Short-term memory binding deficits in Alzheimer's disease
Reply to Parra's commentary

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We share Dr Parra's enthusiasm regarding the potential for early diagnosis of Alzheimer's disease (AD) using tests that measure binding processes in short-term memory. However, in our opinion, further work is required to establish the most suitable tasks for this purpose, ideally by comparing performance in the same cohort over time. Data from such studies would put us on a far firmer footing regarding the diagnostic predictive power of any given test.

A key distinction that has emerged between associative memory tests is whether they probe "relational" or "conjunctive" binding. Conjunctive binding refers to the ability to form a unitary representation of an item composed of several elements, e.g. its shape and colour. By contrast, retrieval of multi-feature items that can be performed by remembering individual parts separately (e.g., identity and location) is considered to depend upon relational binding. Below we consider some issues regarding tasks that use "relational" or "conjunctive" binding processes with respect to early diagnosis of AD.

Memory at the boundaries between normal and abnormal ageing

According to Parra, a good diagnostic task for AD should rely on measures that are not influenced by age, such as the "conjunctive" binding task he and his colleagues have developed (Parra et al., 2010a; Parra, Abrahams, Logie & Della Sala 2010b). In our opinion, the best task should have the highest predictive power when comparing individuals who will develop AD to *age-matched* controls who do not share the same risk factors. The fact that a parameter in a task is sensitive to ageing does not disqualify it from being a sensitive task for diagnosing AD.

On the "What was where?" relational binding task that we have developed (Pertzov et al., 2013), the number of swap (binding) errors does indeed increase with age. Crucially, however this age-dependent increase was abolished by taking into account the age-related decline in recognizing the correct items (Pertzov, Heider, Liang, & Husain, 2015). Therefore, this "relational" binding task can potentially be a useful test for detecting early AD, as demonstrated in our study in people with familial AD (FAD) (Liang et al. 2016).

Format and structure of memory

Parra argues that to unveil binding-specific impairments, a task should demonstrate that impairments in binding cannot be accounted for simply by deficits in processing constituent parts. Furthermore, he contends that this has not been the case for relational memory tasks involving object-location associations (Chalfonte & Johnson, 1996) when tested in healthy old people.

We agree with the first claim that binding-specific impairments should be based on tasks that are able to distinguish the different processes (memory for constituents versus the binding of constituents) but we disagree with the suggestion that relational memory tasks do not adhere to this demand. In fact, our "What was where?" relational memory task succeeded in showing a binding-specific deficit in both patients with focal medial temporal lobe disease (as a result of voltage-gated potassium channel antibody mediated encephalitis; Pertzov et al. 2013) as well as *asymptomatic* mutation carriers for FAD (Liang et al. 2016). In both cases, recognition and localization performance was normal (as assessed by localization of one item and the "nearest item control" analysis for three items) but there was a specific impairment in associating the correct items to their correct locations. These two studies suggest that relational memory tasks are indeed able to "unveil binding-specific impairments" in the context of *normal processing of the constituent parts*.

We also note that the task we used is quite different from those employed by Chalfonte and Johnson (1996). They used different tests of identity memory, location memory and identity-location binding. On each they obtained a single, discrete binary measure of performance (correct or incorrect). In contrast, our task has both a discrete measure of identification accuracy as well as a continuous, analogue measure of location memory. In our opinion, it also has the added advantage of providing metrics of object identity and location memory as well as identity-location binding within the same task.

A new memory paradigm for the early detection of AD

Parra argues that AD progresses in two stages: a sub-hippocampal phase characterised by impairments in context-free memory function such as those assessed by recognition tasks, followed by a hippocampal stage, when impairments in context-rich memory functions (namely associative memory) are observed and which corresponds

clinically to the MCI stage. Although this is an attractive hypothesis based on the Braak and Braak staging scheme of neurofibrillary changes for typical AD (Braak & Braak, 1991), it is not yet firmly established to be correct.

Convincing evidence would require longitudinal studies that follow individuals at risk of AD or FAD from a presymptomatic stage through MCI in which structural and/or functional measurements of the hippocampus and sub-hippocampal structures are made serially along with cognitive tests including both recognition and associative memory tasks. Such studies are currently on-going in familial AD (Bateman, 2012). AD is also a heterogeneous condition in clinic-pathological terms (Dubois 2014; Murray, 2011). As a result, the putative two-stage progression may not apply to atypical cases such as the bi-parietal variant of AD to the same extent.

In our current study (Liang et al. 2016), *asymptomatic* FAD mutation carriers performed significantly worse than age-matched controls in object-location binding, a context-rich memory test, but not on Warrington's Recognition Memory Tests (RMT) for faces and words (Warrington, 1984) which are context-free memory tests. It would be difficult to reconcile these findings with the proposed two-stage hypothesis, at least on neuropsychological grounds. We appreciate that one might argue about the relative sensitivities of these tests. Nonetheless the findings certainly do not provide support for the two-stage hypothesis.

In addition, in our study, the deficits in object-location binding in *asymptomatic* mutation carriers were detectable even when there were no significant differences in total hippocampal volumes compared with age-matched controls. Thus not only is the "What was where?" task able to detect short-term memory impairments in asymptomatic, at-risk individuals before the MCI stage but it also appears to be more sensitive than cross-sectional hippocampal volumetric measurement, at least on a standard established imaging protocol.

Longitudinal studies would have the advantage over cross-sectional studies in being able to assess when changes occur. This is arguably a more sensitive approach for comparing participants' performance on different neuropsychological tests over time. In a longitudinal neuropsychology study of FAD individuals by Liang et al (under

review; also Liang et al., 2010), a cohort of mutation carriers was tested on both the RMT for words and faces and the Camden Paired Associate Learning (CPAL) (Warrington 1996) (an associative memory test) from a presymptomatic stage. Performance on the CPAL declined on average 2.3 years before symptom onset. By comparison, performance on the RMT for words and faces declined 1.8 and 1.4 years before symptom onset respectively.

These results therefore support those in the current paper (Liang et al 2016): a pathological decline in context-rich memory function can be detected during the asymptomatic phase, before the MCI stage. This suggests that both context-free and context-rich memory function declined before the MCI stage, which is in contrast to the pattern that would be predicted by the "sub-hippocampal and hippocampal stages" hypothesis, as framed by Parra.

Lastly, short-interval longitudinal imaging studies have also demonstrated that abnormal hippocampal atrophy rates are detectable in cognitively-normal persons at risk of developing sporadic AD, before the development of symptoms and MCI (Jack et al., 2004; Schott et al., 2010).

In conclusion, to clarify definitively the timing and sequence of cognitive changes in AD from a presymptomatic stage through MCI to dementia would require detailed multi-modal longitudinal studies in an at-risk population. At present, it would appear that impairments in context-rich, relational binding memory functions such as those probed by the "What was where?" object-location test (Liang et al., 2016, Pertzov et al 2013, 2015) can be detected in the asymptomatic stage of AD, and are therefore potentially useful clinical research tools.

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