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Review

Dopamine and training-related working-memory improvement

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ABSTRACT

Converging evidence indicates that the neurotransmitter dopamine (DA) is implicated in working-memory (WM) functioning and that WM is trainable. We review recent work suggesting that DA is critically involved in the ability to benefit from WM interventions. Functional MRI studies reveal increased striatal BOLD activity following certain forms of WM interventions, such as updating training. Increased striatal BOLD activity has also been linked to transfer of learning to non-trained WM tasks, suggesting a neural signature of transfer. The striatal BOLD signal is partly determined by DA activity. Consistent with this assertion, PET research demonstrates increased striatal DA release during updating of information in WM after training. Genetic studies indicate larger increases in WM performance post training for those who carry advantageous alleles of DA-relevant genes. These patterns of results corroborate the role of DA in WM improvement. Future research avenues include: (a) neuromodulatory correlates of transfer; (b) the potential of WM training to enhance DA release in older adults; (c) comparisons among different WM processes (i.e., updating, switching, inhibition) regarding regional patterns of training-related DA release; and (d) gene–gene interactions in relation to training-related WM gains.

Contents

1. Introduction

This review draws largely on a program of research from our own laboratories on brain correlates of working-memory training. There are two main points of departure: first, the neurotransmitter dopamine (DA) is critically implicated in working memory (WM) functioning. Evidence for this claim comes from multiple sources, including studies on patients with Parkinson's disease and Huntington's disease (Bruck et al., 2005; Bäckman et al., 1997), lesion work on rodents (Baunez and Robbins, 1999; Simon et al., 1986), and non-human primates (Boussaoud and Kermadi, 1997; Williams and Goldman-Rakic, 1995), pharmacological challenge studies involving both dopaminergic agonists (Cools et al., 2007; Kelly et al., 1991; Luciana et al., 1992) and antagonists (Fischer et al., 2010; Luciana and Collins, 1997; Ramaekers et al., 1999), as well research showing a direct association between DA markers derived from Positron Emission Tomography (PET) and WM performance (Erixon-Lindroth et al., 2005; Landau et al., 2009). These divergent domains of research converge in demonstrating strong links between DA activity and WM performance (see Bäckman et al., 2006, 2010, for reviews). A key reason why DA is implicated in WM and many other cognitive functions (e.g., episodic memory, speed, fluency) is that it facilitates the responsivity of different neural networks by enhancing the neural signal relative to background noise; an increased signal-to-noise ratio may facilitate the firing frequency and fidelity of the innervated neurons (Bäckman et al., 2006; Cohen et al., 2002; Li et al., 2009).

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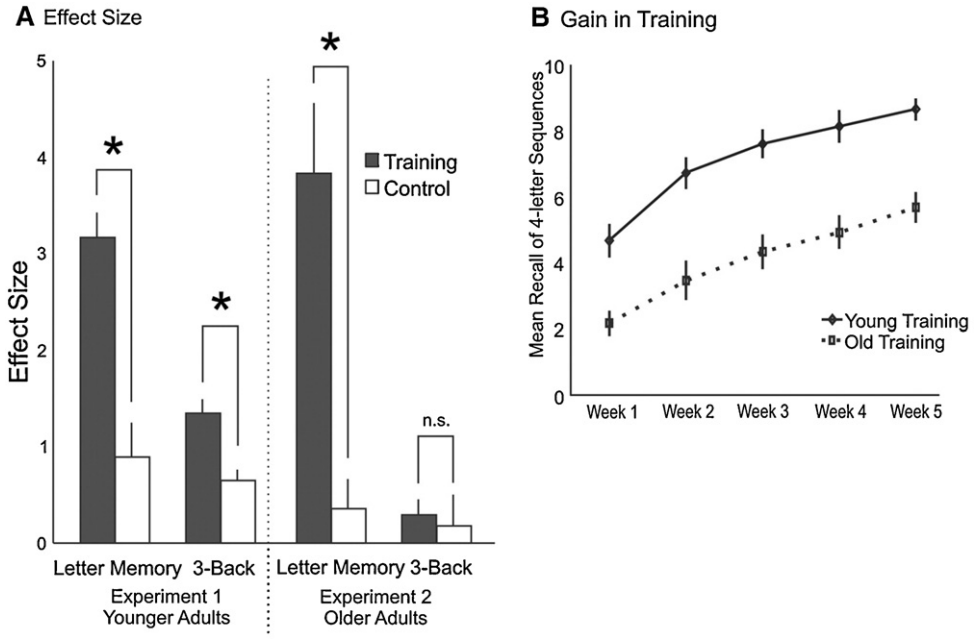

Fig. 1. (A) Letter memory and 3-back performance for training and control groups. The histograms denote mean effect sizes. (B) Training gains in younger and older adults during the five-week intervention period. Error bars are SEM. Asterisks indicate statistical significance; n.s., not significant.
From Dahlin et al. (2008b).

Second, it is possible to enhance WM functioning by means of systematic training (see Dahlin et al., 2009; Klingberg, 2010; Lövdén et al., 2010, for reviews). Different approaches have been used in this research, ranging from training of specific WM functions such as updating (Dahlin et al., 2008a), shifting (Kaarbach and Kray, 2009), and inhibition (Manuel et al., 2010) to composite regimens that involve practicing several different WM functions (Jaeggi et al., 2008; Klingberg et al., 2005; Li et al., 2008; Schmiedek et al., 2010). The training-related gains observed in these studies suggest a considerable degree of WM modifiability.

2. Working-memory improvement

This review is based on the confluence of the two lines of inquiry discussed above. The key question asked is whether DA is implicated not only in WM generally, but also in the ability to benefit from training procedures that seek to improve WM performance. The starting point is a study by Dahlin et al. (2008a,b). In this study, younger and older adults were trained for five weeks (three sessions per week comprising 45–60 min each) in updating information in WM. The criterion was a letter-memory task devised by Miyake et al. (2000). In addition to letters, the training program included updating of colors, numbers, and spatial positions in WM as well as a keep-track task.

Training was adaptive according to a pre-specified algorithm with three levels of difficulty; as subjects became more proficient, task difficulty increased. Subjects were scanned using fMRI before and after training. During fMRI assessment, the letter-memory criterion task and two transfer tasks were administered: a numerical *n*-back task and a Stroop task. A number of other transfer tasks were given outside the scanner pre and post training, tapping episodic memory, speed, verbal fluency, and reasoning (Dahlin et al., 2008a). Fig. 1A depicts gains in letter memory performance during scanning in younger and older adults, expressed as effect sizes. Fig. 1B portrays gain trajectories for the two age groups across the five-week training period for the same letter-memory task assessed outside the scanner. As can be seen, both groups improved greatly from the intervention, although performance of the old at the end of the training period did not surpass that of the young in the early phases of training. Further, Fig. 1A shows a clear performance increment on an untrained 3-back task (that also requires updating) in the young, but not in the old. By contrast, there was no transfer to the Stroop task, which taxes inhibition rather than updating (Miyake et al., 2000). In addition, with the exception of *n*-back, no transfer was observed to the tasks assessed outside the scanner. This pattern indicates that the intervention effect was process-specific; the training did not affect executive functions or cognition in general, but specifically influenced WM updating.

Although both letter-memory and 3-back tax updating, they differ on important dimensions (i.e., memorial content, set size, task pacing, response requirements). In addition, the two tasks exhibited quite different neocortical activation patterns before training (Dahlin et al., 2008b). Thus, the transfer effect observed might reflect the strengthening of a general updating skill. Further evidence for this assertion comes from the fact that the transfer effect was maintained 18 months after the completion of training (Dahlin et al., 2008a). The non-existent transfer effects in the old are consistent with the bulk of age-comparative training work, demonstrating constraints on cognitive plasticity in old age (Li et al., 2008; Nyberg et al., 2003; for review, see Lövdén et al., 2010). As shown in Fig. 1, although both age groups in Dahlin et al. (2008b) showed considerable gains from the intervention, there was a clear advantage of the young at the conclusion of training. Conceivably, a lower level of performance reflects a less proficient updating skill, which may be a critical factor underlying the non-existent transfer effects in the old.

3. The role of the striatum in working memory

Fig. 2 portrays blood–oxygen-level-dependent (BOLD) activation patterns before training for the letter-memory criterion task as well as for the 3-back and Stroop transfer tasks. Several observations from this figure should be highlighted. First, the young exhibited overlapping fronto-parietal activation for all three tasks prior to training, indicating a partly shared executive network. Further, there was robust striatal activity in the young for the

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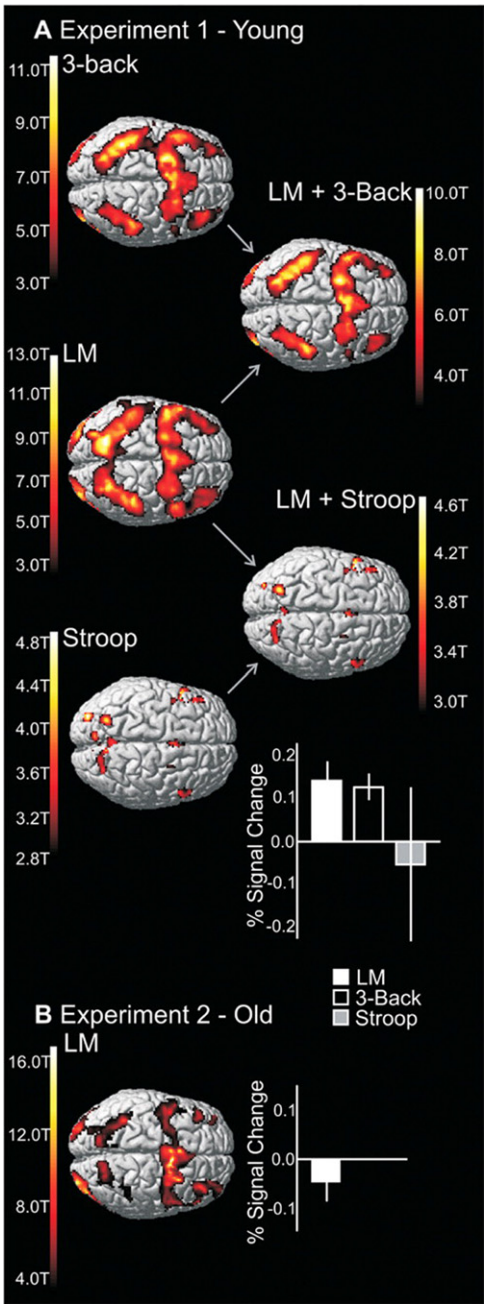

Fig. 2. (A) Brain maps to the left (dorsal view) show activation of bilateral parietal cortex and lateral and medial frontal cortex for all tasks at pretraining. Conjunction analyses of the letter memory (LM) task with Stroop and 3-back revealed overlapping frontoparietal activation patterns for the criterion task and both transfer tasks (cortical maps to the right). The bar graph (bottom) shows the striatal activation profile across tasks at pretraining and reveal overlapping activations in LM and 3-back (plotted at peak $x = -20$, $y = 4$, and $z = 14$). (B) Brain map to the left shows activation of bilateral parietal cortex and lateral and medial frontal cortex for LM pretraining. The bar graph shows no significant striatal activation in LM for older adults (plotted at peak $x = -24$, $y = 10$, and $z = -2$, where selective training-related increases were found). Error bars are SEM.
From Dahlin et al. (2008b).

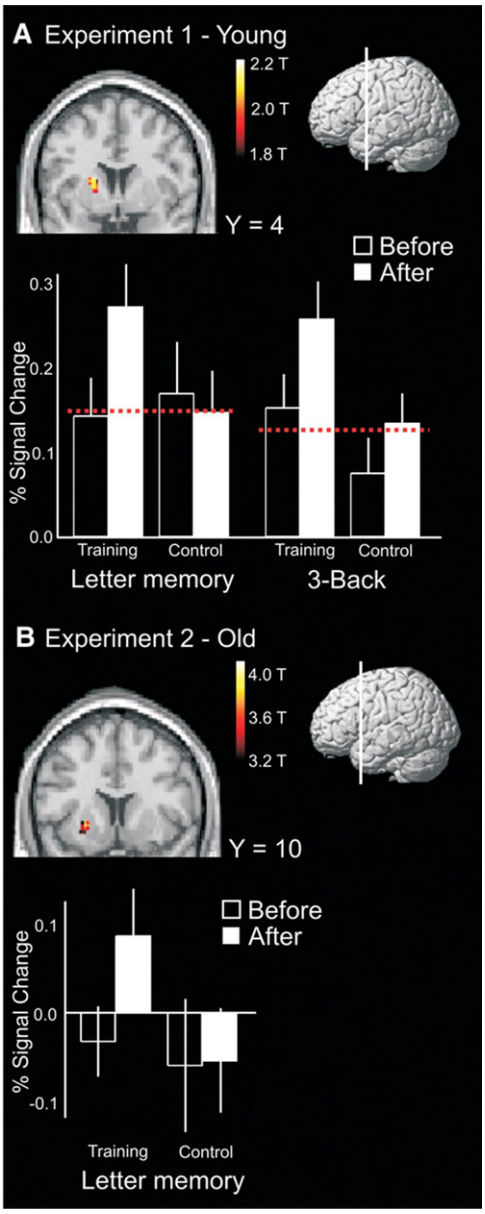

Fig. 3. (A) Left striatum (peak $x = -20$, $y = 4$, and $z = 14$) was activated before training and showed a training-related increase for both letter memory and 3-back in younger adults. The bar graph shows the activation profiles across tasks and sessions. The red line indicates mean baseline bold values for the striatal region (mean of trained before, controls before, and controls after). (B) Left striatum (peak $x = -24$, $y = 10$, and $z = -2$) showed a training-related increase for letter memory in older adults. Error bars are SEM. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
From Dahlin et al. (2008b).

letter-memory and 3-back tasks. The old also exhibited frontoparietal activation during letter memory before training; however, unlike the young there was no pre-training striatal engagement for letter memory and 3-back in the old. The most striking training-related increase in BOLD activity was that the young showed increased striatal activity (with a peak in left caudate) during letter memory post training, and this change overlapped with corresponding striatal activity increases during 3-back (Fig. 3). Further, these activity changes fell within the same region as was activated for these tasks before training. No corresponding pattern was seen in neocortex. Here, the dominating pattern was reduced BOLD activity post training, likely reflecting decreased demands on executive control processes across the course of the intervention.

The parallel training-related BOLD increases for letter memory and 3-back were not seen in the old. Thus, the pattern that emerges from these data suggests that one prerequisite for transfer of learning is that the criterion and transfer tasks engage similar brain systems, and that the tasks are similarly responsive to changes in these systems as a function of training (Jonides, 2004). Further, the data point to a critical role of the striatal complex in WM

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improvement and transfer. Toward this end, marked age-related losses in striatal morphology (Raz et al., 2003; Raz et al., 2005) and neurotransmitter efficacy (Bäckman et al., 2006, 2010) might constrain older adults regarding the magnitude and generalizability of gains from WM training.

The Dahlin et al. (2008b) findings are consistent with other fMRI research indicating that WM functioning in general as well as WM improvement is linked to the striatum. Pharmacological fMRI research is illustrative. Not surprisingly, this work involves challenges with DA compounds; the dopaminergic innervation from midbrain to striatum is particularly dense. Cools et al. (2007) showed that administration of bromocriptine, a DA D2 agonist, improved the flexible updating of WM representations and increased striatal BOLD activity. Conversely, Dodds et al. (2009) demonstrated that sulpiride, a DA antagonist, depressed striatal BOLD activity and affected WM performance. Murty et al. (2011) obtained direct evidence for a specific role of the striatum in updating as opposed to other WM processes. Using a new WM task, these investigators found selectively increased striatal BOLD activity during updating compared to maintenance and rewriting of information in WM. In general, these patterns are consistent with neurocomputational work suggesting that striatal neurons serve a key gating function in letting new information enter WM; the gate closes during memory maintenance and opens when the content of WM is to be updated (O'Reilly, 2006).

With regard to intervention, the training-related alterations in BOLD activity found by Dahlin et al. (2008b) were also observed in an earlier study using a training regimen devised by Klingberg et al. (2002) that involves practicing several verbal and spatial WM tasks over a five-week period (Olesen et al., 2004). However, neither of these studies linked the degree of striatal BOLD increase to how much people actually gained in their WM performance from training. Brehmer et al. (2011) recently addressed this issue in a study with older adults using the training procedure of Klingberg et al. (2002). In Brehmer et al., subjects were scanned during a spatial WM task with two levels of load before and after training. As shown in Fig. 4, under the high-load condition there was a clear relationship between the degree of increased BOLD activity in bilateral caudate and the magnitude of training-related WM gains (here expressed in terms of the WM maximum score attained during the training period). These data suggest that the boost in striatal activity post training serves functional purposes.

4. Working-memory training and dopamine release

Based on pharmacoimaging work with rodents, Knutson and Gibbs (2007) made a strong case that the striatal BOLD signal is influenced by DA activity. Empirical evidence for a striatal DA–BOLD link in humans was obtained in an elegant study by Schott et al. (2008). In this study, participants performed a memory task involving rewarded and non-rewarded items. Increased BOLD activity and increased DA release in ventral striatum were demonstrated for rewarded compared to non-rewarded items. Importantly, there were strong relationships of DA release in ventral striatum to BOLD activity in the same brain region as well as to midbrain BOLD activity (Fig. 5). These data confirm the point that DA activity is critically implicated in functional brain responses within the striatal complex. Although we favor an explanation whereby DA release affects the magnitude of the striatal BOLD signal (Choi et al., 2006; Knutson and Gibbs, 2007), there are alternative possibilities. The striatal BOLD response might mediate DA activity in midbrain by phasically inhibiting GABAergic neurons in pallidum that tonically inhibit the midbrain (Grace et al., 2007). On this view, increased DA release results from rather than causes increased striatal BOLD activity. A third possibility is that there is a reciprocal relationship between these two directions of influence in that DA release affects the BOLD signal inasmuch as the opposite is true. In addition to midbrain and basal ganglia, dorsolateral prefrontal cortex may be critically involved in such interactions (D'Ardenne et al., 2012).

The Schott et al. (2008) findings open up for the interesting possibility that the increased striatal BOLD activity observed after WM training (Brehmer et al., 2011; Dahlin et al., 2008b; Olesen et al., 2004) is associated with increased release of DA. To infer DA release during task performance, quantified with PET, two conditions that vary in cognitive or other demands are typically contrasted. The underlying idea is that binding of the radioligand to DA receptors should be reduced during the more challenging condition relative to the control condition. This is so because, in the former case, binding of the ligand to receptors competes with binding of endogenous DA to the same receptors to a greater extent than in the control condition. In other words, reduced ligand binding is assumed to reflect increased release of DA in response to the cognitive requirements. This so-called displacement principle was initially formulated in the context of pharmacological DA challenges (for review, see Laruelle, 2000), and evidence for displacement has later been observed in both striatal and extrastriatal regions for several cognitive tasks, including verbal WM (Aalto et al., 2005), spatial WM (Christian et al., 2006; Sawamoto et al., 2008), card sorting (Ko et al., 2009; Monchi et al., 2006), interference resolution (Karlsson et al., 2009), and sequential learning (Badgaiyan et al., 2007; Garraux et al., 2007).

To examine whether WM training is associated with DA release, we used exactly the same experimental set-up as in Dahlin et al. (2008b) fMRI investigation in a study with younger adults (Bäckman et al., 2011). Thus, subjects were training for 5 weeks in updating information in WM. Letter memory served as the criterion task and several tasks taxing both WM (e.g., *n*-back) and other cognitive domains (i.e., episodic memory, speed, verbal fluency, reasoning) were assessed before and after training. Critically, however, PET and the radioligand raclopride were employed to determine binding potential for striatal DA D2 receptors. Two reasons motivated the choice of raclopride as opposed to other DA radioligands: first, of all DA ligands available, raclopride has most consistently been associated with transmitter release (for review, see Egelton et al., 2009). Second, whereas extrastriatal receptors, particularly D1 receptors, have been associated with the stabilization of cognitive performance, striatal D2 receptors have been strongly implicated in transient neural processes linked to updating (Bilder et al., 2004; Cools and D'Esposito, 2011; Durstewitz and Seamans, 2008).

Before and after training, raclopride binding to striatal D2 receptors was determined in a single-scan dynamic PET measurement (Alpert et al., 2003), in which binding was compared for two conditions: letter memory versus a structurally equivalent task with no WM demands. On the basis of related research on DA release (e.g., Aalto et al., 2005; Christian et al., 2006; Sawamoto et al., 2008), we expected reduced binding of raclopride to striatal D2 receptors for letter memory compared to the control condition, reflecting greater DA release in response to the elevated cognitive challenge. Of chief interest, however, was whether an additional boost of DA release during letter memory would be observed as a function of the five weeks of WM training.

Fig. 6A displays the behavioral data from this study. As can be seen, there were large intervention-related gains in letter-memory performance. The size of these gains was virtually identical to that observed by Dahlin et al. (2008b) for younger adults using the same training procedure. Also replicating the results from Dahlin et al., transfer was only observed to *n*-back, underscoring the process-specific nature of this form of training. Fig. 6B shows that raclopride binding to striatal D2 receptors were lower during the

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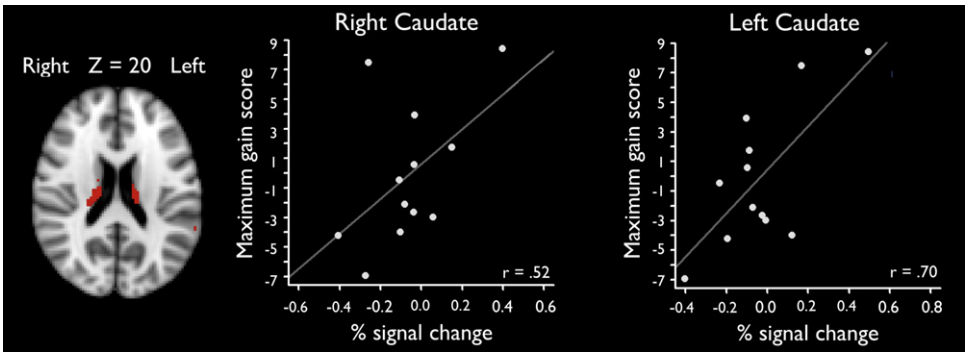

Fig. 4. Performance-related increases in striatal BOLD activity from baseline to post training under high-load working-memory conditions. Regions are plotted where the degree of improvement during the five weeks of adaptive training is correlated with BOLD signal increase from baseline to post training. Scatter plots depict individuals' maximum gain scores (demeaned and orthogonalized to baseline performance) during the five weeks of WM training and mean percent signal change for each subject from a 3 mm spheric ROI around the peak voxels in bilateral caudate showing activation increases from baseline to post training. Anatomical reference is MNI152 space and images are displayed in radiological orientation.
From Brehmer et al. (2011).

letter-memory task relative to the control task before training, reflecting greater DA release in the former condition.

Critically, there was a cluster in left caudate in which there was a training-induced decrease of raclopride binding to D2 receptors (Fig. 6C). Fig. 6D illustrates changes in ligand binding to striatal D2 receptors for the letter memory minus control task contrast pre and post training in the peak of this cluster. Note that the negative binding values (Gz) reflect generally lower binding for letter memory than for the control task. The most striking feature of Fig. 6D is the marked decrease in binding for the letter-memory task following training, indicating increased DA release during WM performance. Interestingly, the left caudate locus of the training-induced striatal effect overlapped with the area in which Dahlin et al. (2008b) observed increased BOLD activity post training. Thus, these findings indicate that training of updating is associated with increased release of striatal DA.

It is of note that another WM intervention study using PET and the Klingberg et al. (2002) training package showed changes in cortical D1 receptors post training, but failed to demonstrate effects on the striatal D2 system (McNab et al., 2009). Regarding the discrepancy in findings between studies, in McNab et al. DA binding was assessed at rest only and the training program employed promoted sustained maintenance processes. As noted, extrastriatal D1 receptors seem to be particularly critical to maintenance of information in WM, whereas striatal D2 receptors are more critical to transient processes such as updating (Bilder et al., 2004; Cools

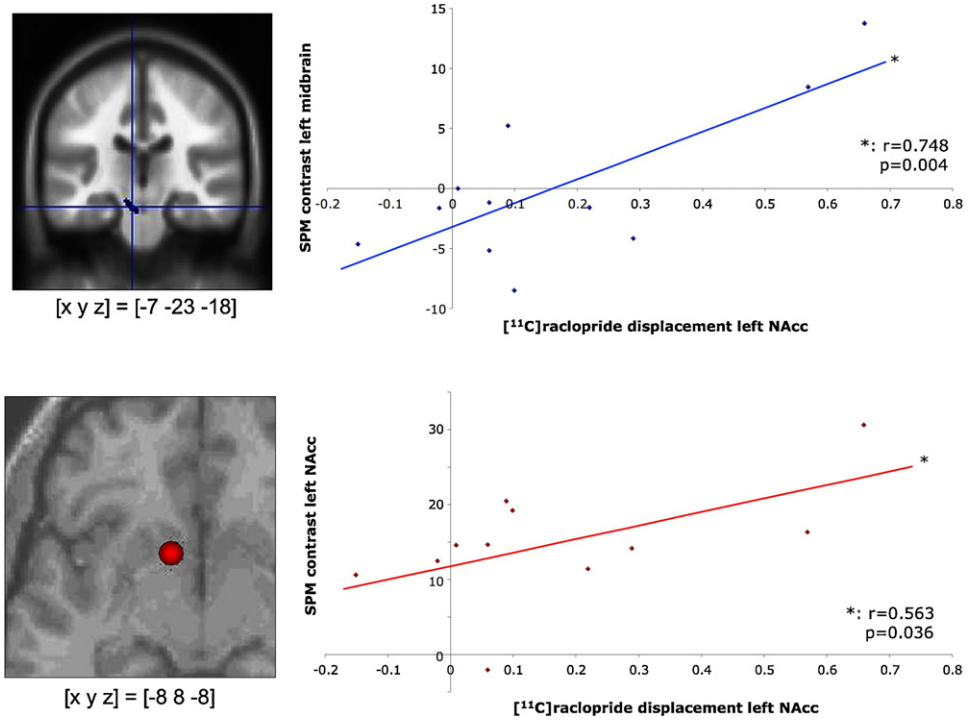

Fig. 5. Correlation of dopamine release and fMRI activations. Top (left): location of the ROI for the left midbrain. Right: across the study cohort, fMRI response in the left midbrain (segmented area) during reward anticipation was significantly correlated with [^{11}C]raclopride displacement in the rewarded relative to the neutral condition. Bottom (left): representative ROI from a single subject. Six-millimeter spheres were centered at the local maxima of the reward anticipation response closest to [*x y z*] = [−6 10 −6] (the coordinate of maximal reward-related BP_{ND} decrease in PET), individually for each subject. Right: a significant correlation was observed between [^{11}C]raclopride displacement and the fMRI response in the left nucleus accumbens.
From Schott et al. (2008).

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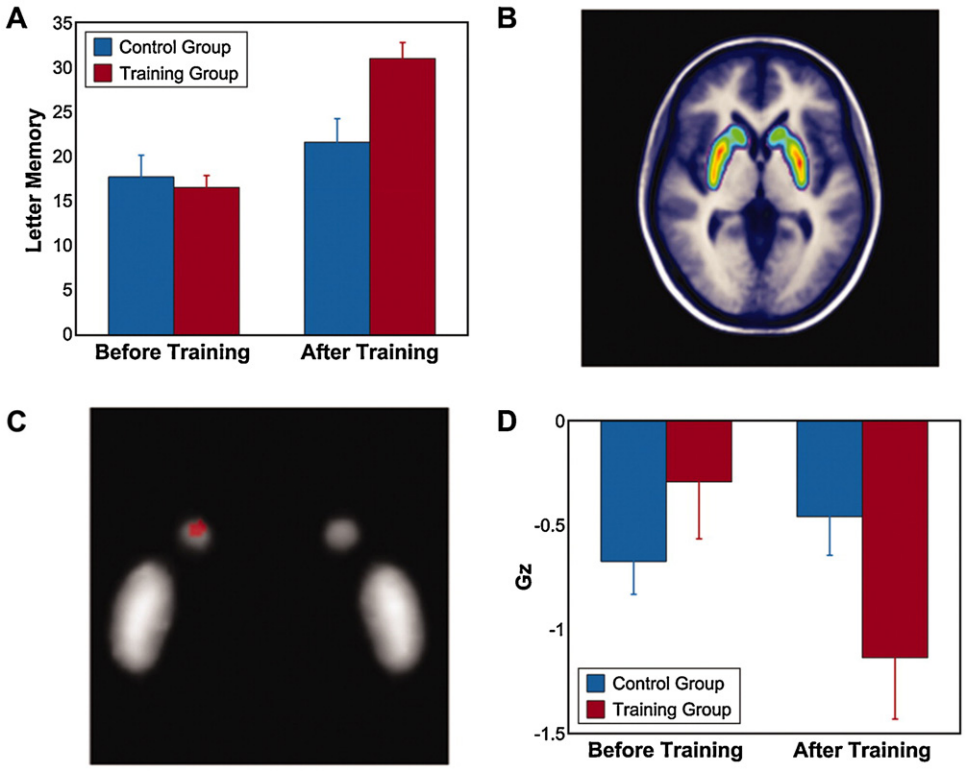

Fig. 6. (A) Differential training-related gains in letter memory (maximum = 40). The groups were indistinguishable at baseline ($P > 0.20$). The training group ($P < 0.001$), but not the controls ($P > 0.20$), improved after training. Error bars are SEM. (B) Lower binding of raclopride to striatal D2 receptors during letter memory compared with the control task before training reflects greater DA release in response to the cognitive challenge ($P < 0.01$). (C). Cluster in left caudate nucleus (x, y, $z = -17$, -7, 22) shows a training-induced decrease of raclopride binding to D2 receptors. The data were thresholded at $P < 0.01$. All voxels ($k = 14$) surviving this threshold are indicated in red on a template-striatum reference slice derived from a mean of all participant images before training. (D). Differential change in the left-caudate peak in controls and trained participants. The bars represent the difference in Gz between the control task and the letter-memory task before and after training. The groups did not differ in Gz at baseline ($P > 0.05$). Negative Gz values reflect lower radioligand binding during letter memory compared with the control task. Error bars are SEM. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
From Bäckman et al. (2011).

and D'Esposito, 2011; Durstewitz and Seamans, 2008). These differences may account for the differential patterns observed with regard to the effects of WM training on DA binding, a key point being that also the DA D2 system seems to be modifiable by training.

5. Working-memory training and genetics

In the past decade there has been an upsurge in work on genetic influences on WM functioning. Based on twin studies, these effects have been estimated to be sizable ranging between 33% and 49% (Ando et al., 2001), and one study even reported that essentially all variance in WM performance was accounted for by genetic factors (Friedman et al., 2008). Given the strong DA–WM link, some of these hereditary influences may be attributed to DA-regulating genes. The initial work on DA-related genes and WM indicated quite sizable effects of allelic variations on WM performance, particularly for the catechol-O-methyltransferase (COMT) polymorphism that regulates presynaptic reuptake of DA in prefrontal cortex (e.g., Bruder et al., 2005; Goldberg and Weinberger, 2004). However, the accumulated evidence indicates that effects of COMT and other polymorphisms on WM are small or non-existent and notoriously difficult to replicate (Barnett et al., 2008; Deary et al., 2010; Payton, 2009). This is perhaps not surprising. It would seem naive to think that single genes could account for much of the variance in complex polygenic phenotypes like WM.

At the same time, effects of different polymorphisms on WM performance may be more easily disclosed in a training context compared to single-assessment performance scores. Cognitive performance is influenced by a multitude of factors, including motivation, test anxiety, test familiarity, alternative strategy use, and relevant prior knowledge. When individuals are closer to their performance limits (e.g., following intensive training), the influence of such variables is likely to be attenuated (Baltes and Kliegl, 1992; Brehmer et al., 2007; Kliegel et al., 1989). Indeed, training research on fluid intelligence and episodic memory reveals that between-person differences are more stable and less confounded by factors like motivation and strategy use after training than at baseline assessment (Baltes and Kliegl, 1992; Brehmer et al., 2007).

In two genetic studies with younger adults (Bellander et al., 2011; Brehmer et al., 2009), we used the Klingberg et al. (2002) paradigm involving training of different verbal and spatial WM tasks. The chief question was whether variations in DA-related genes would affect the magnitude of training-related gains in WM performance. Data for all participants were available during four weeks of training. A unique methodological feature in these studies is that subjects contributed daily performance data across the four-week intervention period. Thus, rather than performing the usual post-pre training contrast, we aggregated the data into weekly performance scores to obtain a more fine-grained picture of the trajectory of training-related gains.

Brehmer et al. (2009) examined variations in the DA transporter (DAT1) gene in relation to WM training gains. The DAT is critically involved in regulating striatal DA availability, as it controls the intensity and duration of extracellular DA levels by rapid reuptake at or near the synapse (Giros et al., 1996). The DAT1 gene displays a polymorphic 40-base pair (bp) variable number of

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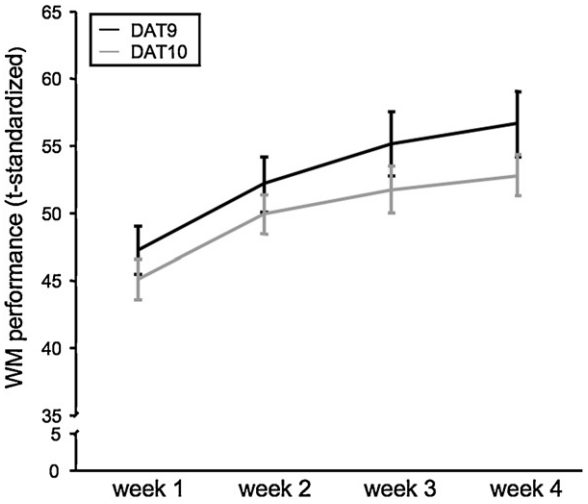

Fig. 7. Working-memory (WM) performance across 4 weeks of training as a function of DAT1 genotype. Error bars are SEM.
From Brehmer et al. (2009).

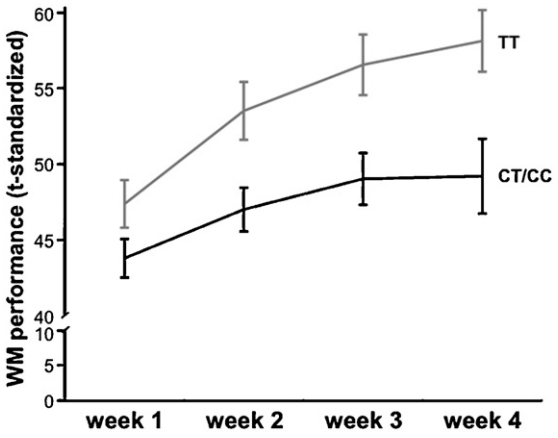

Fig. 8. Working-memory (WM) performance across 4 weeks of training as a function of genotype for the LMX1A SNP rs4657412. Error bars are SEM.
From Bellander et al. (2011).

tandem repeat (VNTR). The 40-bp VNTR occurs most often in the 9- and 10-repeat forms (Vandenbergh et al., 1992). Compared to the 9-repeat allele, the 10-repeat variant has been related to higher levels of gene expression (VanNess et al., 2005). For example, Heinz et al. (2000) reported 22% higher DAT availability in putamen in 10-repeat homozygotes compared with 9/10-repeat carriers. Conceivably, the higher gene expression leads to lower extrasynaptic DA levels and less active dopaminergic pathways (Swanson et al., 2000). Given the strong link between DA availability and WM (Bäckman et al., 2006, 2010), we might thus expect larger gains from WM training for 9-repeat carriers than for homozygotic 10-repeat carriers.

As portrayed in Fig. 7, this was indeed the case in the Brehmer et al. (2009) study. Although those who carry at least one 9-repeat allele and the homozygotic 10-repeat carriers were indistinguishable in the beginning of the four-week training period, WM training gains were greater for the former group at week three and this advantage remained at the termination of the study. It is important to note that the two genotype groups showed similar levels not only in baseline WM performance, but also on tests assessing episodic memory, speed, interference control, attention, and reasoning. This pattern indicates a high degree of specificity regarding the effects of the DAT gene on trajectories of WM gains across the intervention period. Given that (a) the DAT is expressed in striatum and midbrain (Ciliax et al., 1999); and (b) these subcortical brain regions have been linked to phasic DA release through burst firing (Cools and D'Esposito, 2011; Durstewitz and Seamans, 2008), it is conceivable that the larger training-related gains observed among DAT1 9-repeat carriers reflect genotype differences in phasic rather than tonic release of DA.

In a related study, Bellander et al. (2011) used the same basic design in exploring the influence of the gene coding for LMX1A on training-related WM gains. LMX1A is a transcription factor that is critical to the proliferation, differentiation, and maintenance of DA-producing neurons in midbrain (Friling et al., 2009; Nakatani et al., 2010). Previous research shows that allelic variations in three LMX1A single nucleotide polymorphisms (SNPs) are related to risk of Parkinson's disease, suggesting that these SNPs may influence the number of mesencephalic DA neurons (Bergman et al., 2009). Bellander et al. examined two of these SNPs in relation to WM training gains. Although one of the SNPs did not affect the gain trajectory, the other SNP was strongly associated with the magnitude of training-related WM gains (Fig. 8). The allele linked to larger gains had previously been suggested to be associated with higher dopaminergic nerve cell density (Bergman et al., 2009). As with the Brehmer et al. (2009) investigation on the DAT1 gene, the LMX1A genotype groups did not differ in baseline WM performance or on tests of episodic memory, speed, interference control, attention, and reasoning.

The results from these two studies suggest that persons who carry advantageous alleles with regard to DA availability improve more from WM training than those who do not. The fact that these effects were seen for gain trajectories, but not for baseline WM performance or for numerous other cognitive tasks is noteworthy. As such, the findings provide initial evidence for the view that influences of specific DA-related genes on WM functioning may be easier to detect when the cognitive system is pushed toward its limits (e.g., after intensive training).

6. Avenues for future research

Research on the role of DA in WM improvement is still in its infancy. In this concluding section, we delineate several lines for future research that should be worth pursuing. The first of these deals with the issue of transfer of learning. Dahlin et al. (2008a,b) and Bäckman et al. (2011) observed transfer from letter-memory training to *n*-back in younger adults. As noted, although both these tasks tax updating, they differ on numerous dimensions, including memorial content, set size, task pacing, response format, and brain activation patterns prior to training. Thus, the training may have strengthened a general updating skill. Dahlin et al. (2008b) identified a neural correlate of this transfer effect: overlapping caudate BOLD activity for letter memory and *n*-back before training, and increased activity in the same region for both tasks post training (Figs. 2 and 3).

Given that (a) striatal BOLD activity increased for the *n*-back transfer task after the intervention, and (b) the BOLD signal is partly driven by DA activity (Bäckman et al., 2011; Knutson and Gibbs, 2007; Schott et al., 2008), it would be interesting to use PET to examine whether increased DA release after WM training could be demonstrated also for an untrained *n*-back task. This could, for example, be accomplished by adhering to the training procedure of Dahlin et al. (2008b) and assess DA release with PET during a demanding *n*-back task (e.g., 3-back) versus a less demanding *n*-back task (e.g., 1-back), and examine changes in ligand binding to DA receptors as a function of training and task condition. An outcome indicating selectively reduced binding during 3-back after training would indicate that increased DA release could happen

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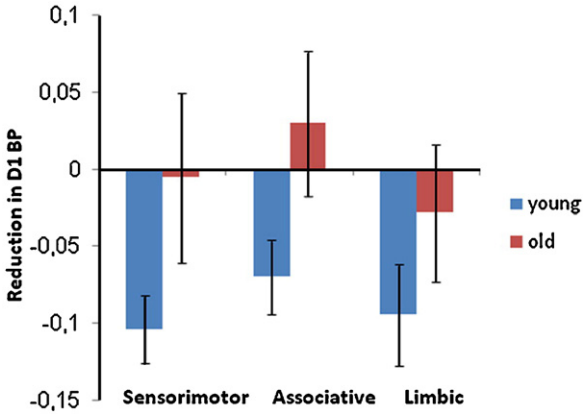

Fig. 9. Reductions in D1 binding potential in young, but not old, persons during the multi-source interference task in sensorimotor, associative, and limbic striatum. Error bars are SEM.
From Karlsson et al. (2009).

also for an untrained task that shares a key underlying process (i.e., updating) with the trained task.

Another interesting issue concerns whether the training-related increase of DA release during letter memory in younger adults (Bäckman et al. (2011) generalizes into old age, that is, whether this form of neurochemical plasticity is preserved in aging. There is evidence both for and against preservation. On the one hand, the older adults in Dahlin et al. (2008b) exhibited clear increases in caudate BOLD activity during letter-memory updating after training (Fig. 3). This suggests that it may be possible to obtain training-related DA release in the letter-memory criterion task also for older adults, to the extent that the DA–BOLD link holds in late life.

On the other hand, in the only study that has examined adult age differences in DA release during cognitive performance, we found evidence for a less modifiable DA system in the old (Karlsson et al., 2009). In that study, DA binding in younger and older adults was determined using PET while subjects were engaged in a task that taxes interference resolution and in a control condition (Bush et al., 2003). As displayed in Fig. 9, whereas the young showed clear decreases in ligand binding to DA receptors in sensorimotor, associative, and limbic striatum (suggestive of DA release) during the interference relative to the control task, the old did not. Thus, the verdict is still out as to whether training-induced DA release can be demonstrated in older adults. Knowledge pertaining to this issue could be obtained by investigating older adults during the same training conditions as used by Bäckman et al. (2011).

Further, it would be of interest to investigate DA release after training of WM functions other than updating, such as switching and inhibition. Psychometric evidence indicates that these components of WM functioning are partially overlapping and partially distinct (Miyake et al., 2000). An fMRI study provided support for this view showing that elevated demands on executive control for both working memory and episodic memory translated into shared modulation of cortical networks (Marklund et al., 2007). Specifically, overlapping tonic (sustained) modulation was observed in fronto-parietal and striatal regions implicated in top-down context processing, and overlapping phasic (transient) load modulation was observed in the posterior intraparietal sulcus implicated in dynamic shifting of attention among internal representations. In addition, in line with diversity of functions, extensive differential sustained and phasic control modulations were observed for episodic and working memory. As noted, several fMRI studies have linked updating to striatal BOLD activity (Dahlin et al., 2008b; Brehmer et al., 2011; Cools et al., 2007; Dodds et al., 2009; Olesen et al., 2004), and Bäckman et al. (2011) found evidence for DA release within the same striatal subregion (left caudate) where Dahlin et al. (2008b) demonstrated BOLD activity related to the updating task. This suggests a certain regional specificity regarding the DA–BOLD link for updating of information in WM. Whether a similar specificity holds true also for switching and inhibition remains unknown.

fMRI research reveals that switching is strongly related to BOLD activity in inferior parietal regions (Collette et al., 2005; Osaka et al., 2012), whereas activity in dorsolateral prefrontal regions and anterior cingulate cortex are typically observed during tasks requiring inhibitory control (Bush et al., 2003; Bush and Shin, 2006). Importantly, as with updating, there is evidence that both switching (Kaarbach et al., 2010; Osaka et al., 2012; Zinke et al., 2012) and inhibition (Manuel et al., 2010; Thorell et al., 2009) are trainable executive processes.

By using radioligands sensitive to binding to extrastriatal D2 (e.g., FLB457) or D1 (e.g., SCH23390) receptors, potential DA release after training of switching and inhibition could be examined to determine whether the regional specificity concerning the association between DA release and functional brain activity seen for updating generalizes to these WM processes.

Finally, the research by Brehmer et al. (2009) and Bellander et al. (2011) suggests that influences of single DA-relevant genes on WM performance are more likely to be detectable in the context of training than for traditional single-assessment performance scores. This may reflect the fact that effects of uncontrolled variables (e.g., motivation, test anxiety, test familiarity, alternative strategy use, relevant prior knowledge) are attenuated when people are closer to their performance maximum, as is often the case following training (Baltes and Kliegl, 1992; Brehmer et al., 2007). The Brehmer et al. and Bellander et al. studies were the first to address this issue and replication is thus needed. This is particularly critical as these studies involved relatively few subjects.

Future large-scale studies also open up for the possibility to examine gene–gene interactions in relation to the ability to benefit from WM training. Several studies reveal interactive effects between DA-related genes and WM performance. These interactions sometimes take the form of individuals carrying disadvantageous alleles both for genes regulating prefrontal DA (COMT) and striatal D2 receptor densities (DRD2, ANKK1) exhibiting especially poor WM performance (Stelzel et al., 2009; Wishart et al., 2011), but in other cases a combination of alleles that confer an optimal balance between prefrontal DA availability and striatal receptor densities is associated with the highest level of performance (Garcia-Garcia et al., 2011; Gosso et al., 2008). Training studies with large sample sizes hold promise to provide novel information on these issues in the context of WM modifiability. Such studies need not be confined to DA-regulating genes, but could also involve genes implicated in other biologically relevant processes such as synaptic plasticity (e.g., BDNF, KIBRA, CLSTN2).

Another extension of this research is based on the fact that the Brehmer et al. (2009) and Bellander et al. (2011) studies included younger persons only. Lindenberger et al. (2008) hypothesized that genetic differences exert increasingly larger effects on cognition as resources recede from high to medium levels of brain functioning, as is the case in normal aging. This hypothesis rests on the assumption that the function relating brain resources to cognitive performance is nonlinear, so that genetic variability is more likely to result in performance differences when resources move away from close-to-optimal levels (Fig. 10). Initial evidence for this model has been obtained in several studies examining working memory and executive functioning (Nagel et al., 2008), verbal episodic memory (Li et al., 2010, in press), and forgetting of pictures (Papenberg et al., in press). All these studies show larger genetic effects on cognitive performance in older compared to younger adults. From this perspective, we might expect that effects of specific genes (or a

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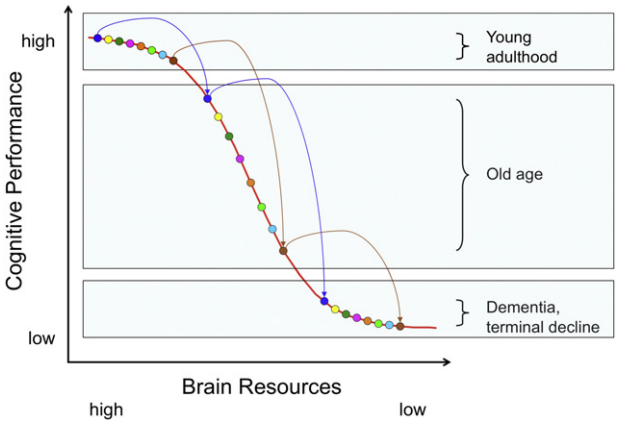

Fig. 10. The resource modulation hypothesis posits that losses in chemical and structural brain resources associated with normal aging modulate the effects of common genetic variation on cognitive performance. As normal aging moves individuals' resources from the top to the middle portion of the resource function, constant amounts of genetic variation translate into increasingly larger performance differences. With depleted resources, genetic effects are expected to dwindle again. The colored circles represent eight individuals with different combinations of genetic polymorphisms as they move from early adulthood over old age to dementia or terminal decline. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
From Lindenberger et al. (2008).

combination of genes) on gains from WM training be magnified in old age.

A key argument in the present review is that DA is critical for the ability to benefit from WM training, and may be implicated in transfer of learning to non-trained tasks. However, it remains unclear whether the DA system is more directly affected by training or whether observed alterations of DA binding after training (Bäckman et al., 2011) result from facilitation of the ability to update the content of WM, such that more updating activity post-training and related synaptic activity drive the release of DA. A more direct effect of training on receptor densities could gradually result from prolonged exposure in the system to DA as a result of repeated updating activities. This, in turn, could lead to long-term adjustments of the concentration of D2 receptors and, ultimately, to a more responsive DA system. A more definite test regarding the mechanisms underlying the role of DA in the trainability of WM updating could be accomplished by including a pharmacological component in future intervention research (cf., Cools et al., 2007; Dodds et al., 2009; Fischer et al., 2010).

Research along the different, albeit conceptually related, lines sketched in this concluding section should further increase our knowledge regarding the intriguing link between DA and WM improvement.

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