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Childhood cognitive development as a skill

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Theories view childhood development as being either driven by structural maturation of the brain or being driven by skill-learning. It is hypothesized here that working memory (WM) development during childhood is partly driven by training effects in the environment, and that similar neural mechanisms underlie training-induced plasticity and childhood development. In particular, the functional connectivity of a fronto-parietal network is suggested to be associated with WM capacity. The striatum, dopamine receptor D2 (DRD2) activity, and corticostriatal white-matter tracts, on the other hand, seem to be more important for plasticity and change of WM capacity during both training and development. In this view, the development of WM capacity during childhood partly involves the same mechanisms as skill-learning.

Background and hypothesis

Theories about child development have been plentiful during the 20th century, but few have integrated neuroscience into these theories. In the relatively new field of developmental cognitive neuroscience, three general theories on development can be distinguished: a maturational view, a skill-learning view, and interactive specialization [1–4].

According to the maturational view, development is driven by genetically pre-programmed, structural maturation of the brain. The skill-learning view emphasizes environmental influences as the driving force of development. Interactive specialization also views the environment as a driving force, but emphasizes that cortical areas change their functional characteristics as a result of the interaction.

These developmental theories are not mutually exclusive, and the proposed processes can coincide or occur at different stages of development. For example, prenatal myelination could provide the necessary structural maturation of connections between language areas, exposure to language in early childhood leads to specialization of the function of language areas in the left hemisphere, and skill-learning could drive reading improvements in later childhood and adolescence [5]. Another example of skill-learning is the suggestion that mechanisms of perceptual training are the same as those for childhood development of face perception [6].

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For executive functions – including WM, inhibition, shifting, and reasoning – the role of training has been unclear and many developmental neuroimaging studies have defaulted to a maturation interpretation. However, a range of different WM training paradigms have now demonstrated that WM capacity is significantly increased by training, including paradigms focusing on visuospatial WM [7–10], dual *n*-back tasks [11], updating [12,13], manipulation [14], and complex WM tasks [15] (reviewed in [16]). The implications of these findings for theories of cognitive development have not yet been explored.

WM training has ignited research on the associated neural plasticity using a range of methods including receptor studies in mice, neurophysiology in monkeys, and human studies using genetics, electroencephalopathy (EEG), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). This review will explore the hypothesis that the neural mechanism underlying training-induced plasticity could provide a model for childhood development. It is hypothesized that:

i The development of WM capacity during childhood depends partly on environmental influence, in other words, training through cognitive challenges in everyday life and education.

ii The neural mechanisms that underlie training-induced plasticity over weeks of WM training are to a large extent the same as those underlying environmental effects over years.

iii Increased WM capacity is caused by strengthened functional connectivity within and between frontal and parietal cortical regions.

iv The neural networks underlying plasticity can be partly differentiated from those of capacity, where striatum, DRD2 activity, and frontostriatal white-matter connections are more important to plasticity (i.e., potential for change; Figure 1).

The distinction between maturation and skill-learning is not equivalent to the distinction between nature and nurture in its most simplistic form because there are genetic predispositions to higher or lower plasticity [17–20] as well as gene–environment interactions where there is genetic predisposition for choosing a particular environment.

This article will first summarize evidence in support of the role of connectivity for WM capacity in both training and development (Hypothesis 3). The role of the striatum and dopamine for plasticity is then reviewed (Hypothesis 4). The

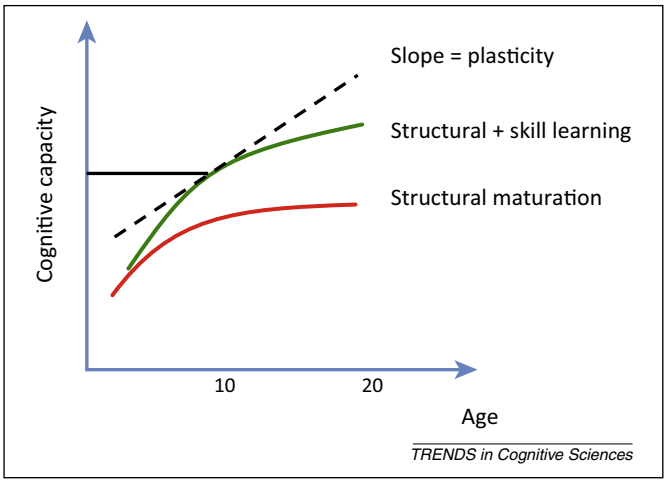

Figure 1. Illustration of how development of working memory (WM) capacity can be determined by structural brain maturation, skill-learning, or both. The height of the curve reflects the current cognitive capacity that can be differentiated from the slope (i.e., the change over time), which reflects the plasticity. Capacity here is assumed to be a quantifiable measure of a cognitive ability. WM capacity can be measured as the maximum amount of information that can be stored, for example, during a spatial-span test. This might correspond to what in earlier developmental theories has been termed 'mental capacity' [59]. Plasticity refers to modification of neural structures, which can be indirectly observed by changes in behavior. According to the hypothesis of the current paper, current capacity is associated with functional connectivity of the cortex. Changes in cortical connectivity are facilitated by the striatum, dopamine receptor D2 (DRD2)-mediated neurotransmission, and corticostriatal connectivity, which are strongly related to the slope of WM development.

relations of this research to theories of development (Hypotheses 1 and 2) are discussed in the concluding section.

WM development would, according to this hypothesis, have many similarities with training of motor and other skills, including the gradual improvement with repetitive training and the reliance on the interaction between striatum and cortex. In this view, development of WM capacity during childhood partly involves the same mechanisms as skill-learning.

Connectivity and capacity in WM development

Neurophysiological data and computational models suggest that the strength of neuronal connectivity and firing rate during the memory delay are important for determining cognitive capacity (Box 1). Several neural mechanisms are known to take place during childhood that could provide a basis for development of cognitive capacity, including: (i) pruning of synapses, that is thought to provide a finer resolution of representation; (ii) myelination of axons, which could influence axonal conduction; (iii) strengthening of connectivity within functional areas or local networks; (iv) strengthening of connectivity between functional areas (e.g., fronto-parietal connections); and (v) changes in expression of genes. In a biologically realistic simulation, the first four of these neural mechanisms were implemented in different neural networks [21], but only the strengthening of synaptic connectivity (neural mechanisms 3 and 4) led to higher delay firing rates and better resistance to distractors. Predictions from this model were also consistent with inter-individual differences in brain activity during a WM task. An increase of BOLD activity with increase in WM capacity during childhood is consistent with most developmental studies (e.g., [22–25]).

Box 1. Neurophysiology of WM

During a WM task, information is thought to be maintained during a delay by persistent activity in prefrontal and posterior areas, including the posterior parietal cortex [60,61]. An important aspect is that the firing rate of neurons during the delay is associated with the accuracy of the memory [41,61].

In addition to areas coding the sensory information, it is likely that WM activity includes a top-down signal from more anterior prefrontal regions (e.g., area 46) that could enhance maintenance or prioritize representations in more posterior frontal areas (e.g., areas 6 or 8) as well as parietal and sensory areas [62–64]. The mechanisms for visuospatial WM are largely identical to those underlying spatially selective control of attention [65].

The concept of sustained neuronal activity as a basis for memory retention has also been described using neuronal network models [41,66]. In these models, information is stored in the activity of a network by recurrent excitatory loops. The models have explored potential hypotheses for mechanisms that could provide enhanced and more stable storage. The models are consistent with neurophysiological data in suggesting that stronger inter-areal connectivity and higher firing rates during the delay are associated with better maintenance [41,63].

These data are consistent with electrophysiological data from young and adult macaque monkeys, where it was found that adult monkeys had stronger functional connectivity within prefrontal areas and a higher firing rate during performance of a WM task [26] (Figure 2A,B).

Increased functional connectivity is thus a prime candidate for producing the observed increases in firing rate and WM improvements during development. Fair and colleagues specifically analyzed changes in connectivity using resting-state data in children and young adults [27,28] (Figure 2C). The principal finding was a weakening of local networks (i.e., between different areas within the same lobe) but strengthening of long-range (>60 mm) connections. The strength of connectivity in functional networks measured as modularity during the resting state is also strongly associated with WM capacity [29].

Connectivity and capacity in WM training

The neurophysiological changes associated with improvement of WM during several weeks of WM training in monkeys include more neurons being activated during both cue and delay periods, and a higher firing rate during the memory delay [30] (Figure 2D). Increased firing rate and more neurons exhibiting delay activity are consistent with the increase in frontal and parietal BOLD signal that has been found in some studies of WM training in humans [14,31,32], although many studies also find decreased cortical activation [33,34]. It should be emphasized that translation of firing rate in a particular population of cells into their BOLD signal is not straightforward. The reasons for these inconsistencies might include differences in the amount of training time, amount of transfer to non-trained tasks (i.e., how much capacity is increased), as well as subtle differences in behavior during scanning, including inspection time and response time.

The effect of WM training specifically on fronto-parietal connectivity has been explored in humans with transcranial magnetic stimulation (TMS) [35]. In this study, functional connectivity was evaluated by activating the parietal cortex using TMS and then recording the elicited electrical

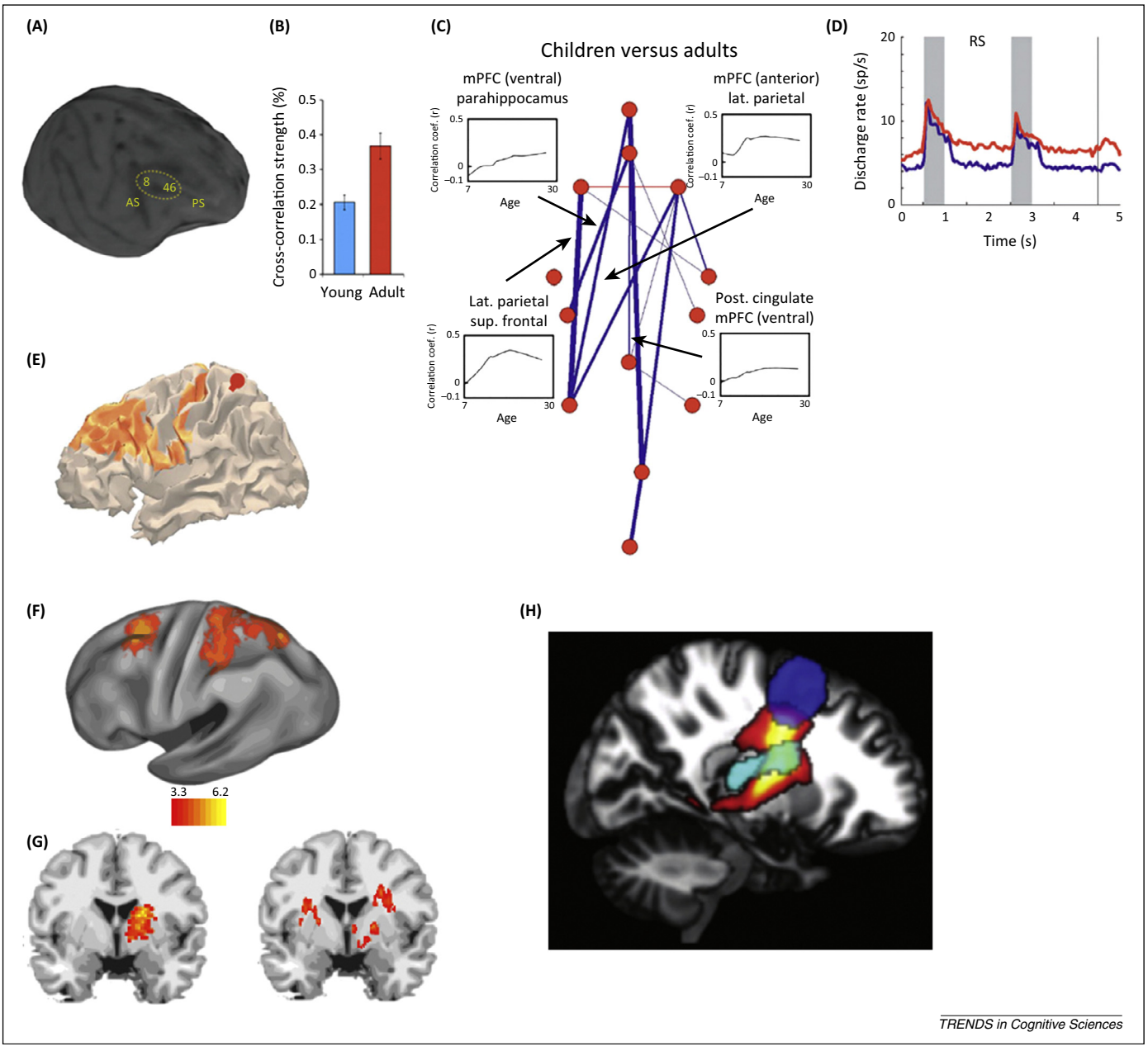

Figure 2. **(A)** Site of electrophysiological recordings in young and adult macaque monkeys during performance of a working memory (WM) task [26]. **(B)** Differences in connectivity and frequency in young and adult macaque monkeys [26]. **(C)** Developmental changes in fronto-parietal connectivity evaluated by resting state connectivity [28]. **(D)** Change in firing rate after WM training in monkeys [30]. **(E)** Changes in connectivity with WM training, evaluated using transcranial magnetic stimulation (TMS) of the parietal cortex (red dot) [35]. **(F)** Fronto-parietal blood oxygen level-dependent (BOLD) activity associated with current WM capacity [56]. **(G)** BOLD signal in basal ganglia and fractional anisotropy (FA) in white matter predict future WM capacity [56]. **(H)** Activity in caudate and FA in frontostriatal connections predict subsequent development of WM in children [57]. Abbreviations: AS, arcuate sulcus; PS, principal sulcus; RS, regular spiking neurons.

response in different regions with EEG. Compared to a control group, the WM training group showed a strengthening of connectivity between the parietal cortex and prefrontal regions (areas 8, 9, 46) (Figure 2E).

Strengthening of fronto-parietal connectivity has also been evaluated in resting-state data. Six weeks of WM training were associated with a strengthening of connectivity between frontal and parietal regions [36]. Strengthened connectivity could also be the mechanism behind enhanced fronto-parietal coherence measured with EEG after cognitive training that resulted in improved performance on a WM task [37].

Dopaminergic transmission in the cortex is dominated by the dopamine D1 receptors, which play an important role in WM performance in monkeys [38]. Using PET, McNab and colleagues showed that the change in WM capacity with training is associated with changes in cortical D1 receptors [39]. This is consistent with data showing that WM training in mice modulates dopamine D1 receptor sensitivity in prefrontal cortex [40]. It has been suggested that this could be related to increased firing rates [41].

In summary, evidence from electrophysiology, computational science, TMS, and neuroimaging together suggests that higher WM capacity is associated with

increased firing rate during the delays and stronger fronto-parietal connectivity. This holds for both training and childhood development.

Striatum in WM training

Several imaging studies have implicated the striatum in WM training [31,42]; Box 2 summarizes the role of the striatum in learning and training. Two studies have reported changes in striatal activity correlated with improvement during WM training [31,32]. A PET study [43] demonstrated that 5 weeks of WM training were associated with an increase in DA release in the caudate nucleus during performance of a new WM task.

The striatum contains a high density of DRD2 receptors, several times higher than that in the cortex. A genetic study investigated how training improvement was predicted by single-nucleotide polymorphisms (SNPs) of several dopamine-related genes [17]. One SNP in the gene encoding ankyrin repeat and kinase domain containing 1 (ANKK1), which is related to dopamine synthesis, was significantly associated with the amount of improvement during WM training. This polymorphism has previously been associated with reduced levels of striatal DRD2 [44], but increased striatal reactivity to DRD2 agonists [45]. In a follow-up study, the same SNP showed an interaction, with carriers of the A allele (previously associated with larger training improvement) demonstrating a positive correlation between ventral striatal activation and WM capacity in adolescents [46].

Other genetic studies have found that the effect of WM training is associated with polymorphisms of the dopamine uptake transporter DAT-1 [18,20] and in LIM homeobox transcription factor 1α (LMX1A), which is implicated in dopamine synthesis. DAT-1 is preferentially expressed in the striatum [47]. The beneficial polymorphism (T allele) is associated with increased expression of DAT-1 [48] and reduced risk of ADHD [49]. DAT-1 polymorphisms have also been associated with spatial WM capacity in children [50]. The role of dopamine in WM training is reviewed in [51].

Together, these studies indicate that dopaminergic transmission in the striatum, in particular involving the DRD2, plays a pivotal role in plasticity associated with WM training.

Box 2. Role of the striatum in learning and training

The striatum and thalamus are tightly linked with most cortical areas via cortical-striatal-thalamo-cortical connections, here referred to as the corticostriatal loop [67]. The striatum can be divided into sensorimotor, associative, and limbic zones, where the ventral striatum is more involved in motivation and connected to orbito-frontal cortex, and the dorsal striatum is connected to motor and association areas, including the dorsolateral prefrontal cortex. The motor functions of the corticostriatal loop were described first, but there is now a well-established role of the loop in reinforcement learning, habit formation, motor skill-learning, probabilistic learning, and more generally in implicit learning through repetition ([68] for review). The hypothesis of the current paper extends the functions of corticostriatal loop to include cognitive training.

A study in mice suggested that striatal function could be subdivided; it was proposed that the ventral striatum is strictly important for skill-learning whereas both ventral and dorsal striatum participate in the performance of the learned skills [69].

Learning during a memory task has been studied in monkeys who practiced a task where cue information was kept in mind during a memory delay [70]. When the rule changed, cue-selective activity in the caudate changed within a few trials. Change in selective activity in the prefrontal cortex was much slower, and the time-course of this change reflected that of the overall behavior of the animal. This finding supports the hypothesis that rewarded associations are first identified by the striatum, which then, via the corticostriatal loop, promotes the slower learning of the frontal cortex that determines the behavioral performance.

The role of the corticostriatal loop in implicit learning is consistent with a study of young adults learning to play a video game, where it was found that striatal size predicted the rate of learning over 20 sessions [71]. By contrast, no correlation was found between learning and the size of the hippocampus, emphasizing the difference between declarative memory and implicit skill-learning.

The corticostriatal loop might thus be a general gating or teaching mechanism that facilitates synaptic modification in the cortex by integrating cortical input from several areas with reward signals from the ventral striatum [72].

Striatum and plasticity in WM development

Development of WM capacity is associated with increased BOLD activity in frontal and parietal cortices (e.g., [22–25]), increased white-matter volume, and increased fractional anisotropy (FA) in fronto-parietal connections [52–54], as well as thinning of cortex in parietal and frontal regions [55].

Few studies have attempted to identify predictors of future WM development. This was the aim of a study by Ullman *et al.* [56] who analyzed data on cortical thickness, BOLD activity, and white-matter structure estimated by FA from a longitudinal study of child development. Using a multivariate analysis method, it was found that BOLD activity, localized around the caudate nucleus and thalamus, as well as FA in surrounding white matter, could predict the WM capacity of children 2 years later. By contrast, fronto-parietal BOLD activity only correlated with capacity measured at the time of scanning (Figure 2F,G).

A follow-up study [57] provided a more detailed anatomical description of these processes. Regions of interest were functionally defined, based on WM-related activity, in the intraparietal and superior frontal sulcus and the caudate nucleus, and tract-tracing defined connections between these regions. In a cross-sectional analysis, frontal and parietal grey-matter volume and BOLD signal, as well as white-matter structure, were associated with capacity measured at the time of scanning. However, when capacity 2 years after scanning was the dependent variable, frontal and parietal activity and structure were no longer significant. By contrast, BOLD activity in the caudate and white-matter measures (FA and volume) of the fronto-striatal and fronto-parietal tracts significantly predicted future WM capacity (Figure 2H). White-matter density in fronto-parietal and fronto-striatal tracts was thus associated with both current and future WM capacity, whereas cortical measures only correlated with current capacity, and caudate measures only with future WM performance.

Concluding remarks and future directions

In summary, higher WM capacity both after training and during childhood development is associated with a higher firing rate during the delay of a WM task and stronger fronto-parietal connectivity, suggesting that the mechanisms for

development and skill-learning are partly the same (Hypothesis 3), in support of the skill-learning view of development (Hypothesis 2). The strengthening could occur as a result of Hebbian learning, a form of activity-dependent synaptic modification where synchronized pre- and postsynaptic activity causes strengthening of the synaptic connection.

Although these results support the existence of skill-learning in WM development, it should be pointed out that skill-learning likely co-occurs with maturational processes: for example, genetically preprogrammed myelination of fronto-parietal axons could increase WM capacity independently of any environmental effects. There could also be interactions where myelination facilitates fronto-parietal communication during training.

In contrast to the development of language, there is no suggestion of hemispheric specialization, or of shifts to frontal activation, in the pattern of fronto-parietal brain activity during performance of visuospatial WM tasks, that would provide support for interactive specialization. However, it has been suggested that some regions are active in early childhood but not later in development, often described as a 'diffuse-to-focal' pattern change, which is consistent with interactive specialization [58].

Box 3. Outstanding questions

- *Question 1. Which cognitive functions can be trained, and what is the best way to do this?*
  The principles underlying WM training could apply to other cognitive functions where performance is determined by cortical connectivity. There are some promising data on training of inhibitory functions [73] and shifting of attention [74]. Comparison of different training approaches and meta-analyses could point to the best paradigms in terms of training tasks, schedule, and intensity. Inhibition is also related to striatal function [75], but what is the role of striatum in performance versus training of inhibitory functions?
- *Question 2. What are the genetics of cognitive capacity and plasticity?*
  Both capacity and plasticity could be heritable, but be related to different genes. The idea of differentiating plasticity from capacity would suggest that genetic studies associating a particular polymorphism with cognitive ability should not necessarily be interpreted as a causal effect on cognition, but instead as a factor modifying the effect of the environment. For example, a DAT-1 polymorphism has been associated with increased risk of ADHD [49], as well as reduced visuospatial WM performance [50]. A DAT-1 polymorphism has also been associated with lower gains from training [18,20], and might thus be a marker for reduced plasticity. Longitudinal studies of genetic associations might test this hypothesis and differentiate overall cognitive impairments from changes in the rate of development.
- *Question 3. What are the relevant environmental factors?*
  Given the experimental evidence for WM malleability, we would expect a similar effect of environmental stimuli on WM, but it is still unclear exactly what the relevant environmental factors are. Although the impact of severe deprivation is clear, the effect of normal variability in environmental challenges is less clear. Education is likely important, as suggested for example by cognitive transfer effects of intensive studying [76] and the effects of schooling on IQ [77]. Other candidates are challenging activities, with frequent, attention and WM demanding training, aimed at improving skills, such as playing a musical instrument [78], which in one study was associated with both higher WM capacity, steeper slope of development, and larger striatal volume [79].

This review suggests that the neural basis of WM capacity might be partly separate from that of plasticity. The same principles are at play in both WM training and WM development, again giving support for a skill-learning view of development. The separation between capacity and plasticity is in principle also consistent with the role of learning in interactive specialization.

The similarities in neural mechanisms between development and training suggest that capacity during development could be partly driven by environmental effects (Hypothesis 1) although the specific environmental factors remain to be determined (Outstanding questions are presented in Box 3).

Childhood development is multi-faceted, and the mechanisms behind WM might be different from that of for example, language, face perception, or social functions. This review only considers the development of WM capacity because much is known from animal and human studies, both during training and development. The principles might generalize to the development of other cognitive capacities relying on cortico-cortical connectivity and the frontostriatal loop (Box 3).

Other key questions in developmental cognitive neuroscience include how cognitive development is influenced by interactions between genes and environment, and by the interactions between stress, motivation, nutrition, physical exercise, and social and emotional factors. Many of these factors are difficult to control or even measure accurately over years of development. Training studies might provide experimental tools to study these interactions and to learn about the neural mechanisms underlying childhood cognitive development.

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