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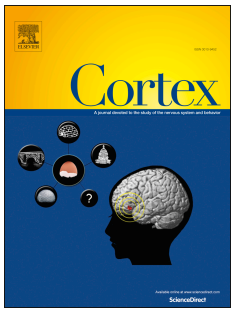

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A commentary on Liang et al.'s paper with regard to emerging views of memory assessment in Alzheimer's disease

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Liang, Pertzov, Nicholas, Henley, Crutch et al. (2016) reported on a study carried out to investigate whether Alzheimer's disease in its familial variant (FAD) affects visual short-term memory (VSTM) for integrated representations comprising visuospatial information i.e., object and location. This is the second study investigating VSTM binding abilities in symptomatic and pre-symptomatic cases of FAD. An earlier study investigated VSTM for integrated representations comprising surface features such as shapes and colours (Parra, Abrahams, Logie, Mendez, Lopera et al., 2010a). The memory function investigated by Liang et al. (2016) is known as "relational binding" whereas that one investigated by Parra et al. (2010a) is known as "conjunctive binding". Visuospatial relational binding deficits in long-term memory (LTM), also known as associative learning impairments, have been previously reported in cases of sporadic AD (SAD) in the clinical (Swainson, Hodges, Galton, Semple, Michael et al., 2001) and prodromal stages (Fowler, Saling, Conway, Semple, & Louis, 2002). Parra, Abrahams, Logie, and Della Sala (2010b) have reported VSTM conjunctive binding deficits in SAD. Taken together, the results from these studies suggest that AD affects memory binding abilities regardless of the variant of the disease, the memory system where bound representations are held, or the nature of such representations (i.e., shapes, colours, locations).

The evidence drawn from rare cases of FAD is expected to support research into AD broadly. I will therefore focus my commentary on memory assessment in AD as a disorder affecting people at different ages. Particularly, I will focus on four areas on which Liang et al.'s study motivates debate: (1) format and structure of memory, (2) the effect of age on memory representations, (3) memory at the boundaries between normal and abnormal ageing, and (4) a new memory paradigm for the early detection of AD.

Format and structure of memory. Liang et al. (2016) used a novel memory test known as the Delayed Reproduction Task (DRT). The DRT measures precision of recall and provides an index of the quality of memory representation (Pertzov, Heider, Liang, & Husain, 2015). Quality is assessed by measuring how accurately the precise location of items scattered on visual arrays can be recalled. The most informative measure drawn from this task, with regard to ageing and AD assessment, is that indexing the ability to keep the two pieces of information together in memory as a unified representation (i.e., item-location). Loss of this ability would lead to what the authors called "swap errors". This ability is seemingly linked to the capacity to retain in memory object tokens (item-location; Treisman, 2006), a function akin to those derived from slot models of memory (Suchow, Fougnie, Brady, & Alvarez, 2014). Hence, impairments found during the DRT may be accounted for either by limited resources (i.e., spatial precision) or limited slots (item-location tokens). Contrary to shape and colour, which can be integrated into a unified representation with own identity detached from context, object and location cannot. This is because each piece of information retains its own identity in the new association (Mayes, Montaldi, & Migo, 2007) and hence remains available throughout the task. To be able to unveil binding specific impairments, a task devised to investigate this function should demonstrate that impairments in conjunctive or relational functions cannot be accounted for by impairments in processing the constituent parts. Unfortunately, this has not been the case for relational memory tasks involving object-location associations when used to assess healthy older adults (Chalfonte & Johnson, 1996). The precision component of the DRT may be linked to the ability to form and hold configural (spatial) representations, whereas the slot component may be linked to the ability to accurately allocate items to the vertices of such

configurations (temporary episodic tokens, Treisman & Zhang, 2006). I will further develop this view in the next section by considering pervious findings from ageing studies.

The effect of age on memory representations. Memory for visual arrays involves memory for items and their arrangement (i.e., ensemble; Brady, Konkle, & Alvarez, 2011). Older people seem to be able to take advantage of configural clues when they are available during the task. This seems to be the case when the number of to-be-remembered locations is small (Olson, Zhang, Mitchell, Johnson, Bloise et al., 2004). When the number of locations increases, healthy older adults struggle to retain such configurations (Cowan, Naveh-Benjamin, Kilb, & Saults, 2006). Previous data from the DRT seems to support this view (Pertzov, Heider, Liang, & Husain, 2015). The DRT requests examinees to remember the location of three items. Although precision deficits indicate that older adults are less able to retain the exact locations of remembered items, thus confirming age-related visuospatial impairments, they could benefit from configural cues to make discrete decisions regarding items allocation to the configuration vertices (object-token). Previous studies suggest that this will be unlikely if visual arrays become more crowded (Cowan et al., 2006; Olson et al., 2004). A reason why older adults struggle to associate information in memory is because relational functions require the integrity of the hippocampus (Cer & O'Reilly, 2006). The hippocampus shrinks with age regardless of risk for AD (Yang, Goh, Chen, & Qiu, 2013). Liang et al. confirmed that successful performance on the DRT heavily relies on the integrity of the hippocampus.

Memory at the boundaries between normal and abnormal ageing. Binding shapes and colours in VSTM declines in asymptomatic cases of FAD (Parra et al., 2010a). This function remains preserved across the life span (Parra, Abrahams, Logie, & Della Sala, 2009; Rhodes,

Parra, & Logie, 2015), and does not rely on the hippocampus (Parra, Della Sala, Logie, & Morcom, 2014; Parra, Fabi, Luzzi, Cubelli, Hernandez et al., 2015). Liang et al. (2016) showed that relational functions carried out during VSTM also decline in pre-symptomatic cases of FAD. However, this function declines in healthy ageing and heavily relies on the integrity of the hippocampus. This would pose challenges if this task was used to assess cases at risk of SAD. Such a limitation of associative memory tasks has long been underestimated and continues to be neglected by current guidelines and consensus papers (Dubois, Feldman, Jacova, Cummings, DeKosky et al., 2010). I will address this issue next.

A new memory paradigm for the early detection of AD. AD seems to progress in two stages, a sub-hippocampal and a hippocampal stage (Didic, Barbeau, Felician, Tramoni, Guedj et al., 2011). The sub-hippocampal stage is driven by the impact of AD on structures such as entorhinal and perirhinal cortex. This is prior to the MCI stage and is characterised by impairments in context-free memory functions such as those assessed by recognition tasks (Parra et al., 2010; Wolk, Mancuso, Kliot, Arnold, & Dickerson, 2013). The onset of the hippocampal stage corresponds clinically to the MCI stage. This is when impairments in context-rich memory functions (i.e., associative memory deficits) become apparent. Recent studies carried out in cases of FAD support this view (Romero Vanegas, Valencia Marin, Aguirre Acevedo, Buschke, & Lopera, 2010). Brain regions subserving context-free memory functions remain unaffected across the lifespan (Insausti, Juottonen, Soininen, Insausti, Partanen et al., 1998) and degenerate in AD much earlier than the hippocampus (Juottonen, Laakso, Insausti, Lehtovirta, Pitkanen et al., 1998; Khan, Liu, Provenzano, Berman, Profaci et al., 2014).

Final remarks. Memories are built and kept via context-free and context-rich functions. Though complementary, they have different lifespan trajectories. To date, tasks aimed at disentangling normal and abnormal ageing trajectories have been biased towards context-rich functions. This longstanding view no longer suits current diagnostic pathways which now focus on the preclinical stages of AD (Rentz, Parra, Amariglio, Stern, Sperling et al., 2013). It has been recently suggested that good preclinical tests for AD should "not show effects of healthy aging" (Logie, Parra, & Della Sala, 2015). VSTM conjunctive binding deficits have been recently suggested among the earliest cognitive changes indicative of the clinical state of AD (Dubois, Hampel, Feldman, Scheltens, Aisen et al., 2016). Future work will be needed to explore how these novel paradigms can be inserted in new clinical algorithms for the early detection of AD.

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