Review Article

Is Emotional Working Memory Training a New Avenue of AD Treatment? A review

Nicola Mammarella*

Department of Psychological Sciences, University of Chieti, Chieti, Italy

ABSTRACT: Emotional working memory training is a new area of research. In this study, we review a series of recent works describing a range of emotional working memory interventions that go from training single affective working memory function to teaching emotion regulation strategies. Generally speaking, research to date has established that emotional working memory may be preserved in Alzheimer's disease. However, much work remains to be done in clarifying what aspects of affective domain is preserved, and testing short- and long-term effects of the trainings as well as their generalization to everyday affective functioning. We conclude by offering suggestions about the development of emotional working memory training for Alzheimer's patients.

Emotional Working Memory Training (EWMT) is an emerging area of research in Alzheimer's disease (AD). Interest in this type of treatment is directly related to the data that show preserved emotional working memory (EWM) in AD. In fact, AD patients have been shown to be able to encode and retrieve valenced information in working memory (WM) as healthy older adults [1]. Although much work has been done to develop cognitive-based interventions to treat WM deficits in AD patients, these studies only focused on the cognitive domain per s é. The current review, instead, presents an updated research literature on WM training with a focus on affective domain. We begin with a description of EWM and discuss its implications for affective rehabilitation in AD, define different affective domains in which WM may be involved, and review a series of interventions that may represent promising new avenues of AD treatment. The central issue is whether good affective WM functions may contribute to cognitive rehabilitative success in AD or vice-versa.

Emotional Working Memory

EWM refers to short-term memory functions that are involved in encoding, maintaining, manipulating and retrieving affective information; it can also be defined as the ability to identify, understand and regulate emotions [2]. It subsumes both the identification of emotions (also called affect or emotion recognition), which is often included among more "passive" or "more automatic" WM functions as well as how emotional information is manipulated and used ("active" or "more controlled" functions). Research findings on the relationship between WM and emotions are new with many studies reporting significant relationships. For example, a series of studies [3] has shown how individuals with higher WM capacity are better at suppressing emotional facial expressions and are more successful at adopting an unemotional attitude while viewing emotionally charged stimuli. The ability to manipulate valenced information in WM is thus a critical component of emotion regulation processes. For example,

*Correspondence should be addressed to: Nicola Mammarella, Department of Psychological Sciences, University of Chieti, Via dei Vestini 31, 66013 Chieti, Italy. Email: n.mammarella@unich.it

negative and positive stimuli elaboration may be attenuated or amplified such that it may increase/decrease peoples's vulnerability to mood disorders [4]. The relationship between WM and neurocorrelates of emotion is also becoming a central issue in the emotion and aging literature [5]. Numerous works have found an interaction between amygdala and orbitofrontal cortex which plays a crucial role in attributing emotional qualities to stimuli. This information is subsequently maintained and manipulated in the dorsolateral prefrontal cortex (PFC) [6]. Given the well-established role of dorsolateral PFC in WM functions [7], it is likely that emotional events capture a greater amount of WM resources that may be less sensitive to pathological aging.

In a recent review, Mammarella and Fairfield [1] reported a series of studies on EWM and AD showing that while some WM functions are still efficient when emotional information is involved, some others are impaired. For example, in terms of maintenance function, negative emotions seem to be maintained in WM and remembered better by AD patients compared to positive and neutral ones. Differently, studies on binding and inhibition are less clear. These data on single WM functions point to a complex pattern of emotion-cognition interaction in AD. On one hand, in fact, the evidence is consistent with the idea that emotional information has a preferential access to WM even in AD. This preferential access means having more opportunities for WM to process emotional information. This assumption is based on the idea that the emotion effect in WM is linked to more automatic and early attentional responses (e.g., fast detection of emotional stimuli). On the other hand, it also highlights that processing of emotional information in WM may fail due to the fact that additional control is required in order to orient attention to this aspect and prevent distraction as in the case of binding and inhibition functions.

In terms of emotion regulation strategies, the few available data also point to the idea that the difficulty to amplify emotion might reflect decreasing controlled processes in AD, while relatively intact suppression of emotion could reflect a greater reliance on automatic mechanisms.

In the next sections, we discuss literature on EWMT following this distinction, that is, with an emphasis on more passive (automatic) vs. more active (controlled) affective WM functions. However, to forecast our conclusions, while a number of passive treatments have been developed to include a single affective component, there is a considerable much work to do in terms of more active EWM training that may specifically target the affective domain in AD.

Emotional Working memory training (EWMT)

While EWMT can be recognized as a distinct type of WM intervention, it shares components of classical cognitive WM training. Both cognitive and affective treatments aim to reduce information processing deficits in different domains. Classical WM trainings differ from EWM treatments in that they focus uniquely on WM functions such as capacity, inhibition, retrieval, etc. of neutral material, while EWMTs focus on targeting WM deficits in how affective information is processed (e.g. how valenced information is processed, how mood states or emotions arise and may be regulated in WM). The main theoretical assumption behind the development of EWMTs is that they should address a broad range of affective impairments such as mood disorders or emotional regulation difficulties, rather than focusing on a single affective function. In fact, behind the conceptualization of EWM there is the clear assumption that this memory component is involved in many complex emotional abilities such as mood and emotion regulation.

Passive EWMT

In terms of emotion recognition, AD patients have been shown to be impaired in emotion decoding abilities. Although the role of confounding variables is still a major issue in these studies, in a recent meta-analysis [8], it has been shown that this deficit does not depend on the severity of disease, general cognitive abilities and recognition of non-emotional face features [9], pointing to an emotional selective deficit in AD.

In terms of brain circuit involved, a recent study [10] found reduced activations in left regions associated with the motor simulation system (the ventral premotor cortex) and in left regions associated with emotional simulation-empathy (the anterior insula and adjacent frontal operculum) when passively viewing a series of emotional faces. This specific deficit in emotion encoding processes can be viewed as a marker of AD. Consequently, emotion recognition processes can be trained to delay the progression of AD pathology. In a typical emotion recognition training paradigm, patients are presented with a series of emotional faces, asked questions relating to the emotional content of each face, and offered several answer choices. If a response is correct, they move on to the next trial, and if the response is incorrect the patient is administered the same trial until the correct answer is chosen. Several concerns have been raised about the efficacy of emotion recognition training in AD. In fact, the use of verbal modality may interfere with the efficacy of the treatment. Recently, Wadlinger & Isaacowitz [11] reviewed a series of affective attentional training paradigms that indirectly called on the role of WM in

emotion regulation. In particular, the authors claim that specific attentional mechanisms may be used to regulate emotions: distraction, concentration and rumination. Distraction means shifting attention from one affective content to another, concentration refers to focus attention on a specific affective content, rumination means rehearsing that content over and over. These mechanisms fall within the definition of attentional deployment strategies and may be also viewed as a series of passive vs. active attentional WM processes. The basic idea is that these functions can be trained in order to affect the content of EWM. Different training procedures have been developed accordingly. For example, in gaze patterns and visual probe training, participant are invited to reorient their attention towards certain affective stimuli. The main procedure consists in a repeated exposure to affective stimuli (e.g., positive pictures) on a computer display and/or repeatedly searching for that affective stimulus. These types of training fall under the category of distraction and may be considered as promoting automatic shifting of attention from negative to positive content. Given that these trainings do not require a greater amount of controlled processes may have an immediate instrumental value when working with AD patients. The immediate implication may be that they may work in the service of orienting and maintaining patients' mood in the positive affective domain.

Active EWMT

In contrast to the single function-based interventions that tackle a specific EWM function as described above, several broad-based interventions have also been developed. For instance, in the Emotion Management Training [12], patients are trained to accurately perceive, interpret, and manage emotional stimuli. It begins with training emotion perception, and in latter phases focuses on teaching coping strategies for regulating emotions. More recently, Schweizer and colleagues [13] developed the first EWMT protocol. Their training uses a EWM dual *n*-back task consisting of a series of faces presented on a 4 x 4 grid on a monitor and a simultaneous word over headphones. Each picture-word pair is followed by a 2500 ms interval during which participants respond via button press if either/both stimuli from the pair matched the corresponding stimuli presented *n* positions back. The 20 daily 20–30 min (depending on level of *n*-back achieved) training sessions consist of 20 blocks of 20_*n* trials. This training relies on the completion of a *n*-back task which involves a series of WM function such as encoding, storage, rehearsal, matching (of current to stored), temporal ordering, inhibition of currently irrelevant items and response execution that make it a particularly well

suited method for manipulating mnemonic and attentional demands and, consequently, for studying the interaction between cognition and emotion.

As outlined before, Wadlinger & Isaacowitz [11]'s review pointed to two more active attentional functions that can be trained in order to affect the content of EWM, that is, rumination and concentration. Although these training may be defined a single-function based, they should be always included in broad-based rehabilitation programs. In this case, in fact, clinical training and meditative training methods invite participants to stop ruminating on internal negative thoughts and engage their attention to external stimuli (e.g., a sound) or focus and sustain their attention on a specific object (e.g., aspect of a scene or body parts). Differently from distraction, these training techniques require more cognitive effort and time. Consequently, it is likely that the efficiency of the WM attentional system or central executive resources will influence their efficacy.

May EWMT be a new way of treatment in AD?

As stated before, active affective WM functions involve the ability to change our experience of and attention to emotional information. The study of these active functions often focuses on the use of regulation strategies such as reappraisal and suppression [14]. Reappraisal serves to change the emotional meaning and significance of an event or stimulus. For example, when viewing a negative picture, one could reappraise this picture in a more positive light. Suppression, instead, is a response-focused strategy and thus occur after an emotional reaction has already occurred.

If we accept the restricted definition of EWM treatments being those with a significant focus on these active affective WM functions, only a few interventions have been developed. Given that EWMT is described as one targeting active affective WM functions, any effects of the treatment on AD can only be speculated. Moreover, we are aware of no published trials evaluating this type of treatment with AD. It is also possible that function-based treatment that supplement training with other active interventions may show positive effects on EWM measures of AD. Studies included in this review are few and vary considerably, so it is hard to attribute differences in efficacy to any one factor involved in rehabilitation success. However we may expect, as for cognitive interventions, that the most extensive and generalizable effects with AD may be found for most intensive and massive affective treatments. At this stage of research, it is impossible to determine which of the numerous treatment components may led to favorable affective outcomes in AD. Most important, the major problem is that most approaches currently taken to remediate

complex affective functions rely much more heavily on cognitively demanding tasks. This type of approach may not be best for individuals with AD. Nevertheless, we believe that the development and testing of EWMT in AD may be a promising new way of AD treatment because it can provide a context to further evaluate the critical role of frontal and subcortical regions in regulating emotion and eventually confine emotional dysfunctions to severe stages. Accordingly, a series of potential avenues of remediation can be pursued.

First, compensating for the deficit by structuring the training in a way that reduces cognitive load. This may be done by adopting an adaptive procedure, beginning with the easiest level for each participant and presenting levels of increasing difficulty as participants' performance improved. In addition, maintenance and processing requests of the task should systematically vary. This hybrid training procedure has been shown to keep the task always challenging favoring, in this way, transfer effects [15].

Second, preceding the EWMT with an intervention specifically aimed at improving WM per sé. Support for the foundational role of WM in successfully targeting these complex affective processes comes from studies [16] showing that executive functions are related to the ability to regulate emotion, especially in terms of planning and monitoring abilities. In particular, the authors found that verbal fluency was strongly related to emotion regulation. In addition, it has been shown that the ability to update emotional information in working memory is a crucial process modulating the efficacy of emotion regulation efforts [17]. These findings can be taken to support the idea that active WM functions needs to be considered in affective trials before engaging in more complex affective processes. This assumption is also supported by studies that showed that WM training improves emotion regulation [18].

At this stage of research, it is thus reasonable to think that cognitive WM rehabilitation may be the first necessary but not sufficient step for EWMT success in AD.

Third, working on implicit EWM. A recent series of studies begun to explore the concept of implicit WM, that is, the assumption that WM can also operate unintentionally and outside of conscious awareness [19, 20]. This idea is extremely fascinating especially in the context of AD treatments because numerous works have shown that implicit emotional processing is preserved in AD. In particular, previous studies reported relatively preserved implicit functions in AD using eye movements recording [21], in tasks that used very short retention intervals [22], in emotional priming paradigms [23] and implicit learning of facial expressions [24].

In addition, neuroimaging findings also point to the hypothesis that AD patients are still able to recruit a network of compensatory brain structures that are associated with implicit emotional mechanisms, in particular amygdala acvitation with no influence on hyppocampus [25]. Although explicit and implicit learning may be dissociable on both cognitive and neural dimensions (for example, the hyppocampus is predominantly associated to explicit learning), a growing number of studies have also highlighted how these two types of learning might interact in the learning process in terms of resource allocation and manipulation of information [26]. Thus, the development of EWMTs based on implicit learning may be a new way of stimulating affective processing in AD patients. It is likely that after intensive treatment of implicit emotional WM functions, AD patients may show benefits on high order affective processing abilities as well.

Last, emotion regulation correlates of WM. Key emotion regulation processes have been shown to occur on the order of milliseconds and thus emerge very rapidly than can be detected via fMRI studies. Scalp-recorded event related potentials (ERPs) have excellent temporal resolution on the order of milliseconds, and thus are capable of capturing such rapid changes resulting from the use of cognitive emotion regulation strategies. ERPs can give us insight into the onset, duration, and interaction of cognitive processes associated with emotion processing. In AD patients, ERPs may be used to examine which aspects of emotion processing are impaired and which remain relatively intact compared to a control population before and after training. In addition, ERPs may inform us on the efficiency of our EWMT procedure. In particular, one ERP that is typically suited for examining emotion regulation strategies is the late positive potential (LPP). The LPP emerges around 200 to 300 ms following stimulus onset and tends to be maximal at centro-parietal recording sites [27]. The LPP reflects increased processing of and facilitated attention to emotional stimuli, such that LPP amplitudes are larger to emotional versus neutral stimuli like pictures, faces, and words [28]. Several studies have shown that LPP is reduced when adults are asked to reappraise an unpleasant stimulus in a more positive light compared to a negative appraisal [29] or when instructed to use cognitive strategies to decrease versus increase subjective emotional responses to emotional stimuli [30]. Most interesting, these changes in the LPP are independent of factors that might increase cognitive load, such as task difficulty [31]. We believe that this may be an extremely relevant new research area in the context of AD treatments' development.

General Discussion

This review highlights the work that needs to be done in the future in the field of EWMT. Research to date points out that several affective domains may be trained with AD, though much work still remains to be done in further refining these treatments, improving their effects on complex affective domains, and demonstrating both the durability of the training effects as well as their generalization to important affective functioning outcomes. The reviewed studies suggest that a) emotion recognition and attentional processes can be trained; b) there is less evidence for emotion regulation, though relatively few studies have focused on this domain. We can thus expect to improve the more simple emotional WM processes like emotion recognition [32, 33], but we may have limited success remediating more complex affective functions in AD [34]. Undoubtedly part of the reason for this is that fewer treatments for these active affective processes have been developed and evaluated. What is clearly needed, similar to what has been developed for WM trials targeting cognition, is a an effort to properly evaluate existing measures, develop new ones as needed, and create a standardized, repeatable battery that can be used in affective interventions with older adults. The majority of studies reviewed here either developed measures specifically for the study, or used measures that had not been adequately evaluated for their psychometric properties and sensitivity to age. Furthermore, there is little data on the potential contribution of other variables that differ between individuals, such as motivational factors A more comprehensive understanding of individual factors (e.g., motivation) that may predict EWM treatment response will allow us to better match treatments to AD patients most likely to respond, as well as direct our efforts at developing and refining treatments for those patients who do not benefit from currently available interventions [35, 36]. Finally, it would be also relevant to refer to different psychophysiological methods and neuroimaging techniques in measuring affective outcomes. For example, facial expressive behavior and heart rate may shed light on the potential mechanisms of change associated with effective interventions in AD.

References

[1]   Mammarella N, Fairfield B (2014). Emotional working memory and Alzheimer's disease: a review. International Journal of Alzheimer Disease. In press

[2]   Mikels JA, Reuter-lorenz PA, Beyer JA, Fredrickson BL (2008). Emotion and working memory: Evidence for domain-specific processes for affective maintenance. Emotion, 8: 256-266.

[3]   Schmeichel B, Volokhov R, Demaree H (2008). Working memory capacity and the self-regulation of emotional expression and experience. J Pers Soc Psychol, 95: 1526-40.

[4]   Kensinger EA, Corkin S (2003). Effect of negative emotional content on working memory and long-term memory. Emotion, 3: 378– 393.

[5]   LaBar KS, Cabeza R (2006). Cognitive neuroscience of emotional memory. Nature Neuroscience, 7: 54-64.

[6]   Watanabe M, Hikosaka K, Sakagami M, Shirakawa S (2007). Reward expectancy-related prefrontal neuronal activities: are they neural substrates of "affective" working memory? Cortex, 43: 53-64.

[7]   D'Esposito M, Postle BR, Rypma B (2000). Prefrontal cortical contributions to working memory: Evidence from event-related fMRI studies. Exp Brain Res, 133: 3-11.

[8]   Klein-Koerkamp Y, Beaudoin M, Baciu M, Hot P (2012). Emotional decoding abilities in Alzheimer's disease: a meta-analysis. J Alzheimers Dis, 32: 109-25.

[9]   Hargrave R, Maddocl RJ, Stone V (2002) Impaired recognition of facial expressions of emotion in Alzheimer's disease. J Neuropsychiatry Clin Neurosci., 14: 64-71.

[10]   Lee TM, Sun D, Leung MK, Chu LW, Keyseres C (2013). Neural activities during affective processing in people with Alzheimer's disease. Neurobiol Aging, 34: 706-15.

[11]   Wadlinger HA, Isaacowitz DM (2011). Fixing our focus: traninig attention to regulate emotion. Per Soc Psychol Rev, 15: 75-102.

[12]   Hodel B, Kern RS, Brenner HD (2004). Emotion Management Training (EMT) in persons with treatment-resistant schizophrenia: first results. Schizophr Res, 68: 107-8.

[13]   Schweizer S, Grahn J, Hampshire A, Mobbs D, Dalgleish T (2013). Training the emotional brain: improving affective control through emotional working memory training. J Neurosci, 33: 5301-11.

[14]   Gross JJ, Thompson RA (2007). Emotion regulation: Conceptual foundations. In: Gross JJ, editor. Handbook of emotion regulation. New York: Guilford Press.

[15]   Borella E, Carretti B, Riboldi F, De Beni R (2010). Working memory training in older adults: evidence of transfer and maintenance effects. Psychol Aging, 25: 767–778.

[16]   Gyurak A, Goodkind MS, Kramer JH, Miller BL, Levenson RW (2012). Executive functions and the down-regulation and up-regulation of emotion. Cogn Emot, 26: 103-118.

[17]   Pe ML, Raes F, Kuppens P (2013). The cognitive building blocks of emotion regulation: ability to update working memory moderates the efficacy of rumination and reappraisal on emotion. PloS One, 8: e69071.

[18]   Engen H, Kanske P (2013). How working memory training improves emotion regulation: a neural efficiency, effort, and transfer effects. J Neurosci, 33: 12152-3.

[19] Hassin RR, Bargh JA, Engell AD, McCulloch KC (2009). Implicit working memory. Conscious Cogn, 18: 665-78.

[20] Magnussen S. (2009). Implicit visual working memory. Scand J Psychol, 50: 535-42.

[21] LaBar KS, Mesulam M, Gitelman DR, Weintraub S. (2000). Emotional curiosity: modulation of visuospatial attention by arousal is preserved in aging and early-stage Alzheimer's disease. Neuropsychologia, 38: 1734-1740.

[22] Padovan C, Versace R, Thomas-Anterion C, Laurent B (2002). Evidence for a selective deficit in automatic activation of positive information in patients with Alzheimer's disease in an affective priming paradigm. Neuropsychologia, 40: 335-9.

[23] LaBar KS, Torpey DC, Cook CA, Johnson SR, Warren LH, Burke JR, Welsh-Bohmer KA (2005). Emotional enhancement of perceptual priming is preserved in aging and early-stage Alzheimer's disease. Neuropsychologia, 43:1824-37.

[24] García-Rodríguez B, Fusari A, Rodríguez B, Hernández JM, Ellgring H (2009). Differential patterns of implicit emotional processing in Alzheimer's disease and healthy aging. J Alzheimers Dis, 18: 541-51.

[25] Rosenbaum RS, Furey ML, Horwitz B, Grady CL (2010). Altered connectivity among emotion-related brain regions during short-term memory in Alzheimer's disease. Neurobiology of Aging, 31: 780-786.

[26] Yang J, Li P (2012). Brain networks of explicit and implicit learning. PLoS One, 7: e42993.

[27] Cuthbert BN, Schupp HT, Bradley MM, Birbaumer N, Lang PJ (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. Biol Psychol., 52: 95–111.

[28] Herbert C, Junghofer M, Kissler J (2008). Event related potentials to emotional adjectives during reading. Psychophysiology, 45: 487–498.

[29] Foti D, Hajcak G (2008). Deconstructing reappraisal: Descriptions preceding arousing pictures modulate the subsequent neural response. J Cognitive Neurosci, 20: 977–988.

[30] Moser JS, Krompinger JW, Dietz J, Simons RF (2009). Electrophysioloigcal correlates of decreasing and increasing emotional responses to unpleasant pictures. Psychophysiology, 46: 17–27.

[31] Hajcak G, Dunning JP, Foti D (2009). Motivated and controlled attention to emotion: Time-course of the late positive potential. Int J Clin Neuropsyc, 120: 505–510.

[32] Mammarella N, Fairfield B, Di Domenico A (2011). Comparing different types of source memory attributes in dementia of Alzheimer's type. Int Psychoger., 12: 1-8.

[33] Mammarella N, Borella B, Carretti B, Leonardi G, Fairfield B (2013). Examining an emotion enhancement effect in working memory: Evidence from age-related differences. Neuropsychol Rehabil, 23: 416-28.

[34] Mammarella N, Fairfield B, Di Domenico A, Borella E, Carretti B (2013). Is working memory affective in Dementia of Alzheimer's Type? Neuroscience Discovery, 1: 4.

[35] Mammarella N, Fairfield B, Di Domenico A (2012). When touch matters: an affective tactile intervention for older adults. Ger and Geront Int,12: 722-724.

[36] Mammarella N, Fairfield B (2013). Where did I put my keys? A 'We' intervention to promote memory in healthy older adults: A controlled pilot study. Gerontology, 59: 349-54.