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# Eye movement desensitization and reprocessing as a treatment for PTSD: current neurobiological theories and a new hypothesis

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Eye movement desensitization and reprocessing (EMDR), a form of psychotherapy for individuals with posttraumatic stress disorder (PTSD), has long been a controversial topic, hampered in part by a lack of understanding of the neural mechanisms that contribute to its remedial effect. Here, we review current theories describing EMDR's potential neurobiological mechanisms of action involving working memory, interhemispheric communication, dearousal, and memory reconsolidation. We then discuss recent studies describing the temporal and spatial aspects of smooth pursuit and predictive saccades, which resemble those made during EMDR, and their neural correlates within the default mode network (DMN) and cerebellum. We hypothesize that if the production of bilateral predictive eye movements is supportive of DMN and cerebellum activation, then therapies that shift the brain towards this state correspondingly would benefit the processes regulated by these structures (i.e., memory retrieval, relaxation, and associative learning), all of which are essential components for PTSD recovery. We propose that the timing of sensory stimulation may be relevant to treatment effect and could be adapted across different patients depending on their baseline saccade metrics. Empirical data in support of this model are reviewed and experimental predictions are discussed.

Keywords: review; eye movement desensitization and reprocessing; EMDR; post-traumatic stress disorder; PTSD; default mode network; cerebellum

#### Introduction

Eye movement desensitization and reprocessing (EMDR) is one of the evidence-based treatments for post-traumatic stress disorder (PTSD) and is recommended by multiple international guidelines.<sup>1–3</sup> To date, EMDR has been used experimentally with some benefit, to treat phobias, mood, and personality disorders.<sup>4–7</sup> EMDR is a structured psychotherapy developed by psychologist Francine Shapiro in 1987,<sup>8</sup> and it became the first psychotherapy with a demonstrated neurobiological effect, specifically altered brain wave activity in response to treatment.<sup>9</sup> During EMDR, patients respond to bilateral sensory stimulation (BLS), either visual, tactile, or audi-

tory, while maintaining specific components of a targeted memory, related emotions, and bodily sensations in mind.<sup>10,11</sup> According to standard EMDR protocol,<sup>12</sup> BLS is delivered at a rate of 1–2 Hz, for 24–36 s blocks, followed by talk therapy where the therapist asks whether the patient has noticed any new information related to the memory. Then, BLS is administered again, this time while the patient focuses on new information, emotions, and sensations. This is continued for about 30–60 min per session, and patients typically complete 6–8 sessions over the course of treatment. By the end of treatment, individuals with PTSD generally no longer show avoidant behaviors and cognitive distortions,



**Figure 1.** Attenuation of PTSD symptoms through EMDR treatment. Traumatic memories in PTSD patients are intrusive and cause subjects to relive the emotional event through flashbacks and nightmares. PTSD patients have difficulty voluntarily retrieving traumatic autobiographical memories. During EMDR, the traumatic memory and related emotions/bodily sensations are held in WM as the subject generates saccades toward bilateral visual targets. When the subject achieves symptom relief, the patient no longer experiences intrusive flashbacks or nightmares and can recall the aversive event with reduced corresponding emotional and physiological arousal. PTSD, post-traumatic stress disorder; EMDR, eye movement desensitization and reprocessing; WM, working memory.

and report that the targeted memory has become less vivid and emotional (Fig. 1).

Clinical trials of trauma-focused therapies have reported similar treatment efficacies for EMDR, traditional exposure therapy, and cognitivebehavioral therapy for the treatment of PTSD.<sup>13</sup> Compared to exposure therapies, EMDR generally achieves symptom reduction in fewer treatment sessions.<sup>14</sup> A review conducted in 2014 evaluated 26 randomized controlled trials of EMDR and concluded that EMDR significantly reduced the experience of depression, anxiety, and subjective distress in individuals with PTSD.<sup>15</sup> Compared to psychotropic medication, EMDR has been shown to be more successful in achieving sustained symptom reduction.<sup>16</sup> A variety of cognitive benefits have been reported by patients following EMDR therapy. These benefits include enhanced episodic memory retrieval, increased accuracy of the recalled memory, increased cognitive flexibility, and improvements in attentional orienting, somatic awareness, mindfulness, and free association.<sup>17-19</sup>

Robust therapeutic benefits of EMDR have been demonstrated. However, since EMDR's initial description in 1987, there have been over 300 primary articles and 95 review articles on the topic debating the potential neural mechanisms that might underlie its therapeutic effects.<sup>19,20</sup> Many of these papers debate the relationship of BLS to its therapeutic efficacy. Ironically, given the therapy's name, eye movements (EMs), the most common form of motor response generated in EMDR, have yet to be recorded during therapy and thus their oculomotor characteristics (i.e., types of EMs and EM metrics) and associated neural circuits have not vet been rigorously tested in the context of clinical recovery. Nevertheless, there are multiple theories grounded in neurobiology and psychology, detailed in the following section that hypothesize as to EMDR's mechanisms of action. Here, we first review recent literature and prominent theories on the contribution of EMs in EMDR and then, based upon recent findings of the temporal and spatial aspects of bilateral horizontal EMs,<sup>21</sup> we propose a novel hypothesis regarding a role for activation of the default mode network (DMN)<sup>22</sup> and cerebellum within BLS delivery that could be used to optimize therapeutic outcome.

#### Theory 1: EMDR taxes working memory

A popular explanation for EMDR's mechanism in trauma recovery is that EMDR interacts with working memory (WM) processes (i.e., visuospatial sketchpad and central executive).<sup>23</sup> EMDR is a dual-attention procedure that requires patients to divide their attention between BLS and an aversive memory. The aversive memory is held in WM, which has a finite pool of resources that temporarily maintains information to conduct cognitive processing, such as reading, counting, or thinking.<sup>24,25</sup> Evidence supports that performance deteriorates when two tasks make demands on

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the limited capacity of WM.<sup>25</sup> During EMDR, EMs and memory recall tax WM's visuospatial sketchpad.<sup>26</sup> Combined, fewer resources are available in WM to visualize the traumatic memory, which is hypothesized to then allow it to become reconsolidated as less vivid and emotionally salient than it was previously.<sup>24,27</sup> This theory is supported by considerable research demonstrating that recall of autobiographical memories during a motor task results in modification of the memory.<sup>10,27,28</sup>

In 2016, van Veen and colleagues tested the effects of taxing the visuospatial sketchpad and central executive on cognitive load by using BLS, similar to EMDR.<sup>24</sup> Young adults responded to a randomly administered auditory tone by pressing a button as quickly as possible while performing either a dualattention task (combined EM and memory recall) or a singular task (memory recall only condition or EMs only condition). Button-press reaction times were longer in conditions where participants performed the dual-attention task, compared to trials where participants simply made EMs or held the memory in WM. The authors concluded that generating EMs while holding a memory in the visuospatial sketchpad and central executive increases cognitive load, as evident by increased reaction times. In a series of experiments, autobiographical memory recall was compared after individuals attended to visual targets (EMs), tactile stimuli (finger taps), auditory stimuli (beeps), and a control condition (no stimulation).<sup>29,30</sup> Individuals reported greater reductions in the vividness and emotionality of memories after attending to visual stimuli versus tactile, auditory, and control conditions, providing some support for EM's stronger taxation of WM compared to other EMDR modalities.29,30

According to the WM hypothesis, if the modality of BLS matches the most salient component of the trauma (i.e., auditory, visual, or tactile), it will evoke a stronger taxing effect on the WM.<sup>28,31</sup> Kristjánsdóttir and Lee tested this concept with healthy participants who were instructed to recall an aversive memory while performing each of two dual-attention tasks (i.e., EMs; listening to counting) and a control condition.<sup>32</sup> Participants reported stronger reductions in the vividness of the recalled memory after EMs, irrespective of the modality of memory. This result is inconsistent with the WM model of mode-specific effects. To explain these findings, the authors reasoned that auditory, tactile, and visual BLS all tax the central executive, but visual BLS also taxes the visuospatial sketchpad and consequently generates a stronger influence on cognitive resources within the WM.<sup>32</sup> Further, it is theorized that through the process of reconsolidation during EMs, the emotional memory trace that is recalled during a dual-attention task is modified to become less visually salient than it was prior to EMDR, thus providing symptomatic benefit.<sup>33,34</sup> This mechanism may explain why EMDR has been shown to produce clinical effects faster than exposure therapies (e.g., see Ref. 14). The dual-attention task during EMDR combined with EM's additional taxation of the visuospatial sketchpad may act to reduce the saliency and focus required by the memory, thereby speeding up the therapeutic process.<sup>27</sup> This theory is supported by a 2013 meta-analysis that compared the treatment efficacy of 15 clinical trials of EMDR with EMs compared to without EMs and found that EMs contribute a significant, moderate effect to symptom alleviation.<sup>11</sup> On the other hand, a randomized clinical study comparing the efficacy of tactile, auditory, and visual stimulation during EMDR demonstrated that all three sensory modalities resulted in symptom reduction.<sup>35</sup> Therefore, although visual BLS and the generation of EMs are supported by the WM literature over other BLS modalities, all forms of BLS used in EMDR may still have clinical impact.

In 2016, Coubard introduced a neurobiological model to account for the popular WM hypothesis.<sup>20</sup> In Coubard's model, the memory reprocessing system is linked with the oculomotor circuit (that propagates EMs) and saccade reaction time (SRT) is used as a neurobiological measure to evaluate the relationship between the two.<sup>20</sup> Coubard concurred with the WM hypothesis that attention required to initiate EMs may lead to higher distractibility for the memory held in mind, thereby allowing it to be more easily manipulated within WM. Coubard used the TIMER-RIDER model to explain that this neurobiological phenomenon occurs through EMDR's modulation of the physical distance between decision-based thresholds in the anterior cingulate cortex (ACC).<sup>20</sup> As per this model, during EMDR, modulation within the ACC leads to higher decision-making skills and fewer express latency saccades, which have the shortest visually triggered SRTs of 80–134 milliseconds.<sup>36–38</sup> In the context of this model, express latency saccades represent control *loss* because their signals travel through early visual pathways to the superior colliculus<sup>39</sup> and bypass the attention–inhibition network. Coubard advised researchers to collect eye-tracking metrics before and after EMDR to measure EMDR's effect on subjects' attention and motor control. Coubard theorized that a reduction in the frequency of express saccades over the course of EMDR will correlate to increased cognitive control through modulation of the ACC.

Coubard's suggestion of collecting eye-tracking metrics pre- and post-therapy is a logical first step to understand EMDR's influence on the oculomotor and cognitive neural systems. By understanding the neurophysiological effects of BLS, we can understand brain structures recruited during EMDR and the neural processes regulated by these structures. This understanding can inform researchers on how to optimize BLS delivery to recruit cortical networks that facilitate patient recovery. In 2010, Kapoula recorded the frequency of smooth pursuit EMs and catch-up saccades pre- and post-EMDR therapy in healthy participants as they performed a smooth pursuit EM task.40 The coherence of smooth pursuit EMs significantly improved after EMDR, and the number of saccadic intrusions (i.e., catch-up saccades) decreased. Although these authors did not report on the SRTs of catch-up saccades (i.e., whether they were express or predictive), these results provide preliminary support for a change in EM characteristics post-therapy to reflect greater oculomotor control. The authors acknowledged that it is important to identify if EMDR improves the quality of other types of EMs.<sup>40</sup>

With regard to Coubard's hypothesis, Kapoula's finding of increased quality of smooth pursuit EMs may indeed be related to greater control of cortical regions, such as the ACC. In an electroencephalography (EEG) study, Pagani observed reduced connectivity between the posterior cingulate cortex (PCC) and ACC in PTSD patients compared to controls as they generated bilateral EMs, providing potential evidence for a role of the ACC in production of bilateral EMs and PTSD pathophysiology.<sup>9</sup> In a functional MRI (fMRI) study, Berman reported that smooth pursuit EMs activate the ACC, frontal eye fields (FEFs), supplementary eye fields (SEFs), intraparietal sulcus (IPS), precuneus, and PCC.<sup>41</sup>

All six of these brain regions were also involved in the generation of predictive saccades, when EMs were initiated before registration of the visual target (SRT < 90 ms).<sup>41</sup> These results were replicated by a positron emission tomography study that investigated the cerebral blood flow correlates of smooth pursuit EMs and predictive saccades.<sup>42</sup> The authors concluded that the EM behavior and metrics for smooth pursuit EMs and predictive saccades were distinct, but both smooth pursuit EMs and predictive saccades activated similar brain networks/ regions.<sup>42</sup>

To examine these research findings in the context of EMDR's visual paradigm, we must consider the stimulus conditions of BLS during treatment. According to standard protocol in EMDR, BLS is delivered at a constant rate (1-2 Hz), between two fixed targets, to induce smooth tracking.<sup>12</sup> Although smooth pursuits are likely generated, literature also supports that under such conditions, predictive motor responses are also produced.<sup>43,44</sup> Therefore, capturing the frequency and nature of smooth pursuits and predictive saccades-that likely both occur during therapy and which share similar neural systems-in real time during EMDR may shed light on the accuracy of Coubard's neurobiological model and provide further evidence for the neurobiological contribution of EMs to treatment.

# Theory 2: EMDR increases interhemispheric connectivity

A second leading theory describing EMDR's benefit is that EMs toward repetitive BLS, either auditory, tactile, or visual, boost interhemispheric (IH) communication between the right and left cerebral hemispheres.<sup>45</sup> This theory is grounded in the primarily contralateral organization of sensory fields, for example, information from the left visual hemifield is initially processed in the right hemisphere and vice versa.<sup>46</sup> Thus, continuous attention to BLS recruits IH activation, necessary to carry out processing. Two recent meta-analyses have reported improved outcomes in EMDR studies that used BLS versus psychotherapy alone, providing some support to the IH communication hypothesis.<sup>11,15</sup> Indirect evidence for increased IH communication associated with bilateral EMs comes from sleep studies where IH EEG signaling is increased during rapid eve movement (REM), a stage where the majority of EMs are bilateral.<sup>47,48</sup> Correspondingly, evidence is mounting for diminished IH activation in individuals with PTSD, as observed by individuals' lower corpus callosum volumes, REM sleep disruption, and impaired episodic memory recollection.<sup>49–52</sup> Thereby, EMDR is hypothesized to normalize IH recruitment in PTSD patients through the activation of both cerebral hemispheres during BLS.

Consistent with this theory, individuals with PTSD have shown an increase in consolidated sleep<sup>53</sup> and EEG coherence in the beta band<sup>54</sup> post-EMDR treatment. Further, an increase in bilateral EEG coherence was reported in individuals performing EMs in response to visual stimuli that was similar to that used in EMDR.<sup>55</sup> Indeed, multiple studies have reported enhanced visual processing (e.g., higher tracking capacity; increased probability of storage of critical items in visual processing WM) when visual stimuli are presented across both visual hemifields rather than in a single hemifield (i.e., the bilateral advantage).<sup>46,56</sup> Laboratorybased studies have demonstrated that bilateral EMs increase memory retrieval (e.g., recall accuracy and number of items recalled) in clinical and general populations.<sup>11,57,58</sup> Likewise, research supports that REM sleep (when bilateral saccades are initiated) plays an important role in memory transfer and consolidation.59,60

On the other hand, vertical EMs or visual fixation (no saccade) conditions, both of which recruit simultaneous bilateral cerebral activity but not in the same alternating IH activation provoked by horizontal EMs, have not demonstrated an effect on episodic memory retrieval.28,57,58 If alternating IH activation is the basis for EMDR's success, engaging in bilateral horizontal EMs should theoretically promote therapeutic effect, regardless of their temporal or spatial characteristics. Yet, in a study comparing horizontal fast EMs (saccades) to horizontal slow EMs (smooth pursuit), only fast EMs (i.e., saccades) were associated with a significant improvement in memory.<sup>58</sup> In a clinical study, three forms of tactile and auditory bilateral stimulation (alternating, intermittent, and continuous) were tested in individuals with PTSD undergoing EMDR.35 All three stimulus conditions promoted symptom reduction, but the alternating BLS conditions demonstrated added effects of reduced subjective distress during memory recall.<sup>35</sup> Together, these results suggest that the temporal and spatial qualities of BLS, and not IH activation alone,

influence episodic memory recall and the patient experience during treatment. In this context, we speculate that IH communication during EMDR might partially contribute to its therapeutic effects, but more research is required to test and potentially optimize stimulus delivery parameters during treatment.

# Theory 3: EMDR adjusts the storage of traumatic memories

Memory consolidation research supports the idea that cognitive aspects of memories are mediated by the hippocampus, whereas emotional components of memories are primarily stored in the amygdala.<sup>18,61,62</sup> During slow-wave sleep, memory traces from the hippocampus and amygdala are combined to form one memory with both cognitive and emotional components.<sup>18</sup> At the cellular level, memories are formed and extinguished through the phosphorylation or dephosphorylation of *α*-amino-3-hydroxy-5methyl-4-isoxazole (AMPA) receptors.<sup>63–65</sup> During traumatic events, it is theorized that there is overpotentiation of AMPA receptors within the amygdala.<sup>18</sup> This in turn reduces the availability of AMPA phosphorylation within the hippocampus generating a predominantly affective memory trace.<sup>18</sup> Consequently, these fragments are prevented from semantic processing and fail to be stored in the declarative memory system and cannot be properly recalled in the future.<sup>66</sup> It is hypothesized that EMDR leads to dephosphorylation of traumatic memory traces maintained in amygdala synapses, thus allowing them to be restored to contain both cognitive and emotional elements. Integration of this memory is speculated to reduce the saliency and fearfulness of the recalled event.

The memory reconsolidation theory is supported by an animal study where application of lowfrequency electrical stimulation (1-5 Hz) in the rat somatosensory cortex caused spike-dependent amygdala depotentiation of AMPA receptors proportional to the stimulation frequency.<sup>63</sup> Longterm depotentiation of AMPA receptors resulted in their removal from the postsynaptic membrane and degradation of the memory trace.<sup>62,63</sup> This was determined by extinction of fear-related behaviors evoked by previously conditioned stimuli. A similar neuronal excitation rate occurs in EMDR (1–2 Hz) and researchers who advocate for this model propose that EMDR's neurological mechanism may be related to depotentiation of amygdala AMPA synapses. It is speculated that emotional memories retained in the amygdala move to the cortex during the EMDR's dual-attention task to become depotentiated and restored. This theory may help account for the seemingly contradictory findings that EMDR reduces the lucidity and emotional valence of a memory, but boosts its ability to be recalled. That is, through EMDR's taxation on the visuospatial sketchpad, the memory is manipulated to become less complex, while through depotentition of AMPA receptors in the amygdala the memory becomes consolidated, less emotional, and is more easily recalled.

In individuals with PTSD, structural abnormalities noted in the anterior insula within the Salience Network (SalN; includes cortical structures (anterior insula; ACC) and subcortical structures (amygdala; ventral striatum; substantia nigra)) may provide putative neurobiological evidence for interference of integration of emotional fragments into declarative memories.<sup>67-70</sup> Pagani and colleagues collected brain wave activity in individuals with PTSD as they produced bilateral EMs during EMDR.<sup>71,72</sup> After successful therapy, individuals demonstrated significantly reduced activation of the orbitofrontal cortex (OFC) and primary visual cortex and increased activation of the fusiform and lingual cortex.<sup>71</sup> The authors offered support for the adjusted storage of traumatic memory theory, theorizing that during EMDR, the traumatic memory moves from emotional brain areas (i.e., OFC) to association areas (i.e., fusiform and lingual cortex) where the memory "is integrated and consolidated."71 In three recent papers, Pagani, Carletto, and colleagues have proposed that this process is achieved by shifting the brain into a mental state similar to slow-wave sleep, when the brain is admissible to memory recall and reconsolidation.73-75 This hypothesis is based on EEG studies that have reported increased prevalence of delta waves (0.5-4 Hz) during bilateral EMs while patients undergo EMDR.9,18,72 Delta waves are present during slowwave sleep and this sleep cycle is understood to play an important role in memory consolidation.<sup>75</sup> The researchers suggest that the cerebellum may be an important anatomical correlate of this theory by highlighting its involvement in associative learning, fear conditioning, sleep-wake cycle, and modulating behavior.<sup>75</sup> Given these points, the researchers encourage future investigation of the cerebellum and its possible involvement in PTSD and symptom recovery. Although the slow-wave sleep hypothesis is speculative at this point, its proposed mechanisms complement Shapiro's Adaptive Information Processing model,<sup>76</sup> REM sleep hypothesis,<sup>48</sup> and the abovementioned memory reconsolidation theory.<sup>18</sup>

# Theory 4: EMDR produces an orienting response and de-arousal

An orienting response is a physiological reflex that occurs in response to sudden, potentially dangerous stimulation, and initially increases sympathetic tone.<sup>12</sup> Production of EMs in EMDR following the presentation of a sudden stimulus induces physiological de-arousal, as indicated by decreased electrodermal responses and heart rate.77,78 Advocates for this model propose that the orienting response followed by BLS in EMDR induces relaxation. What is not yet known is whether de-arousal occurs because the traumatic memory is becoming less distressing due to processing during EMDR, or if the decreased arousal facilitates memory processing so that it is less distressing.<sup>76</sup> Neuroimaging studies probing the effects of BLS on arousal may help distinguish between these alternatives.

Evidence supports that sensory arousal is mediated by the dorsolateral prefrontal cortex (dlPFC).<sup>79,80</sup> In an fMRI study, bilateral alternating auditory stimulation was delivered at a rate of 1.5 Hz while participants processed aversive stimuli (i.e., disgusting pictures) and neutral stimuli (i.e., neutral pictures).81 Researchers observed a significant reduction in the activation of the dlPFC in the alternating auditory stimulation condition compared to a simultaneous auditory stimulation condition and a control (no stimulation) condition. These results suggest that bilateral alternating stimulation delivered at 1.5 Hz dampens the dlPFC neural activity. In a second study, hemodynamic response was captured during memory recall and initiation of bilateral EMs using multichannel near-infrared spectroscopy in PTSD patients pre- and post-EMDR therapy.<sup>82</sup> Post-therapy, recall with EMs evoked a decrease in oxygenated hemoglobin concentration in the lateral prefrontal complex (PFC) compared to recall without EMs. In an EEG study, Pagani et al. observed decreased

signaling in the PFC in individuals with various traumas as they successfully completed EMDR.<sup>71</sup> These physiological findings correlated with symptom reduction and provide some evidence for modulation of PFC activity during EMDR and BLS. The reduced PFC activity observed in these studies could possibly serve as a neural correlate for patients who experienced physiological relaxation response during EMDR. Now that we have reviewed well-described theories on the contribution of EMS in EMDR, we will move on to discussing the neural circuitry of the oculomotor system and the spatial and temporal characteristics of EMs.

#### **Neurocircuitry of EMs**

We acknowledge that tactile and auditory BLS are often used in clinic and have therapeutic impact. However, due to the availability of more research on visually triggered EMs, we herein describe their contribution in the context of EMDR and trauma recovery.

# Paucity of eye-tracking studies in EMDR

There have been few rigorous eye-tracking studies done to investigate the contribution of EMs to EMDR. In eye-tracking experiments, saccades provide quantitative and reliable metrics (amplitude, velocity, SRT, and end-point accuracy) that are subject to detailed analysis.<sup>83</sup> The underlying neural circuitry of saccades includes the frontoparietal network (FPN), basal ganglia, thalamus, superior colliculus, cerebellum, and brainstem.<sup>84,85</sup> These brain regions overlap with areas involved in attention, goal-directed thinking, decision-making, timing, and motor activity. Evidence supports changes in EM performance during childhood, adolescence, and across the lifespan that correlate to structural changes in brain maturation.<sup>86-88</sup> Additionally, abnormalities in EM characteristics have been identified in clinical populations.<sup>89-91</sup> Because EM metrics have been proven to be sensitive to a host of disparate clinical abnormalities or disease states, might the same measures serve as a real-time biomarker for quantifying behavioral interventions, such as EMDR? Below, we describe recent evetracking studies that adopt BLS paradigms similar to those used in EMDR, which may shed light on the contribution of EMs to EMDR therapy.

# Predictive saccades

Predictive saccades have a SRT less than 90 ms, and are initiated before the brain registers the appearance of the target.92,93 The fastest visually triggered (reactive) saccades that humans can initiate (time from target appearance to saccade onset) are about 90 ms, and these are called *express saccades*.<sup>36</sup> Lee and colleagues conducted a series of experiments collecting saccade metrics and fMRI data as participants generated bilateral horizontal predictive saccades at different fixed interstimulus intervals (ISIs) in a task that was similar to the original EMDR approach (see Ref. 8).<sup>21</sup> In this study (Fig. 2A), a visual target alternated between two fixed locations at a constant ISI, such that the participant could predict where and when the target would appear on the screen.<sup>21</sup> Experimenters used video-based eyetracking while healthy adult subjects performed the predictive saccade task with five different predictive ISIs (500, 750, 1000, 1250, or 1500 ms) and one nonpredictive (reactive) condition in which the five ISI values were randomly interleaved (Fig. 2B and C).

In the reactive condition of Lee et al. study, most individuals generated saccades with SRT > 90 ms(black traces in Fig. 2B and C), and the oculomotor regions, including the dlPFC, FEF, parietal eye fields, and SEF, and the cerebellum lobule IV became active and were significantly correlated with each other.<sup>21</sup> On the other hand, when individuals generated saccades in conditions where the bilateral stimulus was delivered at an ISI of 750 ms (i.e., 1.5 Hz)-the rate associated with the highest frequency of predictive saccades-there was significant activation of the cerebellum crus I and the DMN (Fig. 3A and C), and deactivation of brain regions typically associated with the oculomotor circuit.<sup>21</sup> Functional connectivity analysis revealed that for predictive saccade blocks, regions of the DMN (hippocampus, inferior parietal lobule (IPL), medial prefrontal cortex (mPFC), and PCC) were significantly correlated with each other. These results were the same when predictive saccades were triggered by bilateral auditory or visual stimuli. These fMRI and behavioral results support that the oculomotor network and cerebellum lobule IV control the generation of reactive saccades, whereas the DMN and cerebellum crus I give rise to predictive saccades. According to these findings, the temporal characteristics (i.e., predictive versus reactive) of



**Figure 2.** Predictive saccade task (adapted from Lee *et al.*).<sup>21</sup> (A) Paradigm for triggering predictive saccades. (B, C) SRT of young healthy adults performing the predictive saccade task with ISI fixed at 500 ms (red traces), 750 ms (green traces), 1000 ms (gray traces), 1250 ms (blue traces), 1500 ms (orange traces), or varied in the reactive task (black traces). (D, E) SRTs from young healthy adults performing either the predictive task with ISI 750 ms (red traces) or reactive task with variable ISI (blue traces) during brain fMRI. SRTs, saccadic reaction times; ISI, interstimulus interval.

BLS recruit distinct large-scale brain networks. It should be noted that the rate of BLS used in Lee's study (1.5 Hz) is supported by Shapiro's EMDR protocol where BLS is delivered at a rate of 1-2 Hz.<sup>12</sup>

Support for these abovementioned findings comes from two transcranial magnetic stimulation studies.<sup>94,95</sup> In these studies, researchers stimulated the cerebellum crus I/II at 1 Hz and observed increased correlated DMN activity, and functional connectivity (determined by fMRI), as well as decreased signaling of the dorsal attention network (DAN) (i.e., FEF; IPS).<sup>94,95</sup> These results provide evidence that predictable low stimulus frequencies to this region of the cerebellum may increase the activation and functional connectivity of the DMN. Second, the finding of the deactivation of the DAN in these magnetic stimulation studies, as well as an fMRI study by Lee et al., might account for the neural mechanism for the previously discussed EMDR neurovascular studies that reported reduced PFC activity during BLS.81,82

#### Smooth pursuit EMs

Smooth pursuit tracking produces continuous smooth EMs up to 100°/s that attempt to match gaze velocity to stimulus velocity.<sup>96,97</sup> In EMDR, this form of EM is often provoked by a therapist waving a hand between two fixed distances at a rate of 1–2 Hz, and asking the patient to gaze at the hand continually. Evidence supports that the oculomotor quality of smooth pursuit EMs significantly increases post-EMDR therapy compared to baseline.<sup>40</sup> Neuroimaging and neuronal population studies support activation of the cerebellum, FEF, SEF, precuneus, IPS, ACC, and PCC during smooth pursuit EMs.<sup>41,98–101</sup>

The possible relationship between DMN connectivity and smooth pursuit oculomotor performance has been explored in clinical studies of Parkinson's disease (PD) and schizophrenia (SCZ).<sup>102–105</sup> Gorges *et al.* recorded EMs as PD patients and healthy controls initiated visually guided reactive saccades and smooth pursuit EMs.<sup>102</sup> Functional



**Figure 3.** Brain activation produced in the predictive (A) and reactive (B) saccade task (adapted from Lee *et al.*).<sup>21</sup> (A) Functional connectivity map showing areas with correlated activity with seed regions (shown in blue) within the DMN when subjects perform the predictive saccade task. (B) Functional connectivity map showing areas with correlated activity with seed regions (shown in blue) within the oculomotor network when subjects perform the predictive saccade task. (C, D) Schematic representation of DMN active in predictive task and fronto-parietal attention network active in reactive task, respectively. HIP, hippocampus; IPL, inferior parietal lobule; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; PEF, parietal eye field; SEF, supplemental eye field.

DMN connectivity was recorded in the MRI scanner and was correlated with participants' EM performance outside the scanner. The results demonstrated significant correlations between decreased EM accuracy during smooth pursuit and region-to-region connectivity strengths within the DMN regions of the mPFC, PCC, hippocampus, and inferior parietal cortex in the PD patients compared to controls.<sup>102</sup> Second, individuals with SCZ have routinely been shown to have dysfunctional connections within the DMN.<sup>104,106</sup> Multiple studies support smooth pursuit eye-tracking abnormalities in SCZ patients, as evidenced by an increased number of nonvisually guided saccades.<sup>103,105</sup> This is hypothesized to be due to impairments within the smooth pursuit EM system secondary to disruption(s) in the frontal-thalamic-cerebellar circuitry.<sup>103,104</sup>

So far, we have discussed theories explaining EMDR's efficacy, the neurophysiology of the oculomotor circuit, and how it relates to EMDR and clinical groups. Below, we discuss the function of the DMN and cerebellum, and their neural correlates within PTSD pathophysiology.

#### **PTSD** neurophysiology

#### Overview of the DMN

The DMN is defined as a set of brain regions that are reliably more active during resting or passive baseline conditions (i.e., free thought) than during active control of goal-directed behavior.22,107 Research supports three major hubs of the DMN: hippocampus, mPFC, and PCC.<sup>22</sup> Regions within the DMN have been shown to have their own specific roles with respect to internally directed cognition, such as episodic memory, theory of mind, self-evaluation, envisioning the future, social and emotional judgment, and introspection.<sup>106-108</sup> These areas are also involved in processing emotionally salient stimuli related to episodic memory.<sup>5,109</sup> Below, we provide background of these neural circuits, how they relate to PTSD, and predictions regarding their role in treating PTSD through EMDR.

Numerous clinical studies have shown alterations within the DMN in both adults and children with PTSD.<sup>110–113</sup> Multiple PTSD symptoms (e.g., disturbances in sustained attention, WM, social-emotional processing, and selfawareness) correspond to dysregulated DMN brain regions.<sup>52,68,71,113–118</sup> The DMN is considered one of the three intrinsic connectivity networks that make up the neurocognitive model of psychopathology.<sup>119</sup> The other networks are the central executive network (CEN; bilateral FPNs) and the SalN.<sup>119</sup>

Many brain regions of the CEN overlap with the attention/saccade network that is active during pro-

duction of reactive saccades (Fig. 3B and D). Several studies describe abnormal activation within brain regions in the SalN (i.e., ACC and amygdala) of individuals with PTSD.68-70 During taskrelated experiments, individuals with PTSD show increased activity within the DMN and reduced correlated blood-oxygen-level dependent imaging signals within regions compromising the SalN and CEN.111 The dysfunctional association of the DMN with these intrinsic connectivity networks is hypothesized to be a neurobiological basis for the hyperarousal symptoms and reduced internally guided cognition commonly observed in PTSD.<sup>111</sup> Evidence for irregular activation within and across these intrinsic connectivity networks highlights the complexity of PTSD pathology, and how if EMDR treatment is to be effective, its mechanism must target a range of neural networks.

#### DMN: medial prefrontal cortex

The mPFC is an integral part of the DMN and has been consistently linked to social behavior, mood regulation, self-judgment, and motivational drive.<sup>22,120</sup> Considerable evidence supports an inverse correlation between feelings of anxiety in healthy individuals and modulation of the mPFC, such that when feelings of anxiety are elevated, mPFC neural activity is reduced. This inverse relationship is compromised in individuals with anxiety disorders, who maintain high levels of mPFC activity during periods of physiological stress marked by increased heart rate and elevated plasma levels of epinephrine and norepinephrine.<sup>121–123</sup> Similarly, individuals with PTSD have demonstrated irregular signals in the mPFC in fMRI experiments compared to controls.124

The ventromedial PFC (vmPFC) is considered a sensory–visceromotor link that receives sensory input from the OFC and conveys signals to the amygdala, hypothalamus, and the periaqueductal gray matter of the midbrain.<sup>22</sup> An animal-based study found that the vmPFC is critical to detection of whether a stressor is controllable (i.e., escapable) and modulates the brainstem dorsal raphe nucleus and the stress response accordingly.<sup>125</sup> It is proposed that the vmPFC within the mPFC provides "contextualization" of relayed information from the OFC and amygdala,<sup>126</sup> and thus disruption of this area might play a key role in the generation of PTSD symptoms during nonthreatening situations.



**Figure 4.** A new neurobiological model for the contribution of EMs in EMDR. (A) Network abnormalities are evident in limbic regions and the DMN in PTSD. (B) During EMDR, these abnormalities are addressed, leading to symptom relief (C). A new hypothesis for EMDR. The smooth pursuit and predictive saccade task (D) triggers bilateral saccades (SRTs < 90 ms), which correlates to activation of the DMN and cerebellum and deactivation of the fronto-parietal attention network (E). When coupled with psychotherapy (F), EMDR can lead to alleviation of the symptoms of PTSD, presumably by acting on the amygdala and OFC.

The OFC normally inhibits signals from the amygdala; however, research supports reduced OFC volumes in PTSD patients.<sup>49</sup> Furthermore, multiple neuroimaging studies have reported evidence of amygdala hyper-reactivity in PTSD patients when viewing emotional and aversive stimuli.<sup>124,127,128</sup> For this reason, a popular theory detailing PTSD pathophysiology maintains that intrusive symptoms observed in PTSD patients are due in part to a failure of the OFC to inhibit signals from a hyper-responsive amygdala (Fig. 4A).<sup>126</sup> A diminished

responsivity of the OFC and connected mPFC and exaggerated responsivity of the amygdala in individuals with PTSD (Fig. 4A) are proposed to recover over the course of EMDR treatment (Fig. 4B) and eventually normalize during remission (Fig. 4C).

#### DMN: posterior cingulate cortex

The PCC is involved in learning and episodic memory and is often positively correlated with hippocampal activity.<sup>107</sup> The PCC interacts with the vmPFC and dorsal mPFC in multiple processes

including emotion, autobiographical memory, self-reflection, coping with physical threats, and processing aversive material.<sup>61,106,110,129-131</sup> Resting state fMRI studies have shown that PTSD patients have reduced functional correlated activation between the PCC and mPFC.<sup>110,111,132</sup> PCC signaling with the ACC and right amygdala has been shown to correlate positively with current PTSD symptoms and even predicted future symptoms.<sup>110</sup> Nardo et al. reported lower gray matter density in the PCC of people with PTSD and attributed these findings to disturbances in the retrieval of autobiographical memories and their conscious relation to self.<sup>67</sup> In a second study, both the severity and the duration of traumatic exposure were negatively correlated with gray matter volume in the PCC, parahippocampal, and anterior insular cortices.<sup>129</sup> Combined, this neuroscientific evidence provides support for disruptions of the DMN's PCC structural integrity and corresponding processes in PTSD patients (Fig. 4A).

#### DMN: inferior parietal lobule and hippocampus

The IPL is associated with processing facial stimuli, contextual cue processing, and the generalized fear response.<sup>133</sup> Individuals with PTSD exhibit hyperactivation of the IPL in response to conditioned fearful stimuli, as well as an overgeneralized response to nonconditioned fearful stimuli.<sup>134</sup> Increased recruitment of the left IPL during contextual cue processing has been shown to be a significant predictor for successful PTSD treatment response.<sup>133</sup> In a study investigating the impact of EEG neurofeedback in PTSD patients, Kluetsch and colleagues observed greater DMN correlated activity within the PCC, left mPFC, and IPL, posttreatment, compared to baseline.<sup>114</sup>

The hippocampus and parahippocampal gyrus (PHG) are involved in the encoding, consolidation, and retrieval of explicit memories. The PHG has functional connections with the amygdala, insular cortex, and PCC.<sup>117,129,135</sup> Soldiers who were exposed to combat and went on to develop PTSD demonstrated hyper-responsivity of the left hippocampus during a resting-state fMRI condition, as well as irregular correlated neural activity of the hippocampus with the IPL and left amygdala.<sup>115</sup> These regions have been shown to facilitate the processing of episodic memory and emotions, and disruption of the connections between these regions

is suggested to explain memory disturbances in PTSD (Fig. 4A) such as dissociations, flashbacks, and amnesia.<sup>61</sup>

#### EMDR's potential modulation of the DMN

Now that we have summarized relevant studies discussing disruptions of the DMN in individuals with PTSD, we move on to consider clinical studies that have demonstrated modulation of DMN structures following EMDR treatment. First, in a case-study, a bipolar patient's brain activation during a memory task was compared before and after 12 weeks of EMDR treatment.5 Compared to 30 control subjects, the patient demonstrated a failure of task-related deactivation of the DMN (mPFC and PCC/precuneus) before EMDR, which was somewhat normalized after treatment. Post-EMDR, DMN deactivation was significantly correlated with marked improvements on a battery of psychological scales that assessed trauma, mood, functioning, and quality of life. Second, Nardo and colleagues observed a negative correlation between trauma load and gray matter density within structures which form part of the DMN in patients with PTSD.<sup>129</sup> Patients who did not respond to EMDR treatment had significantly lower gray matter density within two of the three main DMN hubs: the PCC and parahippocampus, compared to responders, suggesting that these structures are important to therapeutic success.<sup>129</sup> Third, Pagani and colleagues found that individuals with PTSD who showed clinically significant alleviation of symptoms following a course of EMDR therapy demonstrated increased activation within DMN regions (right IPL and PHG), compared to baseline.<sup>9,136</sup> Furthermore, bilateral EMs made during EMDR were correlated with increased neural activity within the PHG and PCC in the clinical cohort, as well as in healthy control subjects.9

# EMDR's potential modulation of the cerebellum

The cerebellum is strongly recruited during the generation of predictive saccades and smooth pursuit EMs.<sup>21</sup> Research supports cerebellum activation during event timing and automatic motor control.<sup>137–139</sup> Patients with cerebellar lesions have deficits in producing temporally guided movements, as evidenced by decreased temporal sensitivity and impaired timing-related error

corrections.<sup>140,141</sup> fMRI evidence is mounting for an automatic timing system that works in the millisecond range located in the cerebellum.137,139,142 Based on the predictable temporal component of bilateral stimulation in EMDR (that operates in the millisecond range), it is likely that the cerebellum is recruited during therapy. Bergmann has written several papers describing the cerebellum's active communication to structures of emotion processing recruited during EMDR.143,144 Bergman describes direct routes from the cerebellum to the thalamus (and thence to the PFC) and from the cerebellum to the hypothalamus (and thence to limbic structures) as anatomical correlates of this relationship.143,144 Furthermore, Pagani and Carletto's slow-wave sleep model considers the cerebellum as playing an integral role for memory reconsolidation during EMDR.<sup>73,74</sup>

#### A new neurobiological model of EMDR

Based on the abovementioned characteristics of PTSD, mechanisms of action underlying EMDR and EM research, we propose a new model (Fig. 4D-F) describing the contribution of EMs to the success of EMDR and speculate to the corresponding neural networks (Fig. 4A-C) that may underlie their therapeutic action. The purpose of this model is to bridge a critical gap between theories describing the contribution of EMs to EMDR's therapeutic efficacy (i.e., taxation of WM, IH communication, memory reconsolidation, and orienting response/de-arousal) and the corresponding neuro-mechanism of turning on/off large-scale neural networks. We hypothesize that during bilateral predictive EMs and/or smooth pursuit, the cerebellum and large-scale DMN are recruited, and the neural activity of the fronto-parietal attention network is reduced. From this perspective, the production of smooth pursuit and predictive EMs in EMDR serves as a tool to recruit the cerebellum crus I and DMN and their neural processes (i.e., introspection, memory recall, and associative learning) and dampen the PFC signal (i.e., physiological arousal and cognitive load) during therapy. Further, based on neuronal event-related research137,138,145 and transcranial magnetic stimulation studies,<sup>94,95</sup> we hypothesize that within the context of EMDR, cerebellum activity precedes the DMN signal.

Smooth pursuit EMs, predictive saccades, and reactive saccades all recruit IH activity; however,

they selectively recruit distinct oculomotor behavior and neural networks (Fig. 3).<sup>21</sup> A previous study that tested fast bilateral EMs (i.e., saccades) versus slow bilateral EMs (i.e., smooth pursuit) reported different outcomes on episodic memory performance.<sup>58</sup> Thus, although bilateral stimulation evokes IH activation during EMDR, the rate of bilateral stimulation and corresponding motor responses may play a key role in the availability and accuracy of the retrieved memory. We hypothesize that the temporal characteristics of EMs influence DMN activation such that nonpredictable stimuli will not recruit DMN signaling and will likely instead recruit the dlPFC and other oculomotor structures. Activation of these neural areas may trigger an arousal response during episodic memory recall, or create a high cognitive load, thus negating some of the beneficial effects of BLS during traumatic memory recollection. Conversely, taxation of WM using predictive saccades and smooth pursuit EMs during EMDR may reduce dlPFC activity and recruit the vmPFC, attenuating the stress response and suppressing negative affect by inhibiting amygdalar output.146-149 Thereby, vmPFC activation and dlPFC deactivation during predictive EMs and smooth pursuit may reduce arousal and increase internally guided cognition, serving as a neuro-mechanism to reduce clinical symptoms during therapy (Fig. 4B and E).

Testing different BLS parameters and establishing which ones are optimal for causing increased incidence of predictive motor responses (i.e., smooth pursuit EMs and predictive saccades) may be worthwhile to benefit both the patient's experience during therapy and expedite memory recall. This can be tested using a variety of methods, such as (1) measure autonomic parameters (e.g., heart rate and skin conductance) during traumatic memory recall in a predictive and smooth pursuit EM condition compared to during a reactive EM condition; or (2) video-record EMs of individuals with PTSD during EMDR, and measure the incidence of smooth pursuit EMs, predictive saccades, and reactive saccades during each treatment session. It is possible that treatment response may vary based on the incidence of the different EM patterns.

Our next suggestion is that once the DMN is active and the traumatic memory is recalled, key EMDR therapeutic phases facilitate symptom recovery (Fig. 4F), including desensitization, installation, and addressing residual body sensations.<sup>12</sup> Neurobiological correlates of these therapeutic phases may also be impacted by taxation of the WM, IH activation, promoting a mental state similar to what occurs during slow-wave sleep, restorage of the memory potentially through depotentiation of AMPA receptors, and orienting responses/dearousal. It is unclear to what degree these mentioned processes are responsible for the reconsolidation of the memory and this question will require future research to disentangle. Based on the current literature, neural correlates likely involved during these therapeutic phases include limbic structures (e.g., amygdala and OFC), cerebellum, and the DMN.

# Application of our model to other disorders

Our neurobiological model for EMDR may be relevant to other psychiatric disorders. Abnormal signaling and connectivity of the DMN has been observed in multiple psychopathologies besides PTSD, including SCZ, major depressive disorder, and bipolar disorder.<sup>104,106,149</sup> Moreover, individuals with anxiety disorders demonstrate a failure to deactivate the mPFC during stressful tasks.<sup>150</sup> Thereby, predictive bilateral and smooth pursuit EMs might be a practical tool for attenuating DMN activation in people with these psychiatric disorders while they complete concomitant psychotherapy. Using behavioral EM measures (i.e., extracted from video-based eye tracking), therapists and clinicians could adjust EMDR treatment delivery to optimize smooth pursuit EMs or maximize generation of predictive saccades. Performance on eye-tracking tasks may differ between clinical populations<sup>102,105</sup> and could be used as a baseline metric to inform the rate of BLS during treatment. Moreover, real-time eyetracking measures collected during EMDR would provide immediate insight into any changes that occur within cognitive and motor circuits. With a better understanding of how modulation of sensory stimulation affects cortical networks through quantitative analysis of EMs, there is an opportunity to optimize EMDR target delivery to increase its efficacy in enhancing symptom alleviation.

# Conclusion

EM desensitization and reprocessing is a proven therapy for treating PTSD yet there is little to no consensus as to *why* this therapy is effective. Without this knowledge, we cannot know whether standard EMDR treatment parameters are ideal for all patients, or might benefit from subtle adjustments for optimal-and individualized-effect. In this paper, we consider the activation of DMN and cerebellum via predictive and smooth pursuit EMs as a neuro-mechanism underlying EMDR efficacy. Through the activation of the DMN, aversive memories can be recalled into WM, adapted using a variety of EMDR psychotherapeutic tools (e.g., desensitization, installation, and addressing physical sensations), and restored in less lucid and emotionally charged constructs. In the context of treatment, we speculate that the cerebellum plays a role in event-timing, associative learning, and memory reconsolidation. Furthermore, we hypothesize that the deactivation of the fronto-parietal attention network during predictive motor responses triggers a relaxation response during memory recall. In the framework of our proposed neurobiological model, EM metrics should be used to optimize the stimulus conditions during EMDR to enhance neural recruitment and promote a better clinical outcome.

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# **Competing interests**

The authors declare no competing interests.

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