Declarative memory

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Declarative Memory

Wim J. Riedel and Arjan Blokland

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Abstract

Declarative Memory consists of memory for events (episodic memory) and facts (semantic memory). Methods to test declarative memory are key in investigating

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effects of potential cognition-enhancing substances—medicinal drugs or nutrients. A number of cognitive performance tests assessing declarative episodic memory tapping verbal learning, logical memory, pattern recognition memory, and paired associates learning are described. These tests have been used as outcome variables in 34 studies in humans that have been described in the literature in the past 10 years. Also, the use of episodic tests in animal research is discussed also in relation to the drug effects in these tasks. The results show that nutritional supplementation of polyunsaturated fatty acids has been investigated most abundantly and, in a number of cases, but not all, show indications of positive effects on declarative memory, more so in elderly than in young subjects. Studies investigating effects of registered anti-Alzheimer drugs, cholinesterase inhibitors in mild cognitive impairment, show positive and negative effects on declarative memory. Studies mainly carried out in healthy volunteers investigating the effects of acute dopamine stimulation indicate enhanced memory consolidation as manifested specifically by better delayed recall, especially at time points long after learning and more so when drug is administered after learning and if word lists are longer. The animal studies reveal a different picture with respect to the effects of different drugs on memory performance. This suggests that at least for episodic memory tasks, the translational value is rather poor. For the human studies, detailed parameters of the compositions of word lists for declarative memory tests are discussed and it is concluded that tailored adaptations of tests to fit the hypothesis under study, rather than “off-the-shelf” use of existing tests, are recommended.

Keywords

Declarative memory • Episodic memory • Cognition-enhancing drugs

1 Introduction

Declarative memory involves the acquisition and retention of information demanding conscious or explicit learning (Lezak 2004; Squire 1987). Episodic memory is memory for events and experiences and semantic memory is memory for factual knowledge (Squire 1987; Tulving 1972). Both facts and events are encoded by Medial Temporal Lobe structures which comprise a unitary memory system (Squire 2004), as can be seen in Fig. 1. Episodic memory is responsible for storing information about events (or episodes) we have experienced, whereas semantic memory is for storing information about the world, such as the meaning of words. While semantic memory is required to understand and thus encode the words in the first place, remembering a list of words requires episodic memory.

Although historically Tulving (1972) thought that word list learning paradigms, measuring free recall of learnt words, were a typical example of tests of episodic and not semantic memory, he later revised his original definition (Tulving 2002)

Fig. 1 Taxonomy of mammalian memory systems (after: Squire 2004)

stating that episodic memory consists of “what,” “where,” and “when” aspects and that free recall of word lists is almost exclusively drawing on the “what” aspect of episodic memory. The distinction between episodic and semantic memory became somewhat less clear in this respect (Tulving 2002).

Semantic memory involves the learning of factual knowledge (Squire 2004). The most common assessment of semantic memory is the verbal fluency task where participants list off as many words possible beginning with a certain letter. Verbal fluency tasks are considered a measure of strategy-driven retrieval from semantic memory stores and thus they also demand executive functions. Semantic memory is difficult to translate from/to preclinical species, so in this chapter we focus on studies of drug effects aimed at cognition enhancement primarily assessing declarative memory by means of performance tests assessing episodic memory.

2 How Declarative Episodic Memory Is Measured

The knowledge of drug effects on declarative memory in humans is largely based on studies of cognition-enhancing drugs utilizing tasks assessing episodic memory function:

- Verbal tasks such as logical memory tasks (LM) probing recall of distinct events in a short story and verbal learning tasks (VLT) probing recall of word lists
- Nonverbal tasks such as Picture or Pattern Recognition Memory (PRM) probing recognition of pictures or patterns belonging to a list and Paired Associates Learning (PAL), probing object-location recognition

Episodic memory tasks typically involve three processes: encoding, consolidation, and retrieval (Lezak 2004). During the encoding phase, the information presented is acquired and learned. Consolidation is the processing of encoded information into long-term storage for later retrieval. Stored information is then either recognized through prompting or recalled spontaneously during the retrieval phase.

2.1 Verbal Memory

2.1.1 Verbal Learning Tests

Verbal learning tasks exist in many well-known variants such as Rey's Auditory Verbal Learning Test (Lezak 2004; Rey 1958) and the California Verbal Learning Test (Delis et al. 1987). Verbal learning tasks can assess short-term memory (immediate recall) or long-term episodic memory (delayed recall and recognition). Consolidation, or conversely decay, can be inferred from the differential of immediate and delayed recall or recognition. While these tests, using word lists of respectively 15 or 16 words, may be appropriate to diagnose memory deficits, memory testing in neuropsychological and psychopharmacological research often involves normal young or healthy elderly volunteers, who might perform at ceiling level.

As can be seen in Table 1, 24 out of the 34 studies reviewed in this chapter used a VLT to assess declarative memory. List length varies considerably between studies. One study used a 12-word list, seven studies used a 15-word list as in the Rey Auditory Verbal Learning Task (Rey 1958), two studies used a 16-word list as in the California Verbal Learning Task (Delis et al. 1987), two studies used a 20-word list, nine studies used a 30-word list, and two studies used a 70-word list. The latter two probed recognition whereas all former probed free recall. It is beyond the scope of the chapter to list all details of task parameters, so we chose to provide a description of the most used VLT. Ideally a VLT should allow translation from drug effects in healthy young volunteers to drug effects in elderly suffering from memory impairment. Riedel et al. (1999) developed an adapted version of Rey's Auditory Verbal Learning test using 30-word lists (Klaassen et al. 2002; Riedel et al. 1999). In this test, 30 monosyllabic words are visually presented during 1 s at a rate of 1 per 2 s followed by a 1-min period of immediate verbal recall, a procedure that is repeated three times in total. After a 30-min delay in which other (nonverbal) cognitive tests are performed, there is another verbal recall and a recognition test.

2.1.2 Logical Memory

There is one study that uses a formal memory task that has all the hallmarks of a logical memory test (Izquierdo et al. 2008). The generic Logical Memory test, as in the Wechsler Memory Scale III (Wechsler 1997), consists of two stories (A read once and B read twice) that are read to the participant who is probed for recall of free and thematic units. Delayed free recall for both A and B is probed 30 min later. A standard cue is provided if the participant has no memory of a story. The recall

Table 1 Overview of acute and subchronic double-blind placebo-controlled studies describing cognition enhancing drug- or nutrition effects on tests of episodic memory in humans.

Study	Population sample	<i>n</i> (M/F)	Age	Tx	Mechanism	Regimen	Design	Doses	Task	Measure	Effect	Clinical area
Theunissen et al. (2013)	Healthy	11/13	31, 0	Vortioxetine	5-HT	16 d	db-co	10 mg	30 w	Recall	No drug-placebo difference	
Wingen et al. (2006)	Healthy	9/9	31, 4	Escitalopram	5-HT	15 d	db-co	10–20 mg	30 w	Recall	No drug-placebo difference	
Schmitt et al. (2005)	Healthy with PMS Sx	0/16	18–45	Alpha-lactalbumin	5-HT	Acute	db-co	20 g	PRM	Recog	Alfa-lactalbumin improved delayed pattern recognition	PMS
Samuelh et al. (2014)	Healthy	7/9	19–34	Citalopram	5-HT	Acute	db-co	20 mg	30 w	Recall	No drug-placebo difference	
Gron et al. (2005)	Healthy	30/0	23, 9	Donepezil	Ach	30 d	db-pg	5 mg	15 w	Recall	Donepezil improved immediate recall	
Gron et al. (2006)	MCI	42/0	69, 3	Galantamine	Ach	7 d	ca-ctrl	4 mg bid	16 w	Recall	Galantamine improved immediate and delayed recall	Aging, dementia
Slough et al. (2009)	Healthy	43	22–66	Procera AVH	Ach	30 d	db-pg	1,500 mg + 15 mg + 150 mg	QoM	Accuracy	The combination product improved episodic memory accuracy	Aging, dementia
Balsters et al. (2011)	Healthy	6/14	59–77	Donepezil	Ach	4 w	db-pg	5 mg	PAL	Accuracy	Donepezil impaired accuracy	Aging, dementia
Theunissen et al. (2014)	Healthy cannabis preTx	9/6	21, 23	Rivastigmine, vardenafil	Ach, PDE5	Acute	db-co	3 mg (riv), 20 mg (var)	30 w	Recall	Rivastigmine attenuated cannabis-induced impairment of delayed recall	
Izquierdo et al. (2008)	Healthy	50/55	16–82	Methylphenidate	DA	Acute	db-pg	10 mg	LM	Recall	MPH improved consolidation	Aging, dementia

(continued)

Table 1 (continued)

Study	Population sample	<i>n</i> (M/F)	Age	Tx	Mechanism	Regimen	Design	Doses	Task	Measure	Effect	Clinical area
Zeeuws and Soetens (2007)	Healthy	36/0	18–25	d-amphetamine	DA	Acute	db-co	10 mg	20 w	Recall	Improved delayed recall (consolidation)	
Zeeuws et al. (2010b)	Healthy	40/0	18–25	d-amphetamine	DA	Acute	db-co	10 mg	70 w	Recog	Improved delayed recognition (consolidation)	
Linssen et al. (2014)	Healthy	10/10	18–28	Levo/carbi-dopa	DA	Acute	db-co	125 mg	30 w	Recall	No drug-placebo difference	
Hermens et al. (2007)	Healthy	32/0	18–30	Methylphenidate	DA	Acute	db-co	5, 15, 45 mg	12 w	Recall	No drug-placebo difference	
Zeeuws et al. (2010a)	Healthy	17/0	18–30	d-amphetamine	DA	Acute	db-co	10 mg	70 w	Recog	Improved delayed recognition (consolidation)	
Apud et al. (2007)	Healthy by COMT genotype	24/23	18–55	Tolcapone	DA	1 w 6 d	db-co	100–200 tid	15 w	Recall	Trend drug x Gx, val/val Gx improved; met/met Gx worsened	
Randall et al. (2005)	Healthy	29/31	19–22	Modafinil	DA	Acute	db-pg	100, 200 mg	PRM	Recog	Modafinil both doses improved pattern recognition	
Muller et al. (2013)	Healthy	31/33	19–36	Modafinil	DA	Acute	db-pg	200 mg	PRM	Recog	Modafinil improved delayed pattern recognition	
Linssen et al. (2012)	Healthy	19/0	19–37	Methylphenidate	DA	Acute	db-co	10, 20, 40 mg	30 w	Recall	Methylphenidate improved delayed recall	
Kuypers and Ramaekers (2005)	Healthy	9/9	20–39	Methylphenidate	DA	Acute	db-co	20 mg	15 w	Recall	No drug-placebo difference	

Riby et al. (2006)	Healthy	27	20–80	Glucose	Glucose	Glucose	Acute	db-co	25 g	PAL	Recall	Greater immediate recall in glucose vs. placebo condition	Aging, dementia
Christmas et al. (2014)	Healthy	32/0	18–55	Org25935		GlyTRI	Acute	db-pg	12 mg	20 w	Recall	No drug-placebo difference	
Lien-Moolenaar et al. (2010)	Healthy scopolamine preTx	43/0	18–55	R213129		GlyTRI	Acute	db-co	3, 10, 30 mg	30 w	Recall	No drug-placebo difference	
van Ruitenbeek and Mehta (2013)	Healthy	8/8	18–50	Bethistine		Histamine	Acute	db-co	2 × 48 mg	PAL	Accuracy	No drug-placebo difference	
Reneerkens et al. (2013)	Healthy	5/19	18–25	Vardenafil		PDE5	Acute	db-co	10 mg, 20 mg	30 w	Recall	No drug-placebo difference	
Benton et al. (2013)	Healthy	0/285	21, 8	DHA		PUFAs	50 d	db-pg	400 mg	30 w	Recall	DHA impaired recall at 50 days end of treatment	
Jackson et al. (2012)	Healthy	46/94	18–35	EPA, DHA		PUFAs	12 w	db-pg	90 + 450 mg; 300 + 200 mg	15 w	Recall	No drug-placebo difference	
Karr et al. (2012)	Healthy	12/29	18–35	EPA, DHA		PUFAs	4 w	db-pg	720 mg + 480 mg	15 w	Recall	Minor improvement of delayed recall after PUFA	Aging, dementia
Stonehouse et al. (2013)	Healthy low DHA in diet	83/145	18–45	EPA + DHA		PUFAs	6 mo	db-pg	170 mg + 1,160 mg	15 w	Recall	Improved speed of word recognition and improved recall in females	
Stough et al. (2012)	Healthy	74	45–80	EPA + DHA		PUFAs	90 d	db-pg	60 mg + 252 mg	QoM	Accuracy	No drug-placebo difference	Aging, dementia
Vakhtapova et al. (2010)	Elderly with memory complaints	62/60	50–90	PS + EPA + DHA		PUFAs	15 w	db-pg	300 mg + 20 mg + 60 mg	15 w	Recall	PS + DHA only improved 1st trial immediate recall	Aging, dementia

(continued)

Table 1 (continued)

Study	Population sample	n (M/F)	Age	Tx	Mechanism	Regimen	Design	Doses	Task	Measure	Effect	Clinical area
Yurko-Mauro et al. (2010)	Healthy with ARCD	485	>=55	DHA	PUFAs	24 w	db-pg	900 mg	PAL	Accuracy	Better PAL performance after DHA supplementation	Aging, dementia
Lee et al. (2013)	MCI	8/27	>=60	EPA + DHA	PUFAs	12 mo	db-pg	150 mg + 430 mg	15 w	Recall	DHA improved immediate and delayed recall	Aging, dementia
Dangour et al. (2010)	Healthy	411/337	70-79	EPA + DHA	PUFAs	24 mo	db-pg	200 mg + 500 mg	16 w	Recall	No drug-placebo difference	Aging, dementia

MCI mild cognitive impairment, ARCD age-related cognitive decline, Pre Tx pretreatment, Tx treatment, Gx genotype, PMS premenstrual syndrome, ProcerA AVH acetyl-L-carnitine + vinpocetine + huperzine A, EPA eicosapentaenoic acid, DHA docosahexaenoic acid, PS phosphatidylserine, PUFA polyunsaturated fatty acid, GlyTRI glycine transporter reuptake inhibitor, DA dopamine, Ach acetylcholine, 5-HT serotonin, PDE5 phosphodiesterase-5 inhibitor, w weeks, d days, mo months, db double-blind, pg parallel groups, co crossover, ca-ctrl case-control, mg milligrams, tid three times daily, bid twice daily, µg micrograms, N-w N word list, PAL paired associates learning, LM logical memory, PRM pattern recognition memory

and thematic unit scores are again recorded. Fifteen yes/no recognition memory questions are then asked about each story and the recognition memory scores are recorded. The formal memory task used by Izquierdo et al. involved asking the subjects to study a 15-line text with factual information on the 1954 World Cup Soccer for 10 min and then to respond to a questionnaire 2 or 7 days later on 10 of the factual items of the text (Izquierdo et al. 2008).

2.2 Nonverbal Memory

2.2.1 Pattern Recognition Memory

Studies utilized the Pattern Recognition Memory Task or similar variations in which participants identified familiar or new patterns (Muller et al. 2013; Randall et al. 2005; Schmitt et al. 2005). PRM measures the ability to encode and subsequently recognize visual information and is said to provide an assay of medial temporal lobe function (Sahakian et al. 1988). In the encoding phase, 16 patterns appear sequentially on the screen, one at a time, and participants are instructed to remember them. Immediately following the encoding phase, participants carry out a recognition test, in which each pattern from the encoding phase is presented with another pattern of similar form and color, and participants must touch the pattern they saw previously. Twenty minutes following this first recognition test, a second delayed recognition test is administered.

2.2.2 Paired Associate Learning

Boxes are displayed on the screen and open in turn to reveal a number of patterns. Participants are instructed to try to remember the location in which each pattern was shown. After all the boxes have been opened, each pattern is then shown in the center of the screen in a randomized order, and the participant touches the box in which the pattern was located. If an error is made, all the patterns are re-presented to remind the participant of their locations. As the test progresses, the stages become more difficult as the number of patterns to be remembered increases. Performance of the Paired Associates Learning (PAL) test activates the bilateral hippocampi in the Medial Temporal lobe (de Rover et al. 2011).

2.3 How to Measure Declarative Episodic Memory in Animals

By definition declarative memory assumes that memories can be declared, which in humans is the ability to verbalize or to consciously recall information. Clearly, there is no clear evidence that animals can have these abilities (Templer and Hampton 2013). However, as mentioned above, episodic memory has also been defined in terms of “what,” “where,” and “when” (Tulving). When considering this definition it has been shown that animals do have an episodic(like) memory (Clayton et al. 2003). Whether this is directly comparable to humans will be difficult to demonstrate, but it appears that similar brain regions do support the

episodic memory in humans and animals (Allen and Fortin 2013; Morris 2001). So, there appear to be good arguments to state that animals do have an episodic memory, but there may be some differences between animals and humans.

Different tests have been used as models of episodic memory tasks in rodents (for a review, see Fouquet et al. 2010). The most used tasks are the object recognition task, and variations thereof (Dere et al. 2006; Ennaceur and Delacour 1988; Kesner et al. 2008). Other examples are specific procedures in radial mazes (Crystal 2013), odor recognition (Eichenbaum et al. 2010), and some procedures in the classic Morris water task (Zhang et al. 2008). For all these test mentioned, the “what,” “where,” and “when” can be applied. The PAL test has also been developed for rodents by using a touch-screen device (Talpos et al. 2009). However, it has not been claimed that this task could be considered as an episodic test for rodents.

This short overview shows that there are several episodic memory tests for rodents. Although these tests can be defined as an episodic test in animals, the comparability with human episodic tests is limited. Some tests seem not to be translatable to animal studies (i.e., VLT and LM) and some tests are considered episodic memory tests for which not such a claim has been made in animal research (i.e., PAL and spatial Morris task (only specific protocols)). The object recognition task is the most widely task in animal research to test episodic memory. However, there is not a clear human equivalent for this task in human research. Taken together, this indicates that the translation of episodic memory tasks is rather limited.

3 Overview of Studies

3.1 How Searched

For the human studies we searched for publications in the past 10 years, i.e., from 2005 to the end of 2014, about cognition-enhancing substance (either drug or nutrient) effects on at least one test of declarative memory. Most of these publications also contained reports about drug effects on other tests assessed simultaneously, but in this chapter we exclusively focus on the results concerning declarative or episodic memory. We searched PubMed using the search terms:

(episodic OR declarative) drug* cogni* enhanc*
verbal cogni* drug* enhance*
cogni* enhanc* drug* learn* paired*

In addition, publications that also fulfilled the content criterion (cognition-enhancing drug effects on tests of declarative memory) and that were already known to us or became known to us after asking around were added. For the animal studies there is a vast amount of studies in which the effects of many different drugs have been tested. Mostly, the object recognition test has been used for these

purposes. Therefore, we refer to selective (review) studies in which drug effects have been examined.

3.2 Studies

A total of 34 studies were obtained and these are listed and categorized in Table 1. At large, the studies can be categorized on the basis of:

- Mechanism(s) of the substance under investigation
- Single-dose or repeated dose studies. The latter are more important when attributing the clinical meaning of the results, whereas acute single-dose studies are usually focused on a proof-of-principle type of question
- Population sample of subjects. Most studies on cognition-enhancing drugs are carried out in healthy volunteers, although in several instances these are samples described by a particular vulnerability factor, such as elderly with memory deficits or complaints, genotype, relative deficiency of omega-3 fatty acids in the diet, premenstrual syndrome, and scopolamine pretreatment
- Number of items to memorize or memory load. For example, word lists used in the different studies comprised of 12, 15, 16, 20, 30, or 70 words and the number of times they were repeatedly presented was once, twice, three times, or five times. Pattern recognition memory tests likewise present a sequence of patterns or pictures. If the pictures are concrete the test is considered verbal because pictures will be primarily verbalized. Abstract patterns, as used in the PRM and PAL, are more difficult to verbalize and are therefore considered nonverbal. Both are considered tests of episodic memory however. The memory load in PAL is increased in stepwise fashion (2, 3, 6, 8, 10, 12) until subjects reach the highest level or fail
- Number of subjects. Larger studies more often are repeated dose studies and these are deemed more important than smaller sample studies

3.2.1 PUFAs

Nine of the studies are investigating the effect of omega-3 (or n-3) polyunsaturated fatty acids (PUFAs) on declarative memory. All nine are repeated dose studies over a relatively longer period of time. However, not all treatments are the same in that the composition of PUFAs differs and also the age of the groups studied differs. From the four studies in young volunteers, one was negative (Benton et al. 2013), one found no effects (Jackson et al. 2012), and two found at best marginal positive effects (Karr et al. 2012; Stonehouse et al. 2013). In elderly, two trials were positive (Lee et al. 2013; Yurko-Mauro et al. 2010), one where phosphatidylserine was added was marginally positive (Vakhapova et al. 2010) and two found no difference (Dangour et al. 2010; Stough et al. 2012). Although different doses and different compositions of the relative contributions of EFA and DHA were used, there was no obvious relation with dose. Positive effects, if present, were mainly attributed to DHA.

3.2.2 Dopamine

Eleven studies were investigating substances that were thought to be primarily affecting dopamine (DA) of which two studies investigating modafinil are also included. All but one were single-dose studies and all but one were investigating samples of young healthy volunteers. Three were investigating single doses of d-amphetamine of which all three reported positive effects on delayed recall or recognition (Zeeuws et al. 2010a, b; Zeeuws and Soetens 2007). Four were investigating single doses of methylphenidate of which two reported positive effects on delayed recall memory (Izquierdo et al. 2008; Linssen et al. 2012) and two found no difference (Hermens et al. 2007; Kuypers and Ramaekers 2005). The studies that reported positive effects had in common that they were using considerably longer word lists (20, 30, 70 words) opposed to the studies not reporting positive effects (12 and 15 words) and were looking at late stage memory consolidation.

Two studies on modafinil in young healthy volunteers both reported positive effects on pattern memory recognition (Muller et al. 2013; Randall et al. 2005). A study looking at L-Dopa found no effects (Linssen et al. 2014). One study looking at the COMT inhibitor tolcapone found an interaction between drug and COMT (val158met) genotype such that tolcapone tended to improve word recall in healthy subjects with val/val genotype and tended to impair word recall in subjects with met/met genotype (Apud et al. 2007).

3.2.3 Acetylcholine

Five studies reported investigations of subchronic doses of substances where acetylcholine stimulation was the primary hypothesized mechanism of action, although one of them concerned a combination preparation where other mechanisms might also have played a role. Three of these were in elderly subjects, one of these concerned subjects with Mild Cognitive Impairment. Three studies reported improved episodic memory performance (Gron et al. 2006, 2005; Stough et al. 2009), whereas one reported impaired episodic memory performance (Balsters et al. 2011). The latter was in healthy elderly subjects and the only clear factor in which this study was different than the other three reporting positive effects of cholinesterase inhibitors was that Balsters et al. were using PAL, a nonverbal episodic memory task, whereas the other studies were using Word List tests. One study investigated the cholinesterase inhibitor rivastigmine after pretreatment with cannabis, which induced significant impairment of declarative memory performance and observed that a single dose of rivastigmine 3 mg attenuated cannabis-induced impairment (Theunissen et al. 2014).

3.2.4 5-HT

One study successfully demonstrated that cognitive deficits reported as symptoms, among which impaired declarative memory performance, in Premenstrual Syndrome (PMS), can be improved by treatment with a protein mixture called alpha-lactalbumin containing relatively high amounts of the serotonin precursor tryptophan (Schmitt et al. 2005). Three studies in healthy volunteers investigating acute

and subchronic effects of the serotonergic antidepressants citalopram (Sambeth et al. 2014), escitalopram (Wingen et al. 2006), and vortioxetine (Theunissen et al. 2013) on declarative memory performance found no drug effects on word recall.

3.2.5 Miscellaneous (Glycine, Histamine, PDE5, Glucose)

Two studies investigating novel glycine reuptake inhibitors, hypothesized to improve glutamatergic neurotransmission in patients with schizophrenia, were described (Christmas et al. 2014; Liem-Moolenaar et al. 2010). Both were still in the early stage of human drug development investigating safety and mechanism of action. Neither improved or impaired declarative memory, and in both cases the drug may not have been in the dose window leading to an effective concentration to either confirm or reject the hypothesis.

One study hypothesized histamine augmentation to improve declarative memory by means of administration of betahistine to healthy volunteers (van Ruitenbeek and Mehta 2013). No changes were observed on declarative memory performance.

Two studies investigated the effects of acute doses of 10 and 20 mg of the phosphodiesterase-5 inhibitor (PDE5) vardenafil on declarative memory and both found no differences with placebo. One was in healthy volunteers (Reneerkens et al. 2013) and one was in healthy volunteers after pretreatment with cannabis (Theunissen et al. 2014).

One study showed that a drink containing 25 g of glucose improved paired associate learning in young and elderly volunteers. Glucose is thought to act primarily on the hippocampal region in the medial temporal cortex, known to support episodic memory (Riby et al. 2006).

3.3 Translational Issues

At large, there are three hypotheses underlying the majority of the studies reported in Table 1. These include:

- Dietary polyunsaturated fatty acid supplements improve declarative memory
 - Dietary essential fatty acids include omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFA). Two specific n-3 PUFAs, docosahexaenoic acid (DHA), the principal long-chain PUFA comprising 40 % of brain lipids, and eicosapentaenoic acid (EPA) have specifically been investigated. Both are important in the central nervous system, with 50 % of neuronal membranes and 70 % of myelin composed of lipids. DHA status is dependent on dietary intake, and when low, supplementation is hypothesized to improve cognitive function. The most used dietary manipulation is that of fish oil (containing a mixture of EPA and DHA) or DHA alone (Karr et al. 2012; Yurko-Mauro et al. 2010).
- Cholinesterase inhibition improves declarative memory

- Cholinesterase inhibitors are a registered category of drugs against cognitive symptoms of Alzheimer's disease. Cholinergic decline is considered to occur relatively late in the gradual time span of age-related cognitive decline after conversion to clinical diagnosis of probable Alzheimer's disease. It is subject of considerable debate whether boosting cholinergic function by cholinesterase inhibitors is useful in earlier stages, i.e., mild cognitive impairment.
- Enhancement of dopaminergic neurotransmission improves aspects of declarative memory
 - Substances promoting dopamine may have in common that they facilitate memory consolidation. The hippocampus plays a key role in memory consolidation, which relies on novelty. The Ventral Tegmental Area (VTA) projects to the hippocampus through dopaminergic fibers acting on D1 receptors, where it enhances long-term potentiation (LTP) and learning. The hippocampal-VTA loop has been found to be important for novelty detection, for hippocampal LTP, and for memory consolidation (Izquierdo et al. 2008).

3.3.1 Prediction of Results by Preclinical Studies

When examining data from animal studies, evidence for an improvement in object recognition can be found for various drugs classes. Pro-cholinergic drugs like nicotinic agonists and acetylcholinesterase inhibitors improve performance (de Bruin and Pouzet 2006; Prickaerts et al. 2005; Sambeth et al. 2007). There are a limited number of studies using dopaminergic drugs. Most studies tested dopaminergic drugs in deficit models and transgenic animals. One study showed that especially dopamine type-1 receptor agonists can improve object memory (de Lima et al. 2011). Interestingly, acute methylphenidate treatment impaired object recognition performance in healthy animals (Chuhan and Taukulis 2006).

Also for serotonergic drugs, many studies examined the effects in deficit models. SSRIs seemed to have no effects on object recognition performance (Naudon et al. 2007; Valluzzi and Chan 2007). In animal studies there has been special interest in the 5-HT1A and the 5-HT6 receptors in cognition. Interestingly, although 5-HT1A agonists were found to improve memory performance in other tasks (Cole et al. 1994), a 5-HT1A receptor antagonist was found to improve memory performance in the object recognition task (Pitsikas et al. 2003). Also, 5-HT6 antagonists were found to improve memory performance (King et al. 2004; Lieben et al. 2005). There have been many studies that examined the effect of PDE inhibitors on memory performance and all these drugs have been found to improve object memory performance (Reneerkens et al. 2009). Finally, one study was found in which the effects of a PUFA were tested in the object recognition memory (Cutuli et al. 2014). Here an improved memory performance was found in aged animals after 8 weeks of treatment.

Although this is a restricted overview of studies in which the effects of drugs on object memory were examined, it appears that most drugs improve the performance in this task. SSRI appear to be ineffective in this task and one task showed an impaired object memory performance after methylphenidate treatment. When

considering the human data, there seems to be a great discrepancy in findings between species.

3.3.2 Generalizability of Results to Clinical Therapeutic Areas

Impairments of episodic memory have been described in a wide variety of neuropsychiatric diseases: ADHD and schizophrenia (Mehta and Riedel 2006), mild cognitive impairment and dementia (Riedel 2014), as well as affective disorders (Rock et al. 2014). In Table 1, we have indicated clinical significance by referring the meaning of the results to the therapeutic areas under study. Ten studies were in elderly subjects either or not with established memory impairment or complaints. Seven of these studies noted treatment-induced improvement of declarative memory against one that noted impairment whereas two showed no change. One study in females with premenstrual symptoms including poorer performance on episodic memory tasks resulted in observed treatment-induced improvement of episodic memory performance.

Eighteen studies were in young healthy volunteers with no indication of direct clinical relevance as far as a specific population is concerned. However, results indicating treatment-induced enhancement of cognition bear the relevance that the substance is active and is therefore bearing indirect clinical relevance not specifically linked to one therapeutic area. Healthy volunteer studies are mostly relevant in uncovering principles that may be worth pursuing such as the putative manipulability of memory consolidation by means of substances boosting dopamine.

4 Conclusions

In sum, what this review of cognition-enhancing drug studies in the past 10 years shows is that tests of declarative memory are sensitive to indicate effects of cognition-enhancing treatments. There are three different areas of interest at large: (1) dietary effects of PUFAs which seem to work better in elderly groups than in young participants; (2) effects of “symptomatic” cholinergic drugs appear to be effective in supposedly prodromal or preclinical stages of Alzheimer’s disease; and (3) enhancement of declarative memory consolidation by means of dopaminergic stimulation relatively late after learning, in normal young and elderly volunteers.

Enhancement of declarative memory is perhaps one of the most aspired clinical aims in a variety of recognized therapeutic areas such as dementia and its prodromal stages, ADHD, schizophrenia, and affective disorders. However, non-recognized “therapeutic” conditions such as normal aging and even young healthy volunteers aspire enhancement of declarative memory as well. It is clear that this “therapeutic goal” is wider than fulfilling only urgent medical needs. The latter may apply in the case of dementia; however, even in this area, because attention is shifting to prodromal and preclinical stages of dementia (which are characterized by absence of functional impairment and almost no, or completely no symptoms, but presence of amyloid plaques—putative neural substrate of future disease), the boundaries are

fading and the classic medical model of treating disease appears to be shifting to a “prevention paradigm.” As said, this primarily applies to dementia where no proven disease modifying treatment exists, yet is anticipated, so there is an urgent need for early detection of clinical symptoms of which impairment of declarative memory is the very first manifesting symptom. Measuring declarative memory can therefore be applied as a diagnostic and also as a marker of disease progression and the effects of treatments thereon. In that context, the conclusion of the present review can be: there is enough evidence that impairment and enhancement of declarative memory can be measured precisely. There is just no effective treatment yet to prevent age-related cognitive decline, mild cognitive impairment, and Alzheimer’s dementia. This also can be taken to mean that the positive effects of substances such as PUFAs and cholinesterase inhibitors in elderly with mild cognitive impairment are significant, yet of marginal clinical relevance.

We observed that verbal learning tests are among the most frequently used paradigms to assess declarative episodic memory performance. There are pros and cons to each of these tests/dependent variables (LM, VLT, PRM, and PAL) reviewed in this chapter. As said, the most frequently used paradigm VLT seems to be the most sensitive, but according to Tulving (2002) could be considered too selective to be a good general index of declarative episodic memory because it addresses only the “what” aspect of memory and not the “where” and “when.” This also applies to PRM. In PAL, “where” and “what” is probed. LM is the only paradigm that allows “what,” “where,” and “when” encoding of memory. Another objection to VLT that is sometimes heard is that VLT and therefore also LM are too language-dependent and can therefore only be applied within single language areas. It is true that there may be practical advantages to language-free tests of declarative memory such as PAL or PRM, but verbal memory encoding can be considered essential for mankind and therefore it could be a huge omission not to probe it when investigating efficacy of treatments that claim to enhance declarative memory. It can be easily argued that humans can and will verbalize even the most abstract visual information. For example, if subjects are able to employ a strategy to quickly associate each pattern in PAL with a compass heading (e.g., in clockwise direction: North, North-North-East, North-East, East-North-East, etc.), PAL performance becomes an index of verbal declarative memory encoding. Furthermore, there are numerous validated versions of VLT in different languages. In addition, even within one language area, one needs multiple comparable or parallel versions of the same word list in order to be able to apply it repeatedly within the same cohort of subjects over time or in a crossover design. More importantly, there are some other even more specific parameters, which are rarely considered that allow optimization fitted to testing a specific hypothesis. These are:

- Number of words in the list (in the present review this varies between 12 and 70)
- Number of times word list is presented and immediate recall is repeated (1–5)
- Number of syllables per word (monosyllabic, controlled multisyllabic, or uncontrolled)
- Word length (5, 5–7 letters, or uncontrolled)

- Interval between immediate and delayed recall is usually 20–30 min but can be much longer up to multiple days
- Presentation time, inter-stimulus interval, and response-stimulus interval which determine whether the test is paced or self-paced and what the pace is (1 word per second to 1 word/4 s in the studies reviewed here). These parameters are of key importance whether attentional circuits in the brain are triggered. The faster the pace, the more declarative memory performance will become dependent on attentional constraints (or in essence: time constraints)
- Associability—words within one list are usually controlled for high interrelatedness (e.g., no shoe and foot in one list)
- Recall or recognition—most studies probe free recall, but two studies by Zeeuws et al. (2010a, b) use very long lists and only probe recognition; PRM tests also only probe recognition

This review has shown that positive effects of dopaminergic stimulation on declarative memory performance seem to be best measurable using longer word lists with monosyllabic words. Drugs need to be administered not before but after learning and times of assessment of recall or recognition should be long after learning when effects of treatment on consolidation are most manifest. It remains to be shown how such effects on consolidation should be applied beyond single-dose designs at a longer timescale. What we learn from these studies is that tests need always to be tailored to the specifically predicted effects of drugs. There seems to be no off-the-shelf recipe for cognitive tests.

The prediction of animal studies with respect to episodic memory tasks appears to be very limited. First, the comparison on the level of the episodic tasks is poor. Secondly, there are clear species differences in the effects of drugs on episodic memory. Recently, some critical remarks have been made on the translational value of animal models of memory and the comparability of the effects of drugs across species (Blokland et al. 2014; Brodziak et al. 2014). At present, the translational value of episodic tasks appears to be rather poor.

Declaration of Conflict of Interest W. J. Riedel is part-time employed by Maastricht University and has in the past 12 months also carried out consultancy for Cambridge Cognition, Takeda, Lundbeck, and Keyview Labs.

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