Serial position effects scoring in the assessment of memory in Alzheimer's disease and major depression
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Citation

Version: Corrected Publisher's Version
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Downloaded from: https://hdl.handle.net/1887/13714

Note: To cite this publication please use the final published version (if applicable).
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General introduction
Abbreviations

BLA  Basolateral amygdala
CA   Cornu ammonis
CDR  Clinical Dementia Rating
CORT Cortisol
CSF  Cerebrospinal fluid
HPA axis Hypothalamic-pituitary-adrenal axis
HPLC High-performance liquid chromatography
LC   Locus ceruleus
LTS  Longterm store
MHPG 3-methoxy-4-hydroxyphenylglycol
NE   Norepinephrine
NTS  Nucleus tractus solitarius
RAVLT Rey Auditory Verbal Learning Test
SPC  Serial position curve
SPE  Serial position effect
STS  Shortterm store
Alzheimer’s disease

Dementia is manifested by memory impairment and at least one of the following symptoms: aphasia, apraxia and executive dysfunctioning (DSM IV, table 1).

Table 1. DSM IV criteria of dementia

A. Development of multiple cognitive deficits manifested by both:
   1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   2) one (or more) of the following cognitive disturbances:
      a) aphasia: language disturbances
      b) apraxia: impaired ability to carry out motor activities despite intact motor function
      c) Agnosia: failure to recognize or identify objects despite intact sensory function
      d) disturbance in executive functioning, i.e. planning, organizing, sequencing, abstracting.

B. Cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Deficits do not occur solely during a delirium.

D. Deficits not due to psychiatric disease (major depression, schizophrenia).

Alzheimer’s disease (AD) is the most common form of dementia in the elderly, accounting for about 70% of the dementia cases [68]. It is projected that the number of dementia sufferers will increase markedly, placing a heavy financial and emotional burden on the decreasing working-age population [25]. Its insidious onset is characterized by a progressive worsening of memory, which is usually the earliest and most prominent manifestation, and other cognitive dysfunctions (see
table 2). Memory impairment appears to be present before the criteria of probable AD are met. In some cases evidence has been found that it is present many years prior to development of dementia [19,82]. This is consistent with neuropathologic and neuroimaging structural changes of the entorhinal cortex and hippocampus being initially affected in the earliest stage of the disease [21, 51, 54, 86]. These findings suggest that memory impairment is the core symptom of dementia and that research into the biological basis of this memory performance could be improved by development of its assessment.

When memory impairment and other cognitive disturbances become severe enough to interfere with daily activities, a clinical diagnosis of possible or “probable” AD is warranted [62]. This diagnosis can be made by means of the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s disease and Related Disorders Association (NINCDS-ADRDA) (table 2).

Table 2. NINCDS-ADRDA criteria for probable Alzheimer’s disease
1. Dementia established by clinical examination and confirmed by neuropsychological tests.
2. Deficits in two or more areas of cognition.
3. Progressive worsening of memory and other cognitive functions.
4. No disturbance of consciousness.
5. Onset between ages 40 and 90, most often after the age of 65.
6. Absence of systemic disorders or other brain disease that in and of themselves could account for the progressive deficits in memory and cognition.

The main neuropathological changes of AD are generalised atrophy, loss of neurons and synapses, and the abnormal deposition of neuritic plaques and neurofibrillary tangles, spread from the limbic structures to the association cortex of the temporal, parietal, and frontal lobes [24,66,86]. Consequently, other cognitive abilities become
affected.

**Major depression**

Major depression (MD), a mood disorder, is manifested by a range of cognitive impairments (see table 3). Its prevalence is 6%, while its incidence is 0.1% [16].

**Table 3. DSM IV criteria of major depression**

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure.

1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful);

2) markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly every day (as indicated by either subjective account or observation made by others);

3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease of increase in appetite nearly every day;

4) insomnia or hypersomnia nearly every day;

5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feeling of restlessness or being slowed down);

6) fatigue or loss of energy nearly every day;

7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not memory self-reproach or guilt about being sick);

8) diminished ability to think or concentrate, or indecisiveness, nearly every
day (either by subjective account or as observed by others). They may appear easily distracted or complain of memory difficulties;

9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., drug abuse, or medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

In depression attention, learning and memory and executive functions appear the most frequently impaired [1,3,12]. Memory impairment appears to be associated with a mood-congruent bias as it has only been found on the recall of positive and neutral valence words, but not negative valence words [26,32]. This bias has been explained mainly in terms of network theory [20], schema theory [13] or by the process oriented, integrative perspective [94,95].

There is evidence to suggest that recurrent, early-onset MD is associated with significant volume loss in the hippocampus [14,41,81], a brain area associated with memory [85]. These findings have recently been linked to models of decreased hippocampal neurogenesis in MD, suggesting that recurrent depressive episodes may lead to persistent neuronal alterations on a molecular level in the hippocampus [51], and the accompanying memory impairment.
Assessment of memory in AD and MD

Clinical assessment of memory function in AD and MD has mainly focussed on episodic memory performance (see fig 1) (taken from Tulving, 1987)[91].

![Memory Diagram]

Short-term Memory/Store /Working memory

Long-term Memory/Store

Explicit (Declarative) Implicit (Non-declarative)

Facts Events Skills Priming Classical & Operant Nonassociative (Semantic) (Episodic) conditioning learning

Fig 1. Classification of memory: short-term memory is limited (e.g., a phone number) and decays in seconds if not refreshed. Long-term memory is unlimited capacity and spans minutes to a lifetime. Implicit (non-declarative) memory refers to a heterogeneous group of abilities that are independent of the medial temporal lobe system and that modify behaviour without any conscious recollection of content. Nonassociative learning includes habituation and sensitization. Explicit (declarative) memory is dependent upon the medial temporal lobe system and involves conscious awareness of past events; it’s one’s personal, biographical memory. Semantic memory is world knowledge that one remembers in the absence of any circumstances about learning it.

In particular, recall and recognition tasks have been used [30,83] i.e. tasks that require conscious recollection of recently presented information by a direct and controlled search of stored information. Scoring of these tasks has been straightforward and uncomplicated. However, simply tallying the number of words
recalled and using the amount as a measure of performance obfuscates that recall of a list of words underlies two memory processes.

**Serial position effects of free recall**

Serial position effects (SPE’S) of free recall, first discovered by Ebbinghaus (1885) [37] are an intriguing phenomenon, whose potential neuropsychological significance has not been fully researched. This phenomenon emerges when several lists of words of the same length are offered once and the frequency of recall is plotted against the position an item takes in a list. The thus obtained graph has become known as the serial position curve (SPC) of single-trial free recall. Theoretically, however, it is not a genuine curve as values on the X-axis are of a nominal nature. Typical is that the last and first few items – also known as the recency and primacy effect – SPE’S – are more readily recalled than items in the middle of the list, which gives the graph its typical U shape (see fig 2).

![Idealized SPC](image)

**Fig 2.** An idealized SPC of free recall of lists of unrelated, unorganized words

Extensive research into the occurrence of SPE’S effects has shown that they emerge
independently (see table 3). Research into the influence of medical conditions on these effects seems to support this (see table 4). 

Table 3. Differential relations between the SPE’S and experimental conditions 

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primacy</th>
<th>Recency</th>
</tr>
</thead>
</table>
| Acquaintance with the items        | +       | -       | [73]  
| Speed of presentation              | +       | -       | [38]  
| One-item rehearsal                 | +       | -       | [73]  
| Semantic similarity of words       | +       | -       | [5]   
| Phonological similarity of words   | -       | +       | [31,80]  
| If recall is delayed               | -       | +       | [17]  

+ = suppresses recall on  - = does not suppress recall  on

Table 4. Effects of medical conditions on SPE’S on free recall 

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primacy</th>
<th>Recency</th>
</tr>
</thead>
</table>
| Amnesia                                       | +       | -       | [6]   
| Alzheimer                                      | +       | -       | [84]  
| Parkinson                                      | +       | -       | [35]  
| Cushing                                       | +       | -       | [61]  
| Alcohol abuse, diazepam                       | +       | -       | [8,63]  
| Temporal lobe damage                          | +       | -       | [48]  
| Left temporo parietal damage                  | -       | +       | [10,93]  
| Frontal lobe damage                           | +       | +       | [38]  

+ = suppresses recall on  - = does not suppress recall  on
Yet this insight has not resulted in the adoption of SPE’S scoring of memory performance in clinical practice. This is probably due to the fact that the extent of these effects has been judged on the basis of the shape of the SPC, which is an arbitrary way to determine them, as they have been found to vary considerably [27,42,43,45,48,53,90]. Moreover, it is still unresolved whether the primacy and middle part are separate parts [9]. A multi-free recall test of which we want to determine SPE’S of is the Auditory Verbal Learning Test (RAVLT) [75]. This clinical test is relatively brief, easily administered and scoring is uncomplicated. Administration takes approximately 10 to 15 minutes and consists of five presentations and free recall of a 15-word list, followed by the presentation and free recall of a second word list, and a subsequent free recall trial of the first list. After a delay of 20-30 minutes a final free recall trial of the first list is tested. In the current version, recognition is tested by asking the respondent to indicate which of 30 words read aloud were from the first list and not the second list. The RAVLT provides measures of immediate memory, efficiency of learning, effects of interference, and recall following short and long delay periods.

Defining SPE’S in multi-trial free recall is, however, even more difficult than in single-trial free recall as it is unclear what influence rehearsal has on the extent of the SPE’S. Clinical assessment would therefore benefit from a solution of this assessment problem.

Moreover, there is the problem of the theoretical explanation of SPE’S. Three models can be discerned: two modalities interpretations, the ‘modal’ model [4] and the context-activation theory [33], and a processing interpretation based on the encoding model [47]. The two-modality interpretation implies that two memory modalities underlie the SPE’S. The most prominent interpretation, based on the ‘modal’ model [4], is that the primacy effect and middle part (hereafter denoted as prerecency effect) is a reflection of long-term store (LTS) performance, while the recency effect is
a reflection of short-term store (STS) performance [4,42]. According to this model two serially coupled memory modalities exist i.e. STS and LTS. The STS, which is believed to be a partial activation of the LTS, contains all control processes and regulates information transference to and from the LTS. The STS is a limited capacity buffer. Initially, this buffer is empty. When items enter the buffer, the time they stay in the buffer determines how often they are rehearsed and how much information about the items is transferred to and from the LTS. From the perspective of the ‘modal’ model, the recency effect, in immediate verbal free recall, is believed to be representative of the output of this STS buffer.

However, this interpretation contradicts the current classification of memory (see fig. 1) as it is suggested that explicit memory performance incorporates STS and LTS performance. This interpretation of SPE’S is further complicated by the fact that recency effect has also been found in LTS performance. Evidence for this has been found recalling the names of previous presidents of the USA [76], recalling which rugby matches one has attended in the last season [8], recalling which pictures one has seen during the previous year [49], and recalling which operas one has gone to in the last 25 seasons [79].

The same may be argued for the context-activation theory [33], a more recent two-modalities explanation of the SPC. According to this theory the recency effect is associated with a short-term memory buffer, while the prerecency part is associated with episodic memory performance. During storage as well as recall, the lexical-semantic system is activated from the short-term memory buffer. Subsequently, the activated information is placed in the right context and stored in the episodic memory. The strength of association with which information is stored in the episodic memory depends on how well lexical-semantic activities are coupled to the context and determines the quality of recall. The buffer is distinct from episodic memory.

Episodic retrieval involves two stages. In the first stage, the context is used to select items for retrieval, and in the second stage, the selected item is recovered. However,
the context in which items are encoded changes during list presentation as well as during retrieval. Items at the beginning and end of a list, i.e. the prerecency part and recency part, are more accessible during the recall phase because of more enhanced attention of their contexts. Be that as it may, it is again implied that the SPC incorporates STS performance.

An interpretation of SPE’S that avoids a LTS/STS distinction is the encoding model interpretation. It argues that the SPC is representative of two forms of encoding i.e. that the emergence of the primacy effect is representative of effortful encoding and recency effect of automatic encoding [53]. This interpretation is based on the encoding model [47] which claims that two forms of encoding exist: effortful and automatic encoding. The first form is believed to seize a large part of the limited attentional capacity, to occur intentionally, and to improve with practice. Examples of effortful processing are rehearsal, organization, and mnemonic techniques. Automatic processing, on the other hand, is believed to function without attention, to occur without intention, and not to improve with practice. Examples of automatic processing are a sense of time, space, and reading and writing [47].

This interpretation has no problems with why SPE’S are found for STS [2] and LTS performance [7,49,76,79], when taking into account that according to the ‘modal’ model, the STS is a partial activation of the LTS, and SPE’S are representative of an effortful and automatic manner in which information retrieved from the LTS is kept active in the STS.

**SPE’S performance in Alzheimer’s disease and Major depression**

The neuropathological changes in AD of the entorhinal cortex and hippocampus [23, 51, 54, 86] have been found cognitively accompanied by impaired performance on the primacy and middle effect (hereafter denoted as prerecency effect) in single-
[11,37,30,40,68,71,84], as well as in multi-trial free recall [46,58,69] for unorganized, unrelated word lists. However, impaired performance on the prerecency effect in
AD has only been found for the recall of long lists [11,36,39,40,46,58,64,69,71,84], and not for the recall of short lists [36,58,69,71]. On the basis of this it has been argued that the detrimental influence of AD on the prerecency effect is dependent upon the list length [58].

There is evidence to suggest that recurrent, early-onset MD is associated with significant volume loss in the hippocampus [14,81], which may explain the accompanying memory impairment. To the best of our knowledge the involvement of MD in SPE’S of free recall has only been studied thrice using single-trial free recall [22,40,56]. Two studies found impaired memory performance on the primacy effect [22] respectively on the prerecency effect [40]. Why this was not found in the third study [56] may have been due to the fact that memory impairment is only found in 50 to 60% of the cases of MD [59]. As for the involvement of MD in SPE’S of multi-trial free recall, this is still unknown.

The relation between SPE’S performance and stress-hormones in Alzheimer’ disease and Major Depression

Next to neuropathological changes, AD is also accompanied by hypercortisolism in about half of the cases [65,67], and an altered function of the central and peripheral noradrenergic system [50,72]. Since glucocorticoids target the hippocampus [34] impaired performance on the prerecency effect in AD [11,36,39,40,46,58,64,69,71,84] may in part be due to elevated cortisol levels outside reference values. In this connection it has been hypothesized that in AD hypercortisolism act as a co-factor further enhancing pyramidal cell loss in the hippocampus (the glucocorticoid cascade hypothesis) [77], and memory performance decline. However, support for this hypothesis is lacking [87].

There is also evidence that catecholamines modulate memory performance [44]. Loss of noradrenergic neurons in the locus coeruleus (LC), the major noradrenergic source in the brain, has been well established in patients with AD [69], implying that
dysfunction of the central and peripheral noradrenergic system may be another co-factor modulating memory performance. Post mortem studies have consistently shown that the central noradrenergic system is involved with decreased norepinephrine (NE) levels being recognized in many brain areas among which the hippocampus and the amygdala [15,60]. On the other hand, peripheral noradrenergic activity has frequently been found increased in AD. In post-mortem studies, when NE and 3-methoxy 4-hydroxy phenylglycol (MHPG) were quantified together, brain NE concentration was often found decreased, while MHPG concentration was found to be unchanged or higher in AD patients than control subjects [89].

In short, it is suggested that neuronal loss in the LC is associated with decreased central NE metabolism and increased peripheral NE metabolism. Since support of an inverse relationship has been found in AD between NE levels in the brain and cognitive impairment [2,60], this has been interpreted as a compensatory response to reduced cognitive functioning [50]. This may imply that memory impairment on the prerecency effect in AD is modulated by elevated cortisol levels, outside reference values, and dysfunctional noradrenergic activity.

Next to neuropathological changes [14,81], MD is also accompanied by hypercortisolism in 50 to 60 % of the cases [65] and dysfunction of the central and peripheral noradrenergic system, which has been argued to be basic to memory impairment in MD [74]. Since glucocorticoids target the hippocampus [34], which is associated with prerecency effect performance [48], impaired performance on that effect in MD [22,40] may in part also be due to increased cortisol levels, outside reference values, and dysfunctional noradrenergic activity.
**Aims of the thesis:**

The first objective of this thesis was to refine clinical memory assessment of the Rey Auditory Verbal Learning Test (RAVLT) by focussing on the internal validity of SPE’S and determining their extent more accurately.

The second objective was to study the external validity of SPE’S in AD and MD patients as both diseases are characterized by memory impairment on the primacy effect of the SPC, which has been found associated with hippocampal functioning.

The third objective was to study the external validity of SPE’S by focussing on the relation between SPE’S and stress hormones in AD, MD patients and healthy human subjects, as cortisol (CORT) targets the hippocampus, and to explore the involvement of NE in SPE’S.

The first aim will be addressed in chapter 4, the second aim in chapters 2, 3, 6, 7, and the third aim in chapters 3, 5, 6 and 7.

**Chapter 2** reports an exploratory study describing what influence AD has on SPE’S of a modified version of the RAVLT, allowing the study of SPE’S in lists of various lengths.

**Chapter 3** describes a study on the effects of MD and relations of CORT to the SPE’S of a modified version of the RAVLT.

**Chapter 4** focuses on determining the extent of SPE’S in the modified version of the RAVLT more accurately.

**Chapter 5** focuses on the relationships between CORT and NE and SPE’S of the
modified version of the RAVLT, now determined more accurately, in healthy human subjects.

**Chapter 6** focuses on the relationships between CORT and NE and SPE’S of the modified version of the RAVLT, now determined more accurately, in moderate to advanced AD patients.

**Chapter 7** dwells upon the scoring of factor-analytically defined SPE’S and the fact that they offer a more accurate base for the assessment of two memory functions in the RAVLT. In addition, the nature of the underlying functions as well as the most appropriate neuropsychological theory of SPE’S are discussed.

**Chapter 8** summarizes the main findings of this thesis and offers a general discussion and conclusions. The implications for future clinical and research purposes of the main findings are discussed.
References


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