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Is “Learning” episodic memory? Distinct cognitive and neuroanatomic correlates of immediate recall during learning trials in neurologically normal aging and neurodegenerative cohorts

K.B. Casaletto*, G. Marx, S. Dutt, J. Neuhaus, R. Saloner, L. Kritikos, B. Miller, J.H. Kramer

University of California, San Francisco, Department of Neurology, 675 Rising Nelson Lane, San Francisco, CA 94158 USA

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ABSTRACT

Although commonly interpreted as a marker of episodic memory during neuropsychological exams, relatively little is known regarding the neurobehavior of “total learning” immediate recall scores. Medial temporal lobes are clearly associated with delayed recall performances, yet immediate recall may necessitate networks beyond traditional episodic memory. We aimed to operationalize cognitive and neuroanatomic correlates of total immediate recall in several aging syndromes. Demographically-matched neurologically normal adults (n = 91), individuals with Alzheimer's disease (n = 566), logopenic variant primary progressive aphasia (PPA) (n = 34), behavioral variant frontotemporal dementia (n = 97), semantic variant PPA (n = 71), or nonfluent/agrammatic variant PPA (n = 39) completed a neurocognitive battery, including the CVLT-Short Form trials 1–4 Total Immediate Recall; a majority subset also completed a brain MRI. Regressions covaried for age and sex, and MMSE in cognitive and total intracranial volume in neuroanatomic models. Neurologically normal adults demonstrated a heterogeneous pattern of cognitive associations with total immediate recall (executive, speed, delayed recall), such that no singular cognitive or neuroanatomic correlate uniquely predicted performance. Within the clinical cohorts, there were syndrome-specific cognitive and neural associations with total immediate recall; e.g., semantic processing was the strongest cognitive correlate in svPPA (partial r = 0.41), while frontal volumes was the only meaningful neural correlate in bvFTD (partial r = 0.20). Medial temporal lobes were not independently associated with total immediate recall in any group (ps > 0.05). Multiple neurobehavioral systems are associated with “total learning” immediate recall scores that importantly differ across distinct clinical syndromes. Conventional memory networks may not be sufficient or even importantly contribute to total immediate recall in many syndromes. Interpreting learning scores as equivalent to episodic memory may be erroneous.

1. Introduction

Converging neurobiological and behavioral data support the notion of multiple, dissociable memory systems that are broadly divided into encoding, storage, and retrieval stages (Perani et al., 1993; Shallice et al., 1994; Squire, 2004). Parcellation of the individual components of memory processing has deepened our understanding of the neural and cognitive systems supporting mnemonic abilities and the mechanisms by which these may become disrupted and/or enhanced (e.g., Delis, 1991; Kramer et al., 2005; Weintraub et al., 2004). Indeed, a substantial body of literature focused on delayed recall processes (i.e., storage and retrieval) consistently supports the critical role of medial temporal and frontal lobe networks that, when affected, demonstrate predictable patterns of memory impairment across distinct clinical syndromes (Delis, 1991; Wheeler et al., 1997; Zola-Morgan et al., 1986). However, delineation of “encoding” processes has received relatively less attention and its neural and cognitive underpinnings are subsequently not as well understood (Friedman and Johnson, 2000).

Total immediate recall during learning trials is the most commonly used measure of “encoding” and is frequently interpreted as an overall marker of clinical episodic memory abilities, comparable to delayed recall scores (e.g., Albert et al., 2001). These total learning scores are among the most psychometrically reliable metrics in memory paradigms (Benedict et al., 1998; Lacritz et al., 2001; Woods et al., 2006), and are therefore particularly well positioned for application in memory research and clinical assessment of patients longitudinally.

* Correspondence to: Memory and Aging Center, University of California, San Francisco, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94158.
E-mail addresses: Kaitlin.casaletto@ucsf.edu (K.B. Casaletto), gabe.marx@ucsf.edu (G. Marx), shubir.dutt@ucsf.edu (S. Dutt), john.neuhaus@ucsf.edu (J. Neuhaus), rowan.saloner@ucsf.edu (R. Saloner), lisa.kritikos@ucsf.edu (L. Kritikos), joel.kramer@ucsf.edu (J.H. Kramer).

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Yet, clinical lesion studies have long demonstrated a double-dissociation between immediate and delayed recall such that some densely amnestic patients are still able to perform within normative limits on immediate recall tasks, and there are cases of patients with intact long term memory yet impaired immediate recall (Shallice and Warrington, 1970; Vallar, 1990). More recent work additionally supports preservation of immediate recall despite damage to the medial temporal lobes suggesting (at least partial) independence from traditional medial and diencephalic memory structures (Squire, 2004). Though many functional imaging studies have focused analyses on increased hippocampal formation activation (e.g.,(Szaflarski et al., 2004), there is clear appreciation of the role of the prefrontal cortex, particularly the left inferior gyrus (Habib et al., 2003), and potentially even more broadly distributed networks (e.g., parietal-temporal, cerebellum)(Sperling, 2007; Woodruff-Pak et al., 2001) during learning paradigms. Yet, clinical neuropsychologists continue to commonly interpret total learning scores as memory reflecting medial temporal lobe functioning. Taken in the context of the clinical lesion and functional imaging works, total immediate recall may draw upon substantially disparate cognitive and neural systems than delayed recall, raising the question if immediate recall can then be accurately interpreted as “memory,” or if this may be a misnomer. A better understanding of which cognitive and neural factors are associated with immediate recall total learning scores with will both enhance our understanding of memory processing as well as our ability to more accurately interpret the neurobehavioral systems affected in clinical syndromes with immediate recall impairment.

Drawing on theory-based framework of information processing posited by Baddeley and Hitch, we hypothesized multiple cognitive networks may importantly contribute to successful total immediate recall performances (Baddeley, 2003, 2001; Baddeley and Hitch, 1974). Initially, incoming information may be held in a brief echoic store (acoustic store) requiring attentional processes wherein the trace is actively rehearsed (phonological loop) concurrently drawing upon basic phonological processes (e.g., fluency). Additionally, strength of existing semantic knowledge facilitates contextual integration during initial processing. For example, when linguistic processing is disrupted in children with language disorders (e.g., reduced vocabularies) or experimental speech sound manipulation, immediate verbal recall capacities are significantly reduced (Gathercole et al., 1999; Page and Norris, 2003). Not surprisingly, integrity of language-based neural systems, including the left inferior frontal gyrus and inferior parietal lobule, have also been linked to successful immediate echoic recall (Gathercole et al., 1999; Papagno and Vallar, 1992; Thorn and Gathercole, 1999). Following phonological processing, incoming information may be simultaneously organized and manipulated by central executive cognitive processes in an interactive manner with previously learned information in order to be stored for long-term use (Baddeley, 2003). Consistent with this theory, seminal experimental work demonstrates the beneficial effects of depth of information processing via organization during learning (e.g., chunking), supporting the role of cognitive control during immediate recall trials (Mandler and Parker, 1976; Hayes et al., 2007). Relatedly, both functional neuroimaging and clinical lesion studies support involvement of the dorsolateral prefrontal cortices as a major contributing system during the transfer of episodic information into long-term memory (Alexander, 2003; Fletcher et al., 1998; Tulving et al., 1994). Lastly, greater length of time between item presentations (inter-interval presentation) and reduced rate of covert rehearsal during initial learning negatively impacts subsequent immediate recall, suggesting there is also an important speeded cognitive component during verbal encoding (Baddeley, 1986; Cowan, 1992; Cowan et al., 1992). In a complementary framework, Squire and colleagues (2004) additionally suggested that immediate memory processing may in fact be modal-specific, occurring within the neural system(s) where the long-term store will eventually be processed, in conjunction with medial temporal systems. This latter theory provides further support of the need for potentially whole-brain cognitive networks during initial information processing, depending on the type of information to be learned. Together, these models highlight the multifaceted neurobehavioral systems, beyond traditional information storage and medial temporal networks, that may importantly impact total learning scores.

Given its relative complexity, total immediate recall may become disrupted following changes at any one point of the multiple ability areas involved. Understanding how “learning” can manifest in the context of distinct neurological etiologies will aid in disentangling the unique cognitive and neural substrates that differentially contribute to total immediate recall. Therefore, we aimed to characterize the correlates of total immediate recall across demographically-matched cohorts of neurologically normal older adults and several clinical neurodegenerative syndromes – Alzheimer's disease, logopenic variant primary progressive aphasia (lvPPA), behavioral variant frontotemporal dementia (bvFTD), semantic variant primary progressive aphasia (svPPA), and nonfluent/agrammatic variant primary progressive aphasia (nfvPPA). While traditional memory and medial temporal systems are primarily affected in Alzheimer's disease (Rabinovici et al., 2007b), individuals with bvFTD demonstrate particular vulnerability of the frontal and executive networks with relative sparing of long-term memory stores (Bott et al., 2014). On the other hand, distinct language-based networks are disrupted in each primary progressive aphasia syndrome. Individuals with lvPPA exhibit fluent but empty speech with impaired echoic recall and poor word retrieval associated with left posterior temporal and inferior parietal atrophy, svPPA is characterized by fluent speech but prominent semantic (i.e., word meaning) loss and anterior temporal lobe atrophy, while individuals with nfvPPA demonstrate apraxic, effortful, agrammatic speech and impaired complex syntactic understanding with left inferior frontal and insular atrophy (Gorno-Tempini et al., 2011, 2004).

Our primary study aim is to operationalize the neurocognitive processes associated with total immediate recall during a list learning paradigm, as illustrated by a schematic model in Fig. 1. Additionally, given that a subset of study participants completed structural neuroimaging, we secondarily aimed to explore potential neuroanatomic correlates (volumetric regions of interest) of total immediate recall performances within each of the study cohorts. We hypothesized that each of the multifaceted cognitive domains examined and a wide network of brain regions involving fronto-temporal (given their involvement in delayed recall) but also parietal systems (e.g., Jonides et al., 1998) would contribute to total immediate recall among neurologically normal older adults. On the other hand, given their clinical presentation of rapid forgetting and severe hippocampal dysfunction, we hypothesized immediate recall would also draw upon these traditional memory systems in individuals with AD. Among individuals with bvFTD, we anticipated executive control and frontal neural systems to be the primary point of disruption during immediate recall with relatively less

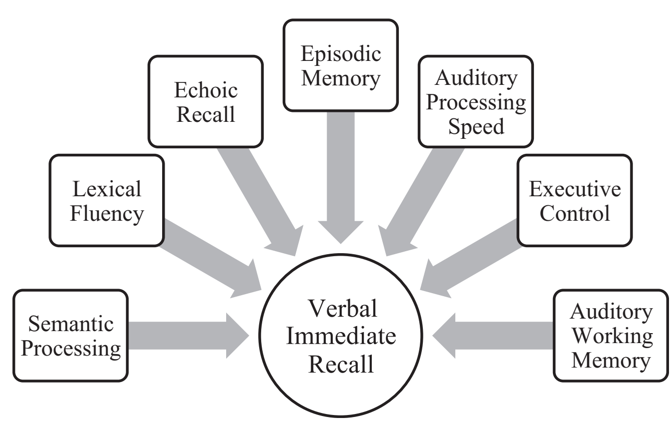

Fig. 1. Schematic diagram illustrating the hypothesized contributing cognitive correlates of total immediate recall during learning trials on a verbal list learning paradigm.