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Memory training in depression

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Cognitive processes are of considerable interest for our understanding of psychopathology and are seen as important factors in the development, maintenance, and recurrence of depression (Beck et al., 2008). One aspect of cognitive functioning which is of particular importance in depression is memory, with much evidence for two phenomena: A general (working) memory impairment regardless of the emotional valence, and specific mood congruent biases (for reviews, see Blaney, 1986; Ellis, & Ashbrook, 1989; Williams, Watts, MacLeod, & Mathews, 1997). General impairments in working memory are associated with the level of depression (Gohier et al., 2009) and it has been shown that impaired working memory for negative information is related to rumination (e.g., De Lissnyder, Koster, Derakshan, & De Raedt, 2010), an important risk factor for the development, maintenance and recurrence of depressive episodes. Furthermore, depressed patients and persons at risk show mood-congruent memory for negative information. These biases are already apparent in children of mothers with depression (Taylor & Ingram, 1999; Joormann et al., 2007). Being able to train memory and positive memory biases would offer a new approach for interventions, targeting important risk factors directly. Such trainings have become available just recently.

To date, most memory training studies in the context of depression target working memory. They build on the premises of affective neuroscience research that cognitive processes, whether or not for emotional material, have a fundamental impact on higher order thought processes, such as emotion regulation (for a review of a process-

oriented theoretical framework in depression vulnerability, see De Raedt & Koster, 2010). In other words, changing the more general problem of working memory operations should also change the more specific problem in thought processes, such as rumination, in currently depressed patients. Accordingly, even though depression is characterized by deficits in control over mood congruent representations in working memory, non-emotional stimuli are frequently used for training programs focusing on working memory in depressed patients. Nevertheless, some trainings also directly target mood congruent memory, and some use attention or interpretation trainings to change emotional memory biases. This review will present a short overview in regard to these three novel treatment approaches. The trainings presented here have in common that they are computer based. The usual outcome measures are mood, depressive symptoms and rumination.

General memory trainings in depression:

The memory task that is mostly used in contemporary training research is the dual *n*-back, a well known and frequently studied cognitive paradigm targeting working memory. For working memory training intentions, the adaptive version of the dual *n*-back task is used (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). In this adaptive *n*-back, participants are presented with a visual and an auditory stimulus sequentially and are required to indicate whether one of both stimuli is similar to the stimulus that was presented *n* steps before. Based on accuracy rates, the difficulty level is adjusted (increases or decreases based on the *n* back); this way the training is tailored to the individual performance level. In moderately dysphoric individuals, Owens, Koster, and Derakshan (2014) observed behavioral and neural evidence for transfer effects of the adaptive *n*-back training on filtering efficiency and working memory capacity, both being depression characteristics. However, changes in depressive symptomatology were not reported. Overall, clinical effects on rumination and depressive symptoms of an adaptive *n*-back training using non-emotional information are limited and there are negative findings (e.g., see Onraedt & Koster, 2014 using participants with heightened rumination scores).

A different non-emotional cognitive training program that seems to have consistent effects on measures of cognitive control, as well as cause a reduction in rumination and depression, is the Cognitive Control Training (CCT) of Siegle and

colleagues (Siegle et al. 2007; 2014; Calkins et al., 2014). This cognitive training is performed in (sub)clinical populations and is used as an add-on intervention, i.e., participating patients continued with their treatment as usual. To train working memory, the adaptive Paced Auditory Serial Addition Task (PASAT, Gronwall, 1977) is used. During the adaptive PASAT participants are presented with a stream of auditory presented digits and are instructed to indicate the sum of the last two digits, which relies on continuously updating working memory. Depending on the accuracy of the responses, the inter-stimulus interval increases or decreases , modifying task difficulty. Even though stimuli are non-emotional, working memory is trained in the presence of frustration and low levels of negative affect. The idea is that prefrontal activity is stimulated due to the emotional reactivity, resulting in the activation of both the frontal and limbic circuit.

In recent studies, the CCT has been combined with non-invasive neural stimulation, such as transcranial Direct Current Stimulation (tDCS), to enhance the activity in the prefrontal cortex during the neurocognitive training (Brunoni et al., 2014; Segrave, Arnold, Hoy, & Fitzgerald, 2014; Vanderhasselt et al., 2015). Even though more research is absolutely necessary, Sergrave et al. (2014) observed that improvement in depressive symptoms sustained at three weeks follow-up only in the group receiving neurocognitive training in combination with tDCS. Brunoni et al. (2014), on the other hand, reported that the sustained effects on depressive symptomatology at four weeks follow-up were most evident in older depressed patients receiving tDCS, making cognitive plasticity a possible modulator of CCT (Brunoni et al., 2014).

Emotional memory trainings

There is also some research reporting effects of working memory training variants with emotional stimuli. One study found that an emotional dual *n*-back training led to improved emotion regulation in a healthy population (Schweizer, Hampshire, & Dalgleish, 2011). The emotion regulation was associated with neural correlates of affective control (Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013). Recently, Iacoviello et al. (2014) demonstrated reduced depressive symptomatology and a reduction in negative affective bias after an emotional faces (as compared to a non-emotional) *n*-back working memory training in a depressed population. In this

latter training, a combination of emotion identification and working memory task was used in currently unmedicated depressed patients.

Studies on the modification of emotional memory (called CBM-memory) started by targeting memory forgetting and suppression. A study by Hertel and Gerstle (2003) was based on the assumption that depressed individuals might successfully suppress and therefore forget positive word pairs more easily than negative word pairs. These authors observed that dysphoric individuals (compared with non-dysphoric individuals) forgot fewer words after having been instructed to suppress them, regardless of valence, and failure to suppress was association with higher levels of rumination. More recently, Joormann, Hertel, LeMoult, and Gotlib (2009) used a similar unaided suppression condition and included two additional conditions in which depressed and non-depressed individuals were provided with substitutes for either the positive or negative words. In line with the previous study (Hertel & Gerstle, 2003), depressed individuals did not exhibit forgetting of negative words in the unaided condition. They, however, showed successful forgetting of negative words in both positive and negative substitute conditions. These studies show that unsuccessful emotional memory suppression might be a core process in depressive rumination. Providing an alternative during suppressing recall of negative material might be a successful strategy to alter emotional memory.

Recently, CBM-memory paradigms targeting explicit emotional memory were tested, but so far only in healthy populations. In two studies, Vrijsen et al. (2014) attempted to modify encoding strategies. In a series of memory tasks, healthy individuals studied emotional words and were then tested for only positive or negative words using word fragments. No evidence for a training effect was obtained, except in terms of memory intrusions: The negative training stimulated incorrect recall of negative words in a community sample. Using a different CBM-memory approach, Vrijsen, Hertel, Maydon, and Becker (submitted) were able to induce training-congruent recall of which the effect was still present at follow-up a week later. In a series of tasks, participants studied positive and negative Swahili-Dutch word pairs. The study trials were followed by a cued recall test of either positive or negative translations. Transference to autobiographical memory, but not memory intrusions, was found. The mixed results underscore that CBM-memory is still in its infancy. Nevertheless,

changing emotional memory processes in the context of depression seems promising and further research on CBM-memory is warranted.

Targeting memory biases via attention or interpretation trainings

There is a growing body of research studying biases an integrative manner, based on the Combined Bias Hypothesis (see Everaert, Koster, & Derakshan, 2012; Hertel & Brozovich, 2010; Hirsch, Clark, & Mathews, 2006). This hypothesis holds that once negative information is attended to, depressed individuals have difficulties in disengaging their attention from it, which results in attention elaboration and biased interpretation. The interpreted meaning is then likely to be stored in memory, setting the state for negative memory bias. Studies considering the influence of attention and interpretation bias on memory bias seem to support this model (Ellis, Beevers, & Wells, 2011; Everaert, Duyck, & Koster, 2013a; Everaert, Tierens, Uzieblo, & Koster, 2013b; Koster, De Raedt, Leyman, & De Lissnyder, 2010).

Interpretation bias modification paradigms (called CBM-interpretation) are generally effective in altering emotional memory processes (Hertel & Mathews, 2011), while the evidence for the effect of emotional attention trainings (called CBM-attention) is weaker. In an unselected sample, an attention training away from threat reduced negative memory intrusions, but did not affect memory bias for trained stimuli in individuals with elevated depression scores (Blaut et al., 2014). Results on the effect of interpretation training on memory bias indicate that individuals recall material - such as the presented ambiguous scenarios - congruent with their previous or current interpretative bias (Hertel, Holmes, & Benbow, 2014; Salemink, Hertel, & Mackintosh, 2010; Tran, Hertel, & Joormann, 2011). Similar training-congruent effects on memory intrusions have been reported for a rumination-specific interpretation training (Hertel, Mor, Ferrari, Hunt, & Agrawal, 2014). Taken together, studies have been successful in altering memory bias via changing processing in another cognitive domain, with most compelling evidence for the effectiveness of CBM-interpretation.

The importance of variables that contribute to training success

Individual differences - such as motivation, expectation, task engagement, increase in working memory - moderate the potential transfer effects of the trainings, both on cognitive processes (Jaeggi et al., 2014) and on clinical response on

depression and rumination (Siegle et al., 2014; Vanderhasselt et al., 2015). Online feedback representing their learning experience could increase the patient's intrinsic motivation (Jaeggi et al., 2014; Siegle et al., 2007, 2014). The adaptive component of the memory training programs (e.g., each individual follows an individual training program) is in line with this recent trend in the literature. Moreover, the preexisting cognitive ability (Jaeggi et al., 2014) and severity of depressive symptoms at baseline (Lohman, 2013) seem to moderate the effects of the training.

Another variable that varies enormously between studies, is the number of training sessions, ranging from one to 20 sessions (Hertel & Mathews, 2011; Onraedt & Koster, 2010; Schweizer et al., 2013). We are at the moment lacking systematical studies on dose response. There are indications from CBM studies in the field of anxiety problems or disorders, that more sessions are related to greater effects (Hakamata et al.; 2010) Hallion & Ruscio, 2011). In contrast, a recent meta-analysis, reports the opposite effect in (subclinical) anxiety and depression (Cristea, Kok, & Cuijpers, 2015). However, no CBM-memory studies were included in this meta-analysis. There is no golden standard of how many training sessions should be performed, as well as the time lapse in between sessions. Possibly, the number of training sessions should not be a fixed factor, but rather a study parameter that could be individually different between patients, e.g. depending on their memory impairment or the strength of the bias. The same rationale could be used for whether the time (e.g., Siegle et al., 2007; 2014) or the number of trials (e.g., Schweizer et al., 2013) per training session should be fixed. Overall, more research investigating these parameters is necessary.

Conclusions

We restricted ourselves to computerized memory trainings in this review. But there are possible other ways to influence memory processes in depression, e.g. via mindfulness training (Williams et al., 2000) or via the memory training program COMET (Ekkers et al., 2011), that might be alternative options but are of a very different nature of the programs presented here. All in all, the computerized memory trainings targeting general deficits in memory or specific emotional effects seem to be an interesting new treatment option, especially as add-on to other interventions.

But at this moment there are many open questions some of a more practical nature, e.g. how many sessions, spaced in what way, for how long would lead to optimal results. It has been shown that emotion regulation is related to a combination of these biases (Joormann & D'Avanzato, 2010). Could we increase effects if we would combine different CBM approaches, e.g. interpretation or attentional training, with memory trainings? Or would a combination of different working memory trainings be beneficial? How long do those training effects last? Do they generalize to other cognitive processes? Would the participants profit more if we would train them under stressful conditions? Based on neural evidence, suppressing emotion reactivity (amygdala based) as a reaction to stress using cognitive processes (prefrontal control) is the mechanism underlying depressive mood recovery. And there are also important theoretical questions: Are we really training working memory, or some other control processes? Very little is known about the cognitive mechanisms, and neuro-cognitive research might be very helpful here.

Future research should also take the individual difference into account, we know very little who is really profiting of those training. It might be important to take the deficits or biases that exist before the training into account. There are also first indication that genetic susceptibility differences play a role in CBM-effects (e.g. Fox, Zougkou, Ridgewell, & Garner, 2011). One of possibility is that training effects are dependent on a number of genes that moderate plasticity and learning (Belsky et al., 2009). Some of these questions have to be answered before those memory trainings will be part of our regular mental health care provision.

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