Vive les differences! Individual variation in neural mechanisms of executive control

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Summary

Investigations of individual differences have become increasingly important in the cognitive neuroscience of executive control. For instance, individual variation in lateral prefrontal cortex function (and that of associated regions) has recently been used to identify contributions of executive control processes to a number of domains, including working memory capacity, anxiety, reward/ motivation, and emotion regulation. However, the origins of such individual differences remain poorly understood. Recent progress toward identifying the genetic and environmental sources of variation in neural traits, in combination with progress identifying the causal relationships between neural and cognitive processes, will be essential for developing a mechanistic understanding of executive control.

It is a ubiquitous fact that individuals differ from each other both psychologically and biologically. Investigating and exploiting individual differences has been a standard research tradition within psychology [1], but has only recently become more strongly emphasized in cognitive neuroscience. The trend is especially prominent in studies of executive control (Figure 1). Here we review a variety of well-established and novel individual difference approaches, the unique methodological considerations that accompany such approaches, and the utility of such approaches both for understanding the neural mechanisms of executive control and the underlying sources of individual variation.

The recent surge in the use of individual difference approaches in cognitive neuroscience likely stems from the increased experimental and inferential power afforded by such approaches. In particular, individual difference analyses provide a convenient means for testing brain-behavior relationships that is complementary to experimental manipulation. As a simple example, activity in a brain region hypothesized to implement interference control might be expected to show within-subject sensitivity to high vs. low interference, yet it may also show between-subject correlation with task performance (Figure 2). Since within-subject and between-subject variance components are statistically independent, individual differences analyses can provide convergent evidence for one's theoretical hypothesis.

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Another important reason to conduct individual differences research is to better understand the existence of highly variable cognitive traits. Such prominent individual differences likely play a critical role in certain cognitive domains, such as executive control. Executive control is increasingly thought of as a construct tightly linked with classic individual difference dimensions of general cognitive ability that have been studied in psychological research for decades–for example, general "fluid" intelligence (gF) and working memory capacity (WMC) [2–4]. Similarly, constructs within the domains of personality and emotion processing (e.g., reward sensitivity, trait anxiety, and emotion regulation) have been recently linked to differences in executive control [5–7]. Thus, as described below, investigators interested in the theoretical mechanisms of cognitive and affective individual differences have been conducting cognitive neuroscience studies of executive control in order to provide support for such theories [8–12].

In the remainder of this review, we discuss some of the applications of the individual differences approaches in selective domains related to executive control, as well as recent efforts to understand the origins and mechanisms that produce individual differences in these domains. Before turning to this discussion, however, we first describe a number of general methodological issues and developments that are central to consider when conducting and interpreting cognitive neuroscience studies based on individual differences (see [13] for a more extensive review).

Methodological considerations

A first issue to consider in conducting individual difference analyses is the size and nature of the sample. Although the typical sample size in cognitive neuroscience studies of executive control is in the range of 15–25 subjects, larger samples may be required in order to consistently detect individual differences effects [14]. The problem is two-fold: 1) studies with small sample sizes will tend to identify only a small fraction of population-level effects in any given sample; and 2), because of increased sampling error, effect sizes derived from small samples will tend to be inflated—often grossly so [15]. The combination of these two problems is apt to lead to an illusory perception that activations are spatially selective and extremely strong [14]; in fact the underlying distribution of effects may be spatially diffuse and much weaker.

A second issue to consider is whether to use an unselected sample (i.e., continuous range), or to pre-select participants into extreme-groups based on a relevant individual difference variable. The latter approach is statistically valid, and generally increases power to detect linear relationships—though at the cost of an increased risk of mischaracterizing the magnitude and functional shape of identified effects [16]. Note, however, that in contrast to the extreme-groups design, it is never advisable to dichotomize an unselected sample into high-low groups post-hoc (e.g., based on median or tertile split), since post-hoc splits are statistically inferior to continuous analyses in virtually all respects [17].

A third issue to consider is to what extent the individual difference measure being used reflects state versus trait influences. Neuroimaging studies most commonly relate brain activation to behavioral or physiological measures that are assessed concurrently (e.g., in-scanner task performance); however, it is important to appreciate that differences in such measures may be heavily context-dependent. For example, people may perform better or worse on an executive control task not only because of stable differences in inherent ability, but also because of transient differences in mood, fatigue level, motivation, cognitive effort, etc. Conversely, studies that employ standard, well-established measures with demonstrable stability (e.g., IQ or Extraversion) are in a better position to make inferences about the trait-like nature of any differences in brain activation. As discussed further below, an exciting variant of the latter

approach is to use genotypic differences (which are necessarily stable) to predict intermediate phenotypic variation assessed with neural measurements.

A fourth issue to consider concerns the reliability of the neural measures used in individual difference analyses. The strength of observed individual difference correlations is critically constrained by the reliability of both the independent and dependent variables (e.g., brain activity). Unfortunately, reliability estimates are not typically computed in individual differences-based cognitive neuroscience studies. When such estimates have been conducted, reliability coefficients have only rarely approached levels considered adequate in the psychometric literature [for reviews, see 18,19]. More generally, because neural measurement reliability is likely to be highly context-dependent (i.e., might vary significantly across brain regions, samples, tasks, etc), it must be computed for each new sample and brain region of interest. Integrating basic reliability estimation into existing software packages (e.g., calculating split-half coefficients across even and odd runs) would allow researchers to explicitly report reliability estimates in a manner consistent with behavioral studies, effectively providing a quality check on the plausibility of reported individual difference results.

A final methodological consideration is the primary statistical approach for detecting individual difference effects. Although by far the most common approach is simple univariate correlation, there has been an increasing shift in the functional neuroimaging community towards more powerful and sophisticated methods, such as those that rely upon multivariate techniques. These include approaches that focus on individual differences in anatomical connectivity, using diffusion MRI [20], functional connectivity [21], and effective connectivity, utilizing techniques such as partial least squares regression (PLS) [22], structural equation modeling (SEM) [23], and dynamic causal modeling (DCM) [24], as well as more general ways of characterizing the complexity of brain networks through graph-theoretic methods [25,26]. Another powerful approach is statistical mediation, which provides a test of whether brain activity in a region (or set of regions) mediates the relationship between two observable variables (e.g., a stable trait index and behavioral performance) [11], or between the effect of another brain region on behavior [27]. Recently, tools have become available to test for such effects across the whole brain [28], potentially leading to a more widespread use of such approaches in the future.

Individual difference approaches in cognitive neuroscience studies of executive control

The use of individual difference approaches has been employed to clarify the role of executive control mechanisms in a number of relevant cognitive and affective domains. Rather than attempt an exhaustive review, we use this space to highlight a few notable investigations that elegantly illustrate this general principle.

Working memory capacity

One area of increased study relates to notions of working memory capacity – the number of items that can be successfully stored and utilized over short durations. A critical question has been the extent to which individual differences in capacity reflect the function of a core storage system (i.e., buffer size or efficacy), or rather an attentional control mechanism that may function to govern access to this system (i.e., filtering out irrelevant information and preventing interference). Both fMRI and ERP studies have pointed to the lateral inferior parietal sulcus (IPS) as a core storage system, in that individual differences in capacity predicts the working memory load level that produces asymptotic activity in this region [29,30]. More recent work has also demonstrated that some of these effects can be explained in terms of attentional filtering effects mediated by lateral prefrontal cortex (PFC) and basal ganglia [9,10]. In one

elegant account combining computational modeling and brain imaging approaches [31], the IPS serves to maintain the separability and integrity of WM representations, while the lateral PFC provides a non-specific excitatory drive input that can dynamically boost IPS capacity, and that may be the fundamental source of WM individual difference effects. Additional evidence suggests an important contribution of dopaminergic modulation in the basal ganglia and PFC to these individual difference effects, as increased dopamine synthesis in the caudate predicts higher WM capacity [32] and, in older adults, increased delay-related PFC activation and WM performance [33].

Trait anxiety

Individual difference approaches have also been used to draw links between executive control functions and stable traits that have been traditionally linked to non-cognitive dimensions such as affect and personality. For example, in the domain of anxiety, one prominent theoretical account suggests that high-anxious individuals may utilize top-down control mechanisms in an inefficient manner, thus showing increased sensitivity to distractor interference [6]. Recent neuroimaging studies have confirmed and extended this idea. In one study, trait anxiety was associated with a reduction in DLPFC activation in response to conflict triggered by distractor interference, selectively under conditions in which attention was not perceptually constrained, and thus available to be captured by distractors [34]. A second study focused on temporal dynamics to demonstrate that the inefficiency of cognitive control in anxiety might be reflected as reduced sustained but increased transient activation to events (particularly distractors) in the PFC and related components of the brain cognitive control network [8].

Reward/Motivation

The domain of reward and motivation provides another opportunity to investigate the interplay between affect-related individual differences and executive control. Personality traits reflecting reward sensitivity and motivation have been found to significantly modulate components of brain reward circuitry during periods of reward anticipation and delivery [35–37]. More critically, in studies in which reward motivation is manipulated during tasks with high cognitive demands, individual differences in reward sensitivity predict the magnitude of motivation-related activation increases primarily in components of the brain cognitive control network, such as lateral and dorsomedial PFC regions, rather than in reward circuitry [38,39]. This pattern was shown most directly in a recent study in which a statistical mediation approach was employed to demonstrate that the temporal dynamics of activation in right dorsolateral PFC could directly predict the relationship between individual differences in reward sensitivity and the magnitude of working memory performance enhancement observed under reward motivation conditions [40]. These results suggest that affect-related personality traits might govern the efficacy by which reward signals trigger the updating and representation of cognitive goals.

Emotion regulation

Individual differences approaches have also been utilized to understand the neural mechanisms of emotion regulation. One attractive theoretical model is that cognitive control mechanisms in the lateral PFC contribute to emotion regulation by providing a top-down attentional bias over on-going emotional responses and evaluation (putatively implemented in subcortical regions such as the amygdala and ventral striatum) based on the current behavioral goal [5]. Recent studies have supported this model using statistical mediation techniques, showing that PFC-amygdala relationships are mediated differently in depressed vs. non-depressed individuals [41], mediate individual differences in autonomic arousal associated with regulation efforts [42], and also can predict individual differences in regulation success [28]. Interestingly, in the latter study it was found that the PFC-amygdala interaction predicted

reduced regulation success, while a second PFC-nucleus accumbens pathway predicted increased success, thus potentially reflecting up-regulation of positive emotions [43].

The origins of individual differences variation: Genetics, environment, and neural mechanisms

A major goal of individual differences research is to identify the sources of variation underlying the observed variation of interest. Behavioral genetics studies have demonstrated that approximately half of the variance in executive control ability can be accounted for by heritable influences [44–46, but see 47]. However, attempts to relate specific genetic polymorphisms directly to cognitive-behavioral differences in executive control function have met with little success, as most identified candidates explain at best a small fraction of variance in executive function [48]. Cognitive neuroscience may provide a solution to this problem by identifying intermediate phenotypes: neurobiological mechanisms that serve as bridging constructs from which to relate genetic and behavioral variation more sensitively than direct gene-behavior correlations. For instance, a strong relationship has been identified between variants of specific genes and individual differences in the activation dynamics of PFC and associated neural circuits during WM and executive control tasks [49].

One such gene, catechol O-methyltransferase (COMT), codes for an enzyme that degrades dopamine in PFC and has a prominent single nucleotide polymorphism (val^{158}met) (Figure 3A). The low-enzyme-activity allele (*met*) is associated with enhanced WM capacity and attentional focus [50,51] and, more recently, it has been associated with more efficiency (lower amplitude) in sustained WM-related activity in PFC [52], likely due to higher tonic dopamine presence in PFC. In contrast, while the high-enzyme-activity allele (*val*) is associated with less attentional focus, it allows for greater cognitive flexibility [53] possibly due to greater sensitivity to transient dopamine bursts, which are thought to initiate WM updates [54,55]. Importantly, these findings point to a mechanistic understanding of the contribution of specific COMT variants to individual differences in neurobiology and behavior.

Having a mechanistic account of a gene-behavior relationship provides several advantages beyond simply identifying a complex set of biomarkers. For instance, it has been shown that the *met* COMT variant is associated both with greater WM capacity [50] as well as trait anxiety [56]. This initially appears to be a somewhat random association, yet a mechanistic understanding of how these COMT variants influence neural processing demonstrates that dopamine (the molecule affected by the COMT enzyme) influences both WM (in PFC) and affect (in striatum) [57]. We expect that mechanistic understanding of other gene-behavior relationships can provide similar insights, as well as novel predictions that can improve understanding even further.

Another major advantage of taking a mechanistic perspective is the ability to identify computational trade-offs in genetic variants. Identifying these trade-offs can lend insight into why major variants exist in the population in the first place. For instance, the COMT val^{158}met genotypes trade off between efficient WM updating (*val*) and robust WM maintenance (*met*) (see Figure 3A). This prominent bimodal distribution in the population may exist because evolution favored optimization of one or the other variant depending on particular environmental contexts [58].

To illustrate, consider several ways in which this trade-off may express itself in actual behavior. The Dual Mechanisms of Control theory [59,60] suggests that *val* individuals might tend towards a reactive cognitive control strategy characterized by increased flexibility yet reduced preparation, while *met* individuals might use a more proactive control strategy characterized by reduced flexibility yet increased preparation. The reactive strategy is likely much faster in

unpredictable contexts (thus creating evolutionary pressure toward the *val* allele in chaotic environments), while the proactive strategy is likely faster and more effective in predictable contexts (creating an opposing evolutionary pressure toward the *met* allele when the environment is stable). The tremendous variability of human experience likely drove the population toward two extremes in this computational trade-off. Similarly, the COMT val[158]met genotype may influence the trade-off between exploration (greater for *val*) and exploitation (greater for *met*) [61], which are also linked to differential evolutionary advantages/risks depending on the environmental context. For instance, a bias towards exploration can lead to greater advantages when the available resources are becoming rapidly depleted, whereas a bias towards exploitation is optimal when the environment is stable and has already been adequately sampled [62,63].

Nevertheless, genetic factors are unlikely to fully account for most individual differences. Environmental influences, such as practice effects, likely account for a large component of variance as well. Supporting this conclusion, it has been shown that WM capacity increases with practice performing particular executive control tasks [64,65]. This practice effect has been shown to increase activity [66] and dopamine receptor density [67] in a fronto-parietal network linked to executive control functions (Figure 3B). These examples demonstrate an important role for life experiences on individual differences, and illustrate the importance of cognitive neuroscience in identifying the exact mechanisms by which different environments can result in observed individual differences.

In addition to bridging the gap between genetic and environmental sources of variation, cognitive neuroscience can also identify links between these factors as they interact to produce individual differences in behavior. Evidence for this kind of gene X environment interaction is emerging from studies of learning and associated neural changes. Recent studies have demonstrated that there is a relationship between learning and brain plasticity in white matter [68], gray matter [69], and functional connectivity [70], as well as between brain plasticity and genetics [71]. However, it remains unclear if these gene-influenced differences in plasticity actually affect experience-dependent learning. Research into the genetic determinants of brain plasticity and the effects of brain plasticity on learning will be essential for addressing this issue, and for understanding the neural bases of individual differences in behavior more generally.

Conclusion

The increased utilization of individual differences approaches in cognitive neuroscience research has advanced our understanding of how neural mechanisms of executive control contribute to a variety of domains, including working memory capacity, personality, motivation, and emotion regulation. Although individual difference approaches involve special methodological considerations and challenges, they represent a complementary approach to standard experimental manipulations that provides increased inferential and explanatory power when testing hypotheses relating the efficacy of putative control mechanisms to successful behavioral performance. More importantly, cognitive neuroscience-based individual differences approaches may provide a bridging level of description and analysis that facilitates understanding of the causal mechanisms linking physiological effects of both genotype expression and experience-dependent changes (i.e., environmental factors) to cognitive and behavioral variation in executive control.

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● Of special interest

●● Of outstanding interest

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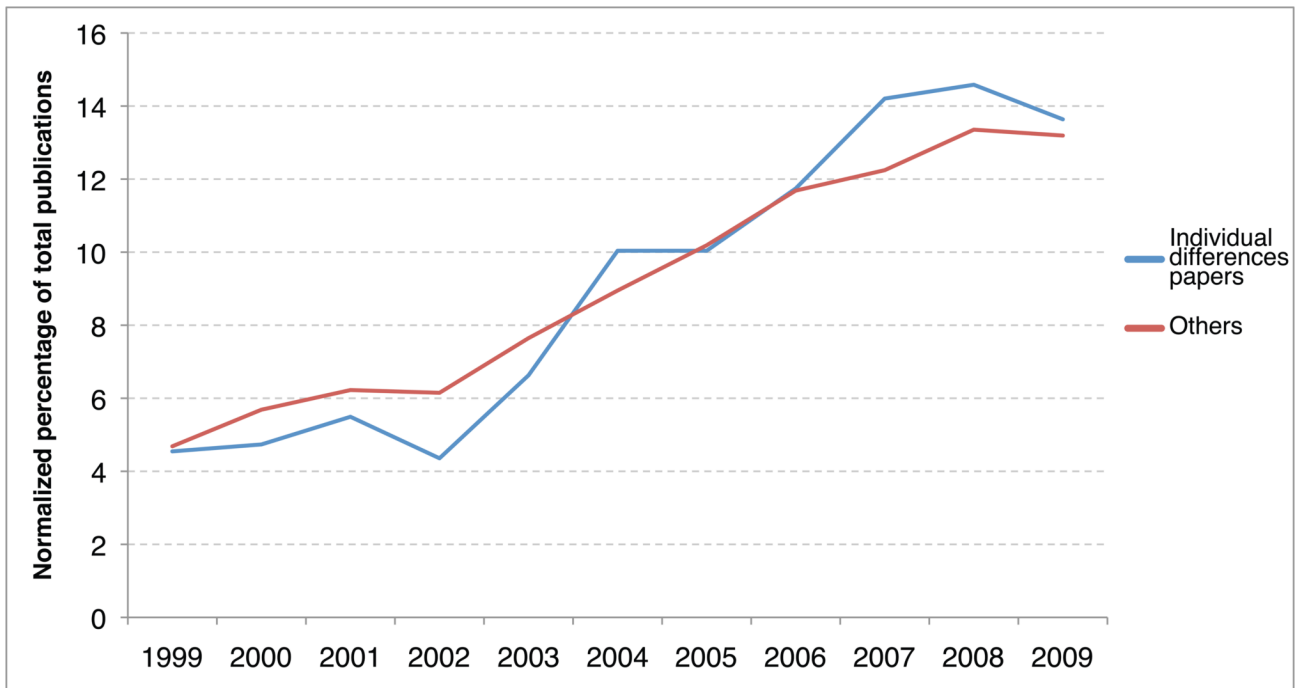
Figure 1. A trend toward increasing use of individual differences measures in executive control cognitive neuroscience research over the past 10 years

The graph illustrates a shift from proportionally fewer individual difference studies early in the decade to a proportionally larger number of individual difference studies over the last several years. The blue line illustrates individual difference studies of the neural basis of executive control, while the red line illustrates such research not including individual difference terms (see below). The publication data were normalized by dividing the number of publications per year by the total number of publications (between 1999 and 2009) in each category.

Source: Scopus. *Search used*: ("individual differences" OR IQ OR PERSONALITY OR "individual variability") AND ("cognitive control" OR "executive control" OR "working memory" OR "response inhibition" OR attention) AND (fMRI OR MRI OR ERP OR EEG OR PET OR MEG OR TMS)
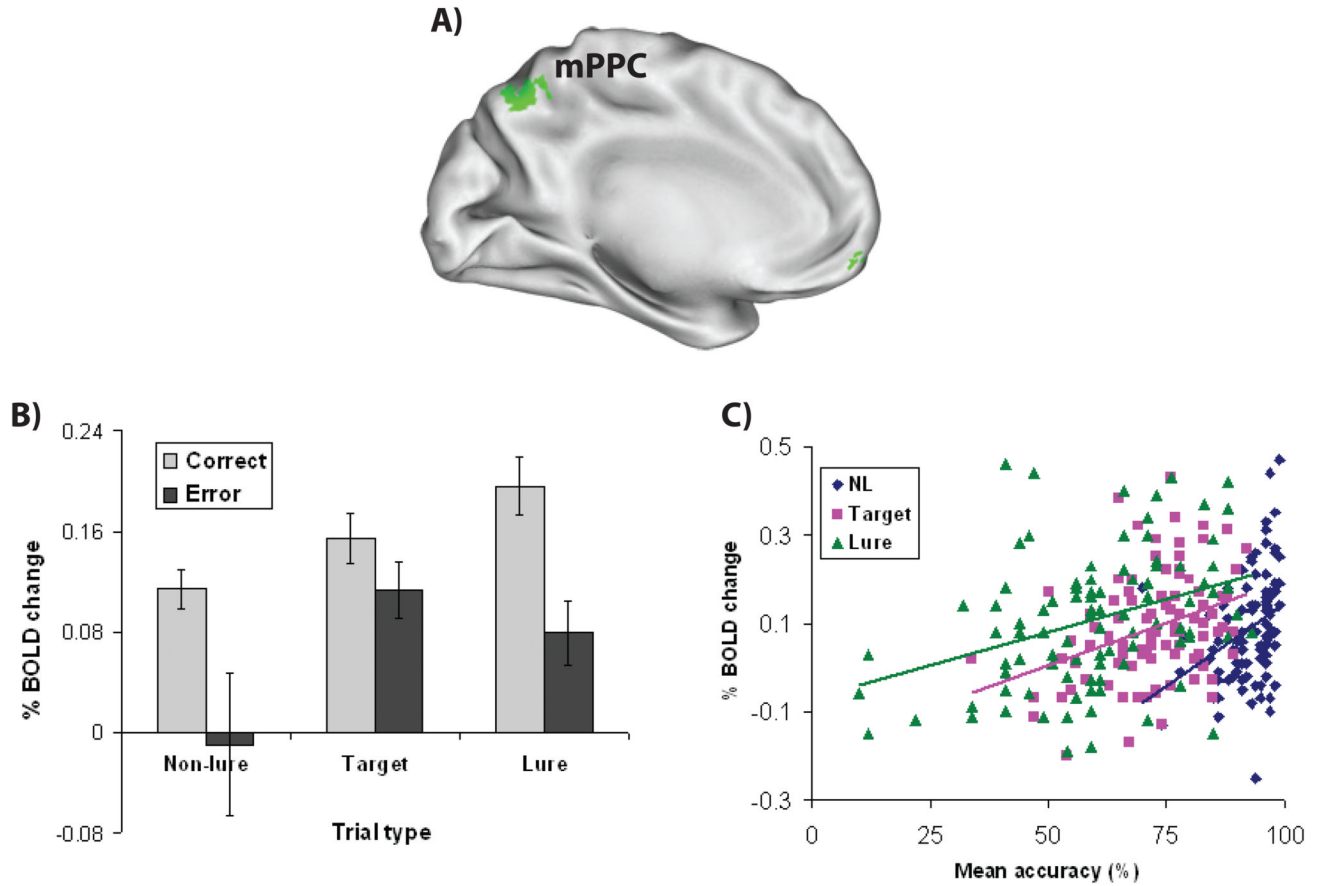
Figure 2. Complementary within-subject and between-subject effects may be present within a single region

In a large fMRI study of working memory (N = 94; unpublished data), **A)** medial posterior parietal cortex (mPPC) showed a convergence of within-subject and between-subject effects, **B)** including both trial-by-trial differences in response accuracy (greater activation for correct responses than in correct responses on high interference [lure] as well as low interference [non-lure, target] trials) and **C)** individual differences in mean response accuracy (the correlation is plotted separately for each trial type, and only for correct responses).
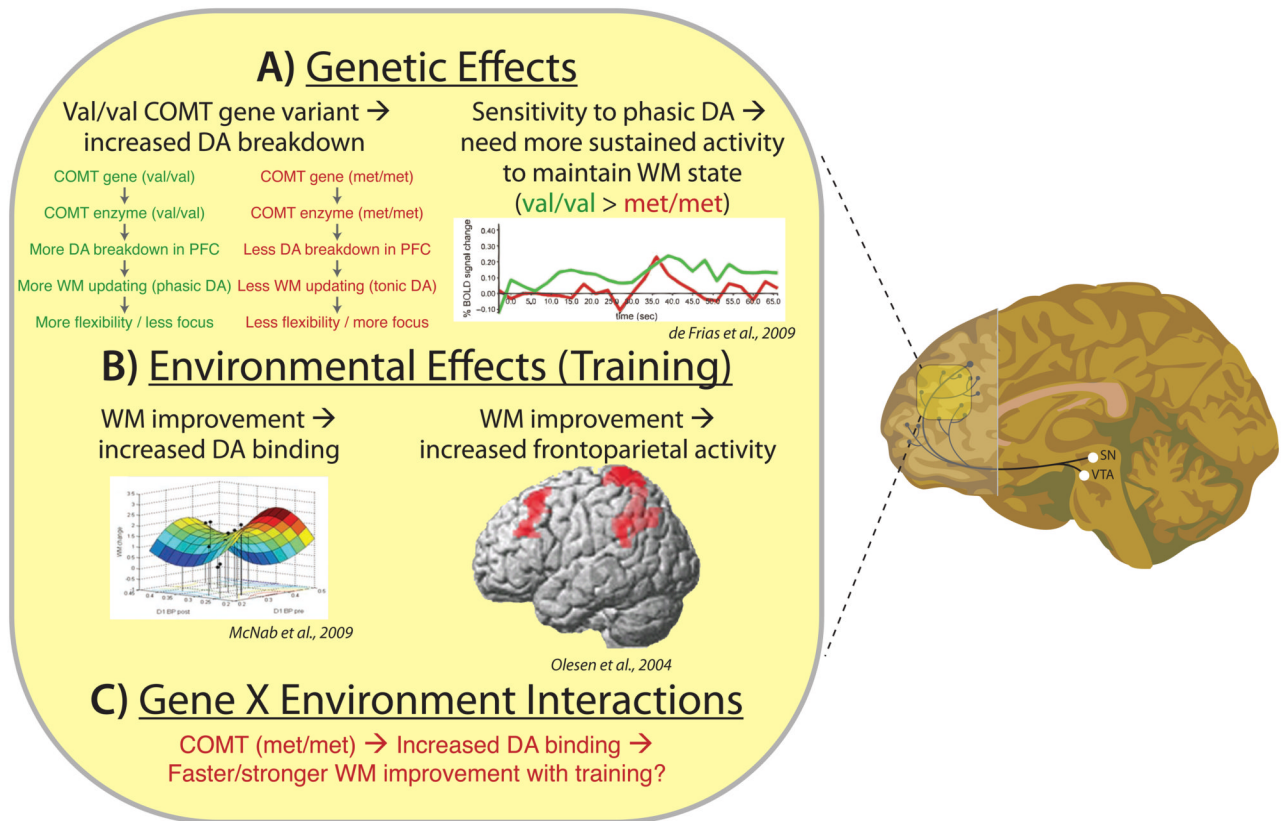
Figure 3. Explaining individual variation in PFC function: An example of how neural mechanisms can bridge the gap between genetic/environmental factors and individual differences

A) PFC activity covaries with the COMT val[158]met variant (on right) [52]. One explanation for this correlation involves the differential breakdown of dopamine in PFC across *val* (more breakdown) and *met* (less breakdown) genotype variants (on left). **B**) PFC dopamine receptor binding (left) and PFC activity during a WM task (right) are modulated by practice performing particular WM tasks [66,67], suggesting that frequently performed day-to-day tasks (e.g., frequently dialing phone numbers from memory) may affect PFC function, which in turn may increase WM capabilities. **C**) Further research is necessary to establish clear gene X environment interactions between COMT variants, PFC function, and individual differences in behavior. We suggest that the *met* variant, which involves slower breakdown of DA, may promote an increase in DA receptor binding (and a possible increase in DA receptors) to allow for faster/stronger increases in WM capacity with practice.