompson, Neary, Richardson & Snowden, 2012; Welsh, Butters, Hughes, Mohs & Heyman, 1991). De mechanismen onderliggend aan een aangetast functioneren van het WG in patiënten met de ZvA zijn echter onvoldoende begrepen. In de literatuur worden er twee tegengestelde standpunten geopperd. Langs de ene kant wordt er beargumenteerd dat patiënten met de ZvA lijden aan een aangetaste werking van de ‘central executive’, een controlecentrum dat verantwoordelijk is voor het aansturen van aandacht. Problemen met de ‘central executive’ zouden leiden tot problemen met het wisselen en verdelen van aandacht tussen twee taken, het onderdrukken van irrelevante informatie, selectie van strategisch gedrag, het updaten van de WG inhoud, etc. (Wilhelm, Hildebrandt & Oberauer, 2013). Inderdaad, meerdere studies tonen aan dat patiënten problemen vertonen bij het uitvoeren van dubbeltaken (Baddeley et al., 1986, 1991) en een variëteit aan taken die executief functioneren meten (Baudic et al., 2006; Bhutani, Montaldi, Brooks & McCulloch, 1992). Deze bevindingen suggereren dat de ‘central executive’ inderdaad een aangetaste component kan zijn die WG problemen in de ZvA tot uiting brengt.

Echter, daar staat tegenover dat executief functioneren doorgaans geassocieerd wordt met frontale hersengebieden, terwijl corticale degeneratie in de initiële stadia van de ZvA vooral meer posterieur en temporaal geobserveerd wordt. Bovendien vertonen deze patiënten ook problemen met taken die weinig executief functioneren vereisen, maar wel berusten op het WG (Stopford et al., 2010; 2012). Meer specifiek, ervaren patiënten met de ZvA grotere problemen met de hoeveelheid aan informatie die verwerkt moet worden dan met het uitvoeren van executieve taken (Stopford et al., 2010; 2012). Dit laatste suggereert dus eerder een algemeen verkleinde WG capaciteit dan een aangetaste ‘central executive’ functioneren.

In dit proefschrift gingen we echter na of er geen groter onderliggend probleem aan de basis ligt van de WG problemen in de ZvA, namelijk problemen met het verwerken van orde in informatie.

Bijna alles wat we doen in het dagelijkse leven vereist het verwerken van seriële volgorde. Ook executieve taken berusten voor een groot deel op efficiënte orde verwerking. WG capaciteit wordt doorgaans zelfs enkel getest aan de hand van taken die expliciet ordeverwerking in de instructies bevatten, e.g., voorwaartse en achterwaartse span taken. Bij span taken worden proefpersonen namelijk expliciet gevraagd om reeksen van getallen in voorwaartse of achterwaartse volgorde te herhalen. Zowel het bepalen van executief functioneren als het meten van WG capaciteit gebeurt aan de hand van taken die een ordecomponent bevatten. In Hoofdstuk 5 wordt er dus nagegaan of een onderliggend probleem met het verwerken van orde een verklaring kan bieden voor het aangetast WG functioneren in de ZvA. Patiënten met de ZvA en hun partners (de partners werden onderzocht als controlesubjecten) werden getest op een ruime batterij aan taken, waaronder een voorwaartse en achterwaartse verbale spantaak en een visuospatiale span taak. Hierbij werd algemeen cognitief functioneren en verschillende aspecten van WG functioneren getest. De belangrijkste bevinden waren de volgende: I) Een gereduceerde WG capaciteit werd enkel geobserveerd wanneer de taak voor extra cognitieve belasting zorgde. Meer specifiek, de WG capaciteit voor patiënten met de ZvA was dezelfde als deze van controlesubjecten bij het uitvoeren van de voorwaartse digit span taak. De achterwaartse digit span taak vereist echter mentale manipulatie van de opgeslagen items om deze in achterwaartse volgorde op te roepen. Deze extra mentale manipulatie leidde tot de observatie van een verkleinde WG capaciteit in patiënten met de ZvA vergeleken met de controlegroep. II)

Patiënten met de ZvA vertoonden specifieke problemen met het richten van de aandacht in het WG om opgeslagen informatie terug op te roepen. Bijvoorbeeld, wanneer gevraagd werden om uit de reeks 'ktbhf' de 4de letter op te roepen, lag een incorrect antwoord gegeven door patiënten doorgaans verder van het juiste antwoord (e.g., antwoord: 'k'), dan een antwoord gegeven door een controlesubject (e.g., antwoord 'b'). Deze twee eerste punten suggereren dus eerder de aantasting van de 'central executive', in plaats van een algemeen verkleinde WG capaciteit.

III) Patiënten vertoonden specifieke en ernstige problemen met het verwerken van orde informatie, een observatie die duidelijk tot uiting kwam in alle gebruikte experimentele taken. Hoewel hun geheugen voor het item zelf (item identiteit) redelijk gespaard bleef, bleek het geheugen voor item orde ernstig aangetast te zijn. Kortom, een verminderde verwerking van de 'central executive' en algemene problemen met het verwerken van orde blijken de centrale problemen die de aangetaste werking van het WG in de ZvA verklaren.

Vele studies gingen reeds na welke regio's, wittestofbanen en functionele netwerken aangetast worden door de ZvA. De ZvA wordt typisch gekarakteriseerd door initiële corticale atrofie in de temporale kwab, dat zich geleidelijk over de temporale kwab en het hele brein uitbreidt (e.g., Killiany et al., 1993; Fox et al., 1996). Bovendien wordt de ZvA ook al beschreven als een dissconnectiesyndroom, waarbij normale communicatie tussen bepaalde hersengebieden niet langer geobserveerd wordt. Zo werd er aan de hand van resting state functional magnetic resonance imaging (rsfMRI) aangetoond dat specifiek executieve aandachtsnetwerken en de default mode network (een netwerk dat geactiveerd wordt bij rust en gedesactiveerd bij cognitieve taken) specifiek verstoord zijn (Buckner, Andrews-Hanna & Schacter, 2008; Mevel, Chételat, Eustache & Desgranges, 2011; Sorg & Riedl, 2007). Ook specifieke wittestofbanen, banen die communicatie tussen verder gelegen regio's toelaten, worden aangetast door de ZvA, waaronder het corpus callosum, superior longitudinal fasciculus en cingular tracts (Zhang et al., 2009; Rose et al., 2000; Kantarci et al., 2010).

Aangezien de bevinding van aangetaste ordeverwerking in het WG in patiënten met de ZvA een relatief nieuw idee is, zijn ook de onderliggende neurale mechanismen onvoldoende begrepen. Slechts één studie rapporteerde de observatie dat patiënten slechter waren in het onthouden van seriële volgorde in een digit span taak, dan het onthouden van items in een random volgorde (Lamar, Catani, Price, Heilman & Libon, 2008). Ze observeerden ook een correlatie tussen verminderde ordeprestaties en de ernst van de leukoaraiosis (i.e., diffuse hyperintensiteiten geobserveerd in witte materie). Voor de studie beschreven in Hoofdstuk 6 ontwikkelden we een gedragsmaat die specifiek de efficiëntie van ordewerking reflecteerde. Deze ordemaat werd berekend voor drie verschillende taken; de voorwaartse en achterwaartse verbale span taak en een visuospatiale span taak. De ordemaat werd vervolgens gecorreleerd met beschikbare neurale beeldvorming van patiënten met de ZvA en hun partners, de controlegroep. We beschikten over anatomische scans om gelokaliseerde corticale verdunning na te gaan, diffusiebeelden die toelieten de integriteit van wittestofbanen te berekenen en rsfMRI om veranderingen in executieve aandachtsnetwerken en het default mode netwerk te analyseren.

Verminderde mogelijkheid om orde efficiënt te verwerken, werd geassocieerd met verschillende veranderingen in de hersenen. Corticale atrofie werd geobserveerd voor frontale regio's, geassocieerd met executieve en aandachtsgerelateerde processen (Baddeley et al., 1986; Shallice, 1988). Ook pariëtale en temporale regio's vertoonden gelokaliseerde corticale atrofie, gelinkt met verminderde ordeverwerking. Analyses van de wittestofbanen vertoonden degeneratie van de superior longitudinal fasciculus, een baan dat posterior gelegen gebieden met frontale gebieden connecteert. De aantasting van de superior longitudinal fasciculus zou onder andere het WG verhinderen om signalen naar pariëtale regio's te sturen om aandacht te reguleren (De Schotten et al., 2011; Makris et al., 2005). Geobserveerde aantasting van het corpus callosum verhinderde de communicatie tussen de twee hemisferen. Ook aantasting van delen van de fronto-occipital fasciculus correleerde met slechtere ordeprestaties.

Resultaten van de resting state netwerk toonden dat het executieve netwerk geassocieerd was met verminderde activatie in frontale en temporele regio's bij slechtere prestaties op de ordemaat. Het default mode netwerk vertoonde vooral verminderde activatie in de linker- en rechter parieto-occipitale fissuur, posterieure gyri cinguli en frontale gebieden.

Kortom, deze resultaten tonen aan dat het verminderde vermogen om orde te kunnen verwerken in het WG geassocieerd is met integriteit van frontale, pariëtale en temporele regios. Dit werd geobserveerd in gelokaliseerde corticale atrofie, maar ook de integriteit van specifieke wittestofbanen en verminderde functionele activatie van bepaalde regio's in het executieve en default mode netwerk.

CONCLUSIE

Doorheen het gehele proefschrift werd het vaak benadrukt: orde is alomtegenwoordig in ons leven. Onderzoek naar ordeverwerking in het WG zou ons moeten helpen begrijpen op welke manier we informatie uit onze externe wereld en interne mentale leefwereld verwerken. De bevindingen gerapporteerd in dit proefschrift suggereren dat we vermoedelijk de impact van orde op het vormgeven van onze gedachten onderschatten. Allereerst observeerden we dat orde geconstrueerd kan worden met behulp van informatie over tijd en ruimte. Wil dat dan ook zeggen dat ons gehele denken gelimiteerd wordt door informatie te verwerken in tijd en ruimte? Zijn er andere modaliteiten van informatie in de leefwereld waartoe onze hersenen niet in staat zijn ze te verwerken, om informatie op een gestructureerde manier waar te nemen? Bovendien stelden we vast dat ordeverwerking een automatisch proces is. Zelfs wanneer een ordestructuur niet nodig is om met gedrag het juiste doel te bereiken, hebben we toch de neiging om informatie serieel te structureren. Meer zelfs, ook bij automatisch ordeverwerking berusten we op het gebruik van spatiale coördinaten om deze informatie mentaal in het WG op te slaan.

Ook in patiënten met de ZvA observeerden we dat het efficiënt kunnen verwerken van orde informatie essentieel is om WG processen normaal te laten functioneren. In patiënten met Alzheimer zagen we dat ze problemen ervoeren met, enerzijds, het aansturen van de ‘central executive’ en verbonden aandachtsprocessen, en anderzijds, het verwerken van seriële orde. Het samen voorkomen van deze twee stelt de vraag in welke mate het kunnen verwerken van seriële orde deel uitmaakt van het takenpakket van de ‘central executive’ of dat ordeverwerking een fundamenteler proces is, dat de ‘central executive’ bindt met de kortetermijn geheugensystemen. Gezien onze bevindingen suggereren dat het kunnen verwerken van orde zo fundamenteel is voor gedrag en het functioneren van het WG, lijkt het waarschijnlijker dat orde onafhankelijk van de ‘central executive’ verwerkt wordt. Verder onderzoek is nodig om hier een duidelijker antwoord op te bieden. In ieder geval geven de analyses van de neurale beelden van patiënten met Zva aan dat ordeverwerking berust op een combinatie van specifieke corticale regio’s en de integriteit van communicerende banen tussen gebieden. Zo blijken vooral corticale integriteit voor (inferieur) frontale, pariëtale en temporale regio’s, de functionele communicatie in deze gebieden, evenals hun verbindende wittestofbanen (superior longitudinal fasciculus, corpus callosum en fronto-occipital fasciculus) gerelateerd te zijn aan aangetaste ordeverwerking. Dit geeft aan dat ordeverwerking en het structureren van informatie voor (WG) opslag tot stand komt door informatieverwerking en communicatie tussen meerdere gebieden, maar niet toegewezen kan worden aan een enkel verantwoordelijke hersenregio.

Al bij al is er nog zo veel te ontdekken over hoe ordeverwerking onze externe en mentale leefwereld vorm geeft, maar dat is iets voor toekomstig onderzoek.

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DATA STORAGE FACT SHEETS

In compliance with the UGent standard for research accountability, transparacy and reproducibility, the location of the datasets used in this dissertation are added below. For each of the empirical chapters (i.e., chapters 2 to 4) a separate Data Storage Fact Sheet is completed, detailing which data and analysis files are stored, where they are stored, who has access to the files and who can be contacted in order to request access to the files. In addition, the Data Storage Fact Sheets have been added to my public UGent Biblio account.

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% Author: Maya De Belder
% Date: 11-12-2014

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===========================================================
========

1a. Main researcher -------------------------------------------
----------------------------
- name:Maya De Belder
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: maya.debelder@ugent.be
```

```
1b. Responsible Staff Member (ZAP) ----------------
-------------------------------------------
- name: Wim Fias
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: wim.fias@ugent.be

If a response is not received when using the above
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2. Information about the datasets to which this
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* Reference of the publication in which the
datasets are reported: De Belder, M., Abrahamse,
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(2015). Serial position markers in space:
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* Which datasets in that publication does this
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----------------------------
- name:Maya De Belder
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: maya.debelder@ugent.be

1b. Responsible Staff Member (ZAP) -----------------
--------------------------------------------
- name: Wim Fias
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: wim.fias@ugent.be

If a response is not received when using the above
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De Belder, M., van Dijck, J. P., Cappelletti, M., & Fias, W. (2016). How serially organized working memory information interacts with timing. Psychological Research, 1-9.

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3b. Other files -----------------------------------
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* Which other files have been stored?
- [ ] file(s) describing the transition from raw
data to reported results. Specify: ...
- [X] file(s) containing processed data. Specify:
excel-file containing processed data
- [ ] file(s) containing analyses. Specify: ...
- [ ] files(s) containing information about
informed consent
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provisions
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stored files and
how this content should be interpreted. Specify:
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* On which platform are these other files stored?
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% Author: Maya De Belder
% Date: 02-07-2015

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1a. Main researcher -------------------------------
----------------------------
- name:Maya De Belder
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: maya.debelder@ugent.be

1b. Responsible Staff Member (ZAP) ----------------
-------------------------------------------
- name: Wim Fias
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: wim.fias@ugent.be

If a response is not received when using the above
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3a. Raw data --

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- [X] research group file server
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* Who has direct access to the raw data (i.e., without intervention of another person)?
- [X] main researcher
- [ ] responsible ZAP
- [X] all members of the research group
- [ ] all members of UGent
- [ ] other (specify): ...

3b. Other files --

* Which other files have been stored?
- [ ] file(s) describing the transition from raw data to reported results. Specify: ...
- [X] file(s) containing processed data. Specify: excel-file containing processed data
- [X] file(s) containing analyses. Specify: SPSS-syntax file with code for linear regression analysis
- [ ] files(s) containing information about informed consent

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- [ ] a file specifying legal and ethical
provisions
- [ ] file(s) that describe the content of the
stored files and
how this content should be interpreted. Specify:
...
- [ ] other files. Specify: ...

* On which platform are these other files stored?
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- [X] research group file server
- [ ] other: ...

* Who has direct access to these other files (i.e.,
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1a. Main researcher ---

- name:Maya De Belder
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: maya.debelder@ugent.be

1b. Responsible Staff Member (ZAP) ---

- name: Wim Fias
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: wim.fias@ugent.be

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2. Information about the datasets to which this sheet applies
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De Belder, M., Santens, P., Sieben, A., & Fias, W. (submitted). Impaired processing of serial order determines working memory impairments in Alzheimer's disease. Submitted to Journal of Alzheimer's Disease.

* Which datasets in that publication does this sheet apply to?:
All data

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3. Information about the files that have been
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3a. Raw data --------------------------------------
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* On which platform are the raw data stored?
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- [X] research group file server
- [ ] other (specify): ...

* Who has direct access to the raw data (i.e.,
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- [X] main researcher
- [ ] responsible ZAP
- [X] all members of the research group
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- [ ] other (specify): ...

3b. Other files -----------------------------------
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* Which other files have been stored?
- [ ] file(s) describing the transition from raw
data to reported results. Specify: ...
- [X] file(s) containing processed data. Specify:
excel-file containing processed data
- [ ] file(s) containing analyses. Specify: …
- [ ] files(s) containing information about
informed consent
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provisions
- [ ] file(s) that describe the content of the
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how this content should be interpreted. Specify:
...
- [ ] other files. Specify: ...
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* On which platform are these other files stored?
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- [X] research group file server
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- name:Maya De Belder
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: maya.debelder@ugent.be

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- name: Wim Fias
- address: Henri Dunantlaan 2, 9000 Gent
- e-mail: wim.fias@ugent.be

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* Reference of the publication in which the datasets are reported:
De Belder, M., van Dijck, J-P., Santens, P., Doricchi, F., Sieben, A., Aerts, H., & Fias, W. Compromised order processing in Alzheimer’s dementia demonstrated by cortical thickness, DTI and rsfMRI. Submitted to Neuroimage:Clinical

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Neuroimaging data

3. Information about the files that have been stored

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3a. Raw data ---

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- [X] researcher PC
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- [ ] responsible ZAP
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3b. Other files ---

* Which other files have been stored?
- [ ] file(s) describing the transition from raw data to reported results. Specify: ...
- [X] file(s) containing processed data. Specify: excel-file containing processed data
- [ ] file(s) containing analyses. Specify: …
- [ ] files(s) containing information about informed consent
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- [ ] other files. Specify: ...

* On which platform are these other files stored?
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- [ ] other: ...

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* Who has direct access to these other files (i.e.,
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