Understanding genetic, neurophysiological, and experiential influences on the development of executive functioning: the need for developmental models

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Flexibility is a cornerstone of adaptive behavior and is made possible by a family of processes referred to collectively as executive functions. Executive functions vary in efficacy from individual to individual and also across developmental time. Infants and young children, for example, have difficulty flexibly adapting their behavior, and often repeat actions that are no longer appropriate. And although older children do not typically make such striking errors, they have more difficulty exercising control than adolescents and adults. Such developmental variability parallels (at least in some respects) inter-individual variability in executive functions. Individuals who suffer damage or dysfunction in regions of the prefrontal cortex, for example, often experience difficulty in flexibly adapting their behavior to changes in context. As well, genetic differences between individuals are strongly associated with differences in executive control. Parallels between developmental and inter-individual variability suggest hypotheses about possible mechanisms underlying the development of executive functions but carry risks when interpreted improperly. Overcoming these pitfalls will require mechanistic characterizations of executive functioning that are more deeply rooted in developmental principles. © 2010 John Wiley & Sons, Ltd. *WIREs Cogn Sci* 2010 1 709–723

THE DEVELOPMENT OF EXECUTIVE FUNCTIONING—AN OVERVIEW

Executive functioning (EF) refers to higher order cognitive processes that adjust perception, thinking, and behavior in light of changing contextual demands. Opening the refrigerator before dinner, for example, we might look for the things we need to make a salad. However, opening the refrigerator after dinner, we might look for the pudding we had planned to have for dessert. Thus, simple everyday activities, like opening the fridge, afford a variety of further actions; selecting the one that is most appropriate requires a capacity to adjust one's responses to the demands of the current context. Psychological flexibility of this kind is made possible by EF.

Psychologists have developed many different means of assessing EF and its development, and in general these methods reveal striking advances during the early years of life. Perhaps most well known are stimulus–response compatibility tasks[1] in which participants respond to one feature of a stimulus (e.g. its color) while ignoring another feature that is strongly associated with a competing response. Examples include the Color-Word Stroop task,[2] the Eriksen flanker task,[3] and the Simon task[4] (Figure 1). Responses are typically slower and more error-prone on incompatible trials, in which task-relevant and task-irrelevant features specify opposite responses,

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than on compatible trials, in which relevant and irrelevant features specify the same response, and the magnitude of this difference (referred to as an interference effect) is considered an index of executive control. Stimulus–response compatibility tasks have been successfully adapted for use with children as young as 2 years,[5,6] and in general, interference effects decline with increasing age.[7]

Response-inhibition tasks require strong prepotent responses to be inhibited in favor of a weaker alternate response. Examples include the A not B task[8–12] (Figure 1), Go No-Go tasks,[13,14] Delay of Gratification tasks,[15] and anti-response (e.g. anti-saccade,[16] anti-imitation[17]) tasks. Variants of these tasks have been developed for use with children of a wide range of ages,[18–20] as well as non-human primates,[21] and the general trend is that inhibitory control improves with increasing age.[22]

Finally, switching tasks require participants to alternate between different ways of classifying stimuli. In card sorting tasks (e.g., Refs 23,24), participants sort cards that vary along different dimensions, such

as color and shape (Figure 1). Of interest is whether participants err when the sorting criteria change. Task-switching paradigms present participants with stimuli that can be classified in different ways, for example an array of three '1's. Participants need to switch between classifying stimuli in one way (e.g., identifying the digit) and classifying them in a different way (identifying the number of digits). Responses are typically slower and more error-prone on switch trials relative to repeat trials, and this difference, referred to as the switch cost, declines with increasing age[25,26] (although see Ref 27).

In general, then, developmental differences in EF are observed across a variety of tasks and continue in some cases into early adulthood. This age-related variability parallels inter-individual variability in EF in a number of respects, which has led to hypotheses about mechanisms underlying the development of EF. For example, adults with damage or dysfunction in lateral prefrontal cortex (PFC) exhibit behavioral inflexibility that parallels the behavior of young children. This has led to the hypothesis that developmental changes
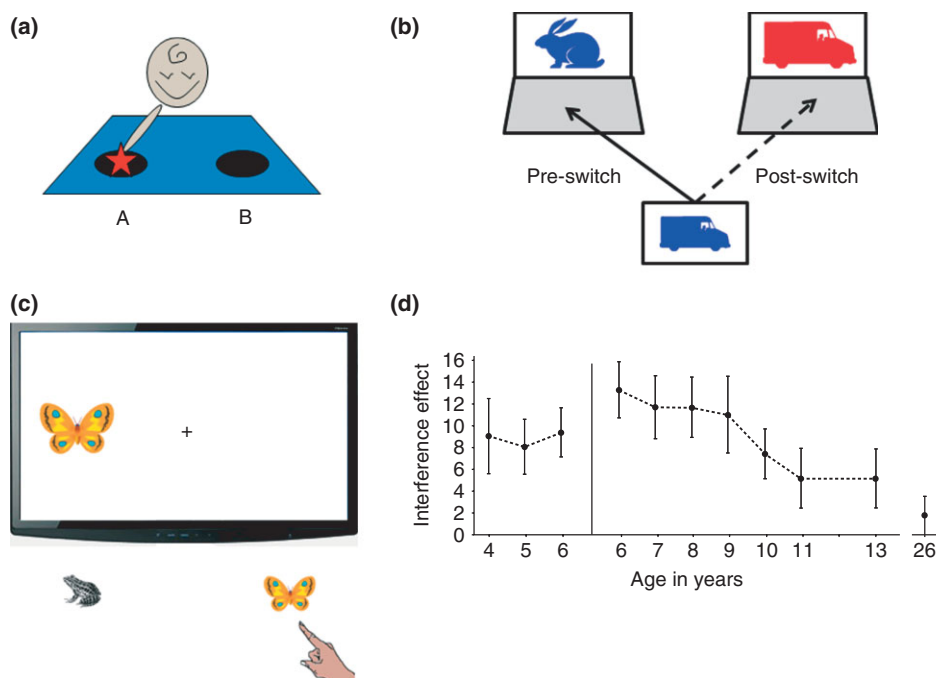

FIGURE 1 | A selection of tasks commonly used to study executive functioning early in development. (a) In the A not B task, 7- to 12-month-old infants retrieve a hidden toy from one location (A) and then watch as the toy is hidden at a second location (B). Correct retrieval requires that infants actively maintain the recent hiding location and inhibit searching at A. (b) In the Dimensional Change Card Sort, preschool-aged children sort bivalent cards one way (e.g. by color) and then are instructed to switch and sort the cards in a new way (i.e. by shape). Correct switching requires that children actively maintain the new rule and inhibit attention to previously relevant stimulus features. (c) In the Simon task, children respond to the identity but not the spatial location of the stimulus. Correct responses demand that children inhibit irrelevant stimulus–response mappings. (d) Age-related decrease in interference effects in the Simon task adopted from Davidson et al.[7] illustrates developmental changes commonly observed in executive functioning tasks. Note, one group of 6-year-olds were administered a protocol designed for young children, and a second group were administered a protocol designed for older children and adults.

in EF are linked to changes in lateral PFC function. Similarly, inter-individual differences in EF have been associated with both genetic and experiential influences, and this has led to hypotheses about genetic and experiential influences on the development of EF. Although the study of inter-individual variability affords a useful starting point for thinking about mechanisms underlying developmental change, there are risks and shortcomings with this approach. This paper addresses several of these weaknesses and argues that to advance our understanding of genetic, neural, and experiential mechanisms underlying the development of EF, we require models that are more firmly rooted in developmental principles.

AGE-RELATED CHANGES IN CORTICAL FUNCTION AND THE DEVELOPMENT OF EF: IS IT JUST ABOUT LATERAL PFC?

One of the most dominant hypotheses in the field of developmental cognitive neuroscience in the past 20 years is the idea that age-related changes in EF reflect changes in working memory[28–30] and inhibitory control,[28,30,31] core executive functions that can be localized in lateral PFC.[28,30,31] Lateral PFC is a large region of the cerebral cortex anterior to the precentral sulcus (see Figure 2(a)) that is well positioned to fulfill higher order regulatory functions owing to dense connections with sensory and multimodal association cortices, cortical and subcortical motor systems, and limbic structures involved in emotion, reward, and memory. By almost any anatomical measure, it is among the slowest developing brain regions. Gray matter decreases and volumetric increases that continue into adolescence in many areas of cortex[32] are, for example, most protracted in dorsolateral regions of PFC[33] (i.e., anterior middle frontal gyrus), due in part to regressive processes such as synaptic pruning[34] as well as progressive processes such as myelination.[32]

At the core of the lateral PFC account is evidence that patients with damage or dysfunction in lateral PFC exhibit behaviors that parallel those of infants and young children.[28,30,31] In a landmark study, Milner administered the Wisconsin Card Sorting Task[23] to a group of patients with lesions to the dorsolateral prefrontal cortex (DLPFC).[35] Although patients had little difficulty acquiring the first sorting rule, they had difficulty switching and using a new sorting criterion when required to do so. Some patients even showed apparent verbal–behavioral dissociations, showing persistent and erroneous use of the old rule while stating they knew that this
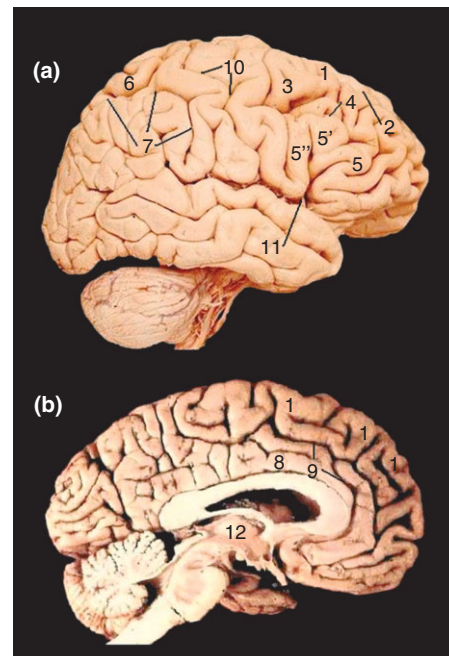
FIGURE 2 | Brain structures associated with executive functioning in humans along: (a) lateral and (b) medial surfaces. 1, Superior frontal gyrus; 2, superior frontal sulcus; 3, middle frontal gyrus; 4, inferior frontal sulcus; 5, inferior frontal gyrus; 5′, inferior frontal gyrus, pars triangularis; 5″, inferior frontal gyrus, pars opercularis; 6, superior parietal lobule; 7, intraparietal sulcus; 8, anterior cingulate cortex; 9, cingulate sulcus; 10, central sulcus (note: this structure is not commonly associated with EF, but is identified only as an important landmark); 11, anterior insular cortex; and 12, thalamus.

was incorrect. This pattern of behavior parallels the performance of 3-year-old children in the Dimensional Change Card Sort task (DCCS),[24] who have little difficulty sorting cards using one set of rules, but often fail to switch when asked to sort the same cards using a different pair of rules (Figure 1). Moreover, like patients, 3-year-olds show apparent verbal–behavioral dissociations, by correctly answering basic questions about the new rules while at the same time persisting in their use of old rules.[24] Monkeys with lesions to DLPFC exhibit similar inflexibility, both in dimensional shifting tasks,[36] and in multi-location search tasks. Diamond and Goldman-Rakic, for example, administered an analog of Piaget's A not B task to a group of adult monkeys with lesions to bilateral DLPFC, a group with lesions to parietal cortex, and a group of unoperated controls. On A-trials, a food reward was hidden and covered at an 'A' location, and after a brief delay, monkeys searched for the reward. On B-trials, a food reward was hidden at a second 'B' location. Monkeys were allowed to search for the reward after 0-, 2-, or 10-s delays. Monkeys in all groups performed

well in A-trials. On B-trials, parietally lesioned and unlesioned controls performed well at all delays, but DLPFC-lesioned animals searched incorrectly at the A-location following 2- and 10-s delays. The disinhibited pattern of behavior exhibited by the DLPFC-lesioned animals parallels performance of infants in the A not B task, who also search correctly on A-trials, but perseverate on B-trials after short delays.[21]

Despite a sizeable body of evidence that age-related changes in EF are associated with changes in the function of lateral PFC,[37–44] there are a number of critical challenges for the lateral PFC account. One criticism is that from a cognitive standpoint, this account explains developmental change in terms that are largely indistinguishable from its description (for discussion, see Ref 45). For example, while it is not incorrect to describe perseverative sorting in the DCCS as an instance of inhibitory failure,[30] to then explain the behavior in the same terms leads to theoretical circularity. Second, in contrast to what is implied by the lateral PFC account, lateral PFC is not functionally dormant early in development, but is robustly active even in young infants.[46] In fact many tasks that require ancillary working memory-like operations are associated with age-related decreases, not increases, in lateral PFC activity.[47] Even cases in which lateral PFC is reported as less active in children than adults should be interpreted carefully, as it may be that PFC is active in children for both experimental and control trials (leading to a null activation using standard subtraction techniques) but not in adults.

Perhaps most fundamentally though, there is growing evidence that complex cognitive operations that support EF are not localized in lateral PFC, but are distributed over a network of regions, including anterior cingulate, lateral prefrontal, medial prefrontal, and posterior parietal cortices, as well as subcortical structures such as the basal ganglia and the thalamus,[48,49] with the organization of this network changing dramatically over development.[50–52] Particularly compelling are studies that examine functional networks in the brain through the use of functional connectivity analysis (for review, see Ref 53). In contrast to standard functional magnetic resonance imaging (fMRI) analyses, in which voxels (or small volumes of the brain) are analyzed independently, functional connectivity analysis examines patterns of covariance in the signal timecourses of multiple spatially segregated voxels or brain regions. The results reveal functional networks or constellations of brain regions that work together to implement particular cognitive functions, such as EF[49] (see Figure 3).

Applied to the study of development, functional connectivity analysis has revealed striking age-related changes in the organization of brain networks that support EF. Fair and colleagues, for example, report evidence of increasing complexity in the EF network with development, as reflected in increasing segregation and integration in the function of multiple discreet brain regions that support EF.[50,54] In their study, Fair et al. extracted MRI signal timecourses from 39 putative EF brain regions for children, adolescents, and adults. The strength of each pairwise connection was computed as the temporal correlation of the two signal timecourses. The 75 strongest pairwise correlations were then plotted separately for each age group. The results revealed a number of dramatic changes in the organization of the EF network over development. Of particular interest was a gradual segregation of the EF network into distinct cinguloopercular and frontoparietal networks over development, as well as a gradual integration, or strengthening, of long-range connections within the frontoparietal network. Cinguloopercular and frontoparietal networks are thought to implement control over distinct timeframes, with the former supporting long-term stable maintenance of task sets and the latter supporting moment to moment adjustments in task performance.[55] The developmental emergence of these two networks through integration and segregation points to a potential learning mechanism by which stable task sets are gradually derived from the rapidly adapting dynamics of the frontoparietal network. As children develop and become more experienced, derived task sets may be efficiently retrieved and maintained by the cinguloopercular network.

Another promising approach to the study of functional connectivity and the development of EF is through the use of independent components analysis (ICA).[56] In this approach, fMRI data sets are decomposed into a series of spatially independent components to reveal groups of brain regions that share a similar pattern of hemodynamic signal change—namely, groups of regions that are functionally connected. Components can then be selected on the basis of how well they fit predictors from a standard design matrix. Using this approach, Stevens et al. examined age-related changes in functional connectivity and its association with developmental changes in response inhibition.[52] Adolescent and adult participants were administered a standard Go No-Go task and the fMRI data sets were submitted to ICA. Correct rejects were modeled separately from hits and false alarms, and the resulting predictor was used to select three best-fitting components, including separate frontostriatal-thalamic and frontoparietal networks. Analysis of age-related differences revealed greater connectivity in the frontoparietal network during
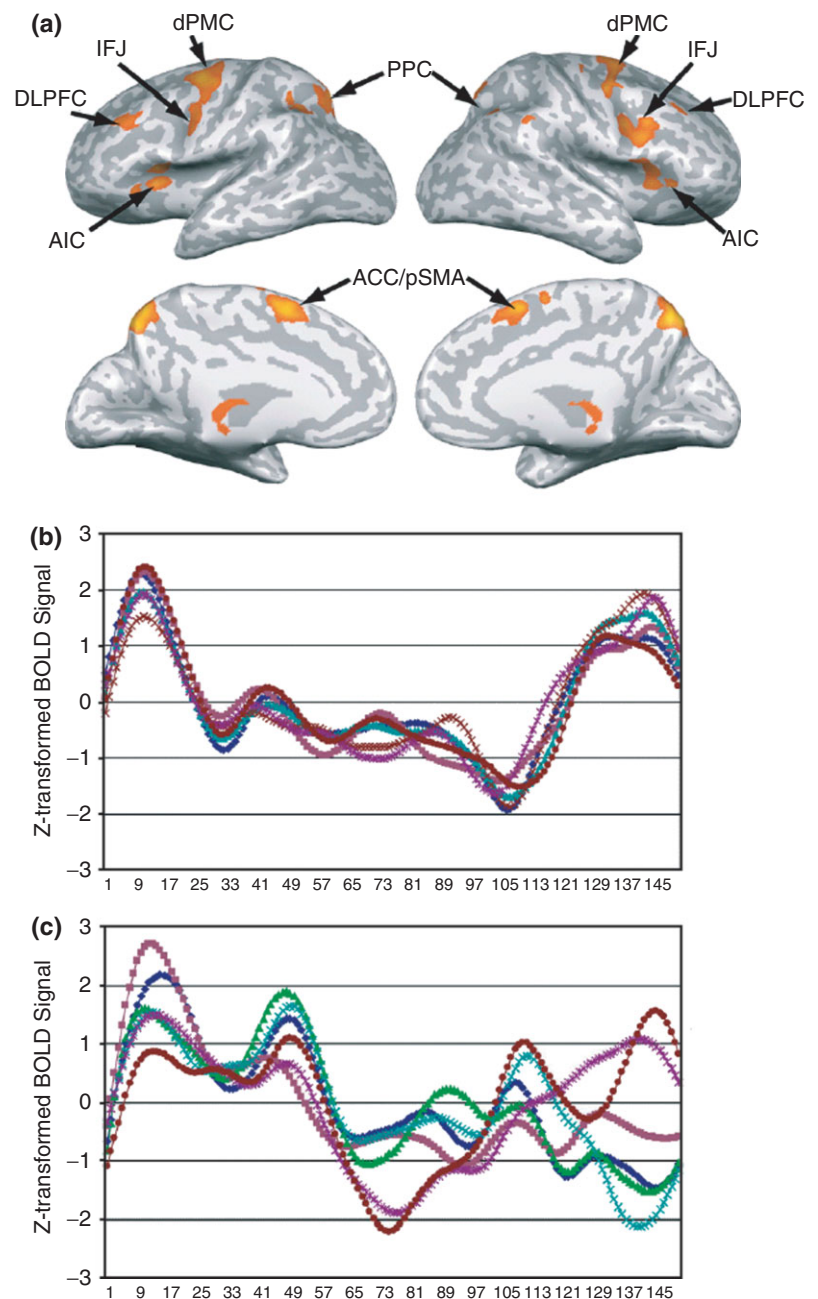
FIGURE 3 | The executive control network as revealed by switching. (a) Brain regions activated by switching include dorsolateral prefrontal cortex, inferior frontal junction, dorsal pre-motor cortex, anterior cingulate cortex/pre-supplementary motor area, anterior insula, posterior parietal cortex, and thalamus. Signal timecourses extracted from regions within the network show greater temporal coupling (b) than regions that fall outside the network (c), suggesting that executive functioning is not localized but emerges out of the interaction of a distributed set of brain regions.

response inhibition in adults compared to adolescents. The results parallel aspects of Fair et al.'s findings but extend these results by directly linking age-related differences in functional connectivity with differences in a targeted aspect of EF, in this case response inhibition.

Taken together, these findings highlight two aspects of EF and its development that are at odds with the standard lateral PFC account. First, EF broadly defined, cannot be localized to lateral PFC, but is supported by a broad network of brain regions that work together to implement complex cognitive functions. Second, developmental changes in EF likely relate to changes in the organization of a broad network rather than changes in the function of a single region. As such, the findings highlight the risks associated with using individual differences observed in adults as a model for development.[28,30,31] Although lateral PFC follows a protracted developmental course, it does not function independently or uniformly over time. Clarifying the association between developmental changes in EF and age-related changes in brain function therefore demands models that lend greater clarity to the term 'executive functioning' and that are more firmly rooted in developmental principles. This

becomes even more evident when we consider genetic and experiential influences on the development of EF.

GENETIC AND EXPERIENTIAL INFLUENCE ON THE DEVELOPMENT OF EF

There has been a recent surge of interest in understanding genetic and experiential influences on the development of EF and associated cortical regions, and the findings appear to point in opposite directions. On the one hand, studies of genetic influence suggest that the development of EF is under strong genetic control,[57] while on the other hand, there is mounting evidence for the role of experience in shaping the development of EF. Properly distinguishing between inter-individual and developmental variability suggests that this contradiction may be more apparent than real, but also highlights the fact that we know little about how genes and experience interact to produce developmental changes in EF.

Quantitative and molecular genetics are two techniques that have been used to examine genetic influences on EF. Quantitative genetics examines the proportion of population-wide variance on a specific trait, such as EF, that is attributable to genetic influence. This influence, termed heritability, can be quantitatively estimated by examining covariance patterns

on specific traits between family members with different degrees of genetic relatedness, such as monozygotic (MZ) and dizygotic (DZ) twins who share 100% and 50% of polymorphic genes in common, respectively. For example, in the traditional Falconer estimation, additive genetic influence (*A*) is estimated as:

$$A = \text{sqrt} \left[2(\text{Cov}_{\text{MZ}} - \text{Cov}_{\text{DZ}}) \right]$$

shared (i.e., family) environmental influence (*C*) is estimated as:

$$C = \text{sqrt} \left[(2*\text{Cov}_{\text{DZ}}) - \text{Cov}_{\text{MZ}} \right]$$

and unique environmental influence (*E*) is estimated as:

$$E = \text{sqrt} \left(1 - \text{Cov}_{\text{MZ}}\right)$$

Solving for *A*, *C*, and *E*, either by means of the traditional Falconer estimation[58] or using more advanced path analysis,[59] yields estimates of the extent to which individual differences on a particular trait derive from genetic, shared environmental (e.g., family dynamics), and unique (i.e., individual) environmental influences. Quantitative genetics studies of adults suggest that EF is among the most heritable of cognitive phenotypic traits, with genes accounting for upward of 90% of population-level variance in EF.[60] The anatomy

a: 5–11 yo   b: 12–19 yo   c: Difference
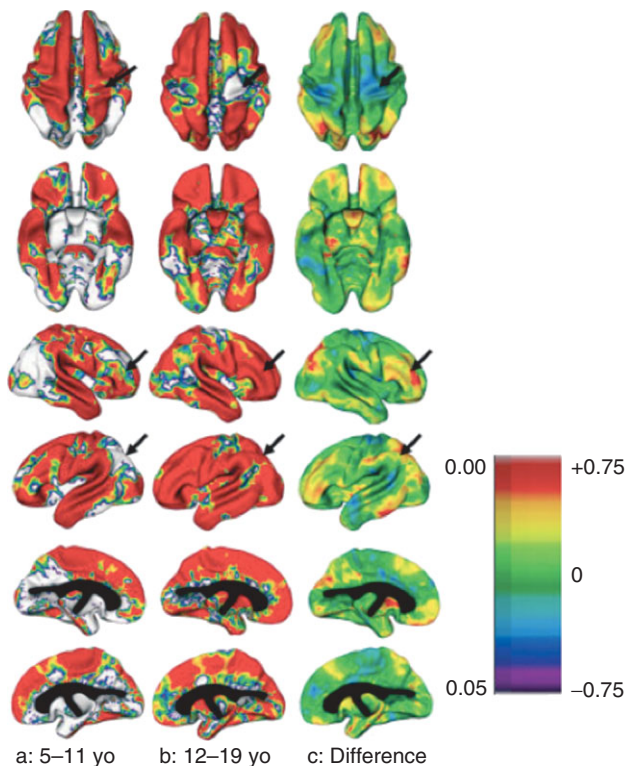
FIGURE 4 | Age-related changes in heritability of gray matter thickness for younger and older children. Columns (a) and (b) show areas that are significantly heritable for younger (a) and older (b) children. Column (c) is a map of differences in heritability, created by subtracting values of the younger group from those of the older group. Arrows indicate regions where heritability changed over development, which includes increases in the heritability of thickness of dorsolateral prefrontal and posterior parietal cortices (see Ref 61, figure 5, p. 170).

of brain regions comprising the EF network also appear to be highly heritable. Genetic influences, for example, account for as much as 52% of the variance in cortical thickness in DLPFC, medial PFC, and posterior parietal cortex,[61] with heritability measures in these regions increasing significantly between childhood and early adulthood[61] (Figure 4). Molecular genetics takes a more fine-grained approach to the study of genetic influence on EF, by examining associations between polymorphic variations in genes that code for molecules that are critical for PFC function, such as the neurotransmitter dopamine, and measures of EF and brain functioning. Polymorphic variations in these genes lead to structural variations in their associated protein products and are associated with variations in EF and PFC functioning in adults[62–64] and children.[57,65,66] Taken together, then, quantitative and molecular genetics studies suggest that EF develops under strong genetic control.[57]

At the same time, there is growing evidence that various forms of experience have a profound and lasting effect on EF, including training[57,67,68] (but see Ref 69), the quality of child-rearing environments,[70–73] and culture.[74] Task-switching training, for example, benefits task-switching performance, especially for children and older adults, as well as performance in other EF tasks and more general measures of intellectual functioning.[73,75] The positive influence of training on EF has also been documented in preschool[67,68] and elementary school aged children[57] (but see Ref 69). The quality of children's social environments also appears to significantly impact EF (for review, see Ref 76). Differences in children's socioeconomic status (SES), for example, appears to have a strong and lasting influence on EF early in development, with children from affluent and well-educated families outperforming children from less-privileged families on measures of EF.[70,71] Day-care programs that promote skills such as regulatory self-directed speech, working memory, and inhibitory control have also been shown to have a positive effect on children's EF.[72] Finally, children raised in Asian cultures that value impulse control and self-regulation outperform their North American counterparts on measures of EF.[74]

On initial examination, evidence that various forms of experience profoundly impact the development of EF appears to contradict quantitative and molecular genetic evidence that individual differences in EF and its associated cortical anatomy derive almost entirely from genetic influences. How is it possible that the capacity to resist temptation or flexibly use different rules be both amenable to training and subject largely to genetic influences? While these propositions

appear to be contradictory, both can be—and likely are—actually true. The apparent contradiction derives in part from a failure to distinguish inter-individual and developmental variability as well as a common misconception of what heritability actually measures.

Inter-individual variability in EF refers to the fact that at any particular age, some individuals achieve higher scores on measures of EF than others, whereas developmental variability refers to the fact older children achieve higher scores on measures of EF than do younger children. These are two distinct sources of variation, and it is simply incorrect to assume that they have common underlying influences. This fact is often overlooked when interpreting the results of quantitative and molecular genetic studies of EF, most of which concern individual differences in EF at particular ages, but not variability across ages. As such, extant evidence derived from studies of individual differences among children[57,65,66] actually provide little basis for inferring genetic influences on development, as some have argued.[57] To properly reveal such influences, one would need to estimate heritability from longitudinal data, by examining, for example, whether concordance for longitudinal change in EF is greater for MZ than for DZ twins. To my knowledge, these data do not exist. In fact, evidence that polymorphic variations are associated with EF in similar ways for children and adults,[57,65,66] for example, not only reveals nothing about genetic influences on the development of EF, but is actually rather surprising given the profound changes in the structure, function, and connectivity of prefrontal and parietal cortices that occur over development.[50–52] By the same token, evidence that experiential variables such as practice, child-rearing environments, and culture are associated with individual differences in EF early in development does not in itself shed light on whether and how these factors contribute to developmental changes in EF. Clarity on these matters awaits more detailed longitudinal study.

These issues relate to a more general misconception about the measure of heritability that can make genetic and environmental studies of EF appear contradictory. The critical point is that heritability is an estimate of genetic contributions to variance around a population mean rather than influences on the mean itself. Environmental treatments such as training, child-rearing experiences, and culture can (and likely do) exert an influence on EF, but likely do not disrupt the ordinal positioning of individuals around the treatment mean. As such, environmental experiences that have an upward (or downward) influence on EF will leave estimates of heritability entirely unaffected (for discussion, see Refs 60,77).

Evidence that EF is a highly heritable facet of the human cognitive phenotype, therefore, does not contradict the role of experience in shaping the development of EF and its underlying cortical anatomy. At the same time, much of what we currently know about genetic and environmental influences on EF actually concerns intra-individual rather than developmental variability, and reveals little about how genes and experience interact to produce developmental outcomes. Current findings, therefore, point to the importance of both genetic and experiential factors on the development of EF, but understanding the critical question of how they interact to produce cognitive phenotypic variability will require a framework that is more securely rooted in developmental principles.

TOWARD TRULY DEVELOPMENTAL MODELS

Insights into the study of individual differences have provided powerful and influential models for framing developmental inquiry. At the same time, these models present important limitations that can distort and even obfuscate our understanding of development. Clarifying the nature of EF, its neural instantiation, and the genetic and experiential interactions underlying its development, require frameworks that are more deeply rooted in developmental principles. Gene–environment interaction models and formal computational models represent two promising possibilities.

Gene–environment interaction models

One particularly powerful framework for understanding genetic and environmental contributions to developmental change was put forward by Scarr and McCartney.[77] In contrast to the study of heritability, which is directed at partitioning genetic and environmental contributions to intra-individual variability, Scarr and McCartney's model is directed at the question of how genetic and environmental influences interact to produce developmental change. As such, it avoids the stale clash of nature versus nurture in favor of a complementary interaction of nature and nurture. At the heart of the model is the idea that many of what are considered environmental influences on development are actually genetic in origin. This is not to suggest that the environment has no influence on the development of psychological structures, but that structures cannot develop *de novo* out of experience. Experience is shaped by and elaborates on what is genetically prior. They specify three examples. Passive gene–environment interaction refers to the association between the family environment in which a child

is raised and the child's genes. Such an association is only operative for children who are biologically related to their parents, and reflects the fact that in these instances both the family environment and the child's genes are correlated with the parents' genes. Thus, parents who routinely plan, delay gratification, or reflect on the consequences of their actions may have children who do the same, not because in modeling these behaviors they provide their children opportunities for observational learning, but because parents and their biologically related offspring share a common genetic influence. Evocative gene–environment interaction refers to the association between genetically influenced behaviors exhibited by the child and the responses these behaviors evoke from the social and physical environment. Children who, by virtue of their genes, plan and reflect in advance of taking action, for example, will tend to enjoy greater mastery over their physical environment and receive more favorable accolades from teachers and peers than children who, by virtue of their genes, act impulsively. Differences in the environments of children who think prospectively and those who act impulsively then may not be causative of individual differences, but may be evoked by genetic influences intrinsic to the child. Finally, active gene–environment interaction refers to the association between environments (or niches) that a child actively selects and the child's genetically influenced behavioral characteristics. Again, children who differ in their capacity to plan and forgo immediate gratification, for example, will gravitate toward different social and environmental niches, and the resulting differences in experience may not cause but follow from genetic differences between children. This is not to suggest that differences in experience have no impact on development. They most certainly do. It is simply that the kind of environments that children experience will be shaped by their genotype. Consequently, phenotypic variability reflects an interaction of genetic and environmental influences. Critical to Scarr and McCartney's model is the idea that passive, evocative, and active gene–environment interactions change in their relative influence over development. Early in life, when children have little ability to navigate and select unique environments, passive influences tend to predominate. However, as children become more able to explore their world and select different environments, active influences assume greater influence.

The model makes a number of predictions that are distinct from those of strict genetic-determinist and naïve environmentalist accounts. Particularly relevant in the present context is the prediction that concordance in phenotypic traits should increase
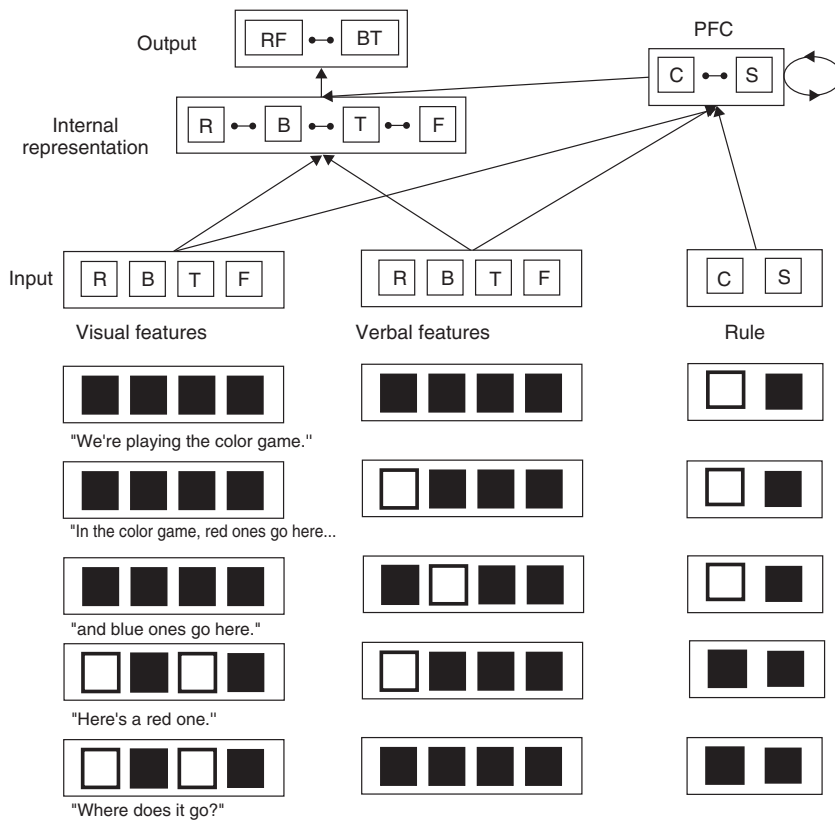
over development for MZ twins but decrease for DZ twins. Both predictions stem from the hypothesis that the influence of active gene–environment interactions should increase with development whereas passive influences should recede. Early in development, when passive gene–environment influences predominate, similarities in intrauterine and family environments will cause DZ twins to appear more similar than what might be predicted on the basis of their genetic similarity. However, as active gene–environment influences become increasingly influential over time, the genetic differences in DZ twin pairs should become increasingly evident. The opposite trend should be observed with MZ twins. As active gene–environment interactions become increasingly influential, the genetic identity of the MZ twin pairs should become increasingly evident.

The model and its associated predictions provide a powerful framework for understanding evidence concerning environmental influences on EF in childhood and changing patterns of heritability in the underlying cortical anatomy of EF over development. For example, while it might be tempting to interpret strong and specific associations between SES and EF in early childhood[70,71] as a product of parental child-rearing practices,[73] these associations may in fact reflect passive gene–environment interaction. Adults who routinely plan and delay immediate gratification will be more likely to attain high educational status and model these behaviors for their children compared with adults who do not. Given that children can acquire these components of EF through means of observational learning, it is possible that mechanisms of social learning might explain associations between SES and childhood EF.[73,76] However, given that

academic achievement and EF are both highly heritable, and parents and their biological offspring are genetically related, it is conceivable that parents who plan and delay gratification have children who do the same because of their common genetic heritage. The model also potentially sheds light on why heritability estimates of anatomical structures that support EF, such as prefrontal and parietal cortex, increase over development. Figure 5, for example, presents cross-twin correlations for measures of gray and white matter volume for younger (Y) and older (O) MZ and DZ twins. As discussed earlier, Scarr and McCartney's model predicts that the influence of active gene–environment interactions should become more pronounced over development, resulting in opposite changes in the similarity of EF anatomy among MZ and DZ twins. Consistent with these predictions, cross-twin correlations in frontal and parietal gray matter volumes, as well as total frontal and parietal lobar volumes (that include gray and white matter) tend to increase over development for MZ twins and decrease for DZ twins[78] (although the pattern does not hold for frontal and parietal white matter volumes). More recent evidence suggests that age-related increases in heritability are largely confined to executive brain areas including dorsal prefrontal, orbital prefrontal, and superior parietal cortices (Figure 6). While these data may also point to age-dependent gene expression, they are consistent with the idea that genes cause individuals to evoke and select environments that then further influence the development of EF and its associated neural circuitry. Such evidence underscores the need to distinguish individual and developmental variability in studies of experiential and genetic influences on EF. Patterns of individual differences change across

FIGURE 5 | Cross-twin correlations for gray and white measures in neuroanatomic regions of interest. Correlations for monozygotic (MZ) and dizygotic (DZ) twins are given, as are correlations for younger (MZY, DZY) and older (MZO, DZO) twin pairs. In general, the data reveal increasing correlations for MZ twins and decreasing correlations for DZ twins over time, as is predicted by gene–environment interaction models of development.

	MZ	DZ	MZY	DZY	MZO	DZO
Total cerebrum	.91	.44	.89	.58	.91	.21
Total gray matter	.84	.41	.81	.56	.86	.22
Total white matter	.91	.53	.82	.43	.92	.53
Frontal gray matter	.82	.46	.77	.55	.84	.43
Frontal white matter	.90	.47	.79	.31	.91	.44
Total frontal lobe	.89	.45	.84	.51	.90	.37
Parietal gray matter	.80	.29	.80	.45	.80	.07
Parietal white matter	.90	.46	.83	.39	.91	.45
Total parietal	.88	.30	.86	.45	.87	.16
Temporal gray matter	.83	.45	.74	.62	.86	.23
Temporal white matter	.91	.65	.80	.62	.93	.60
Total temporal	.92	.53	.87	.65	.92	.34
Caudate nucleus	.83	.39	.72	.42	.88	.38
Corpus callosum	.84	.32	.90	.37	.76	.20
Lateral ventricles	.68	.40	.65	.66	.69	−.14
Cerebellum	.86	.73	.86	.81	.83	.41

FIGURE 6 | Neural network model of Dimensional Change Card Sort task performance. Activity presented to various input units as shown in the bottom 5 rows of the figure, propagates through the network by means of feedforward connections and establishes a bias to sort by features that are deemed relevant in pre-switch trials. The network's ability to overcome this bias and correctly switch in post-switch trials depends on how well prefrontal cortex (PFC) units actively maintain a representation of the post-switch sorting rule. The model provides a mechanistic account of how inhibitory control is achieved and how the development of PFC leads to improvements in EF. R = red, B = blue, T = truck, F = flower, C = color, S = shape.

development, and it is precisely these changes that provide a window into how genes and environment interact over development to produce variation in EF.

Computational models of development

Computational models of development are formal mathematical models that simulate the development of information processing according to biologically plausible principles.[79,80] These models have been applied to the study of the EF[81] and its development[10,82,83,84] and represent an important advancement over standard accounts that relate the development of EF to PFC-mediated changes in inhibitory control[31] and working memory.[28–30]

First, computational models are mechanistic characterizations of information processing that by their very nature instantiate the distributed nature of EF and its neural implementation.[49–51] As such, these models provide an explicit framework for thinking about *how* attention and responses are inhibited, for example, *how* the developmental changes in cortical function contribute to age-related advances in cognitive control, and *how* cognitive functions emerge from the interaction of multiple brain regions.[10,82,83] To illustrate, consider a neural network model of the DCCS[83] shown in Figure 6. The model consists of several different layers including: (1) input layers that

serve as a proxy for sensory structures and that allow for the presentation of individual trials to the network; (2) a PFC layer that maintains a representation of the current sorting rule; (3) a hidden layer that serves as a proxy for multisensory posterior cortex and integrates PFC and input activity; and (4) an output layer that serves as a proxy for motor/pre-motor cortex and that registers the network's response on each trial. The model implements critical aspects of neural information processing insofar as connections between units within layers are inhibitory (i.e., simulate the influence of GABAergic interneurons) whereas connections between units in different layers are excitatory (i.e., simulate the influence of excitatory pyramidal cells; for discussion, see Ref 85). Repeated experience sorting cards one way (e.g., by shape) strengthens connections between units that process these features and leads to a bias to continue sorting cards in this way. When the sorting rule changes (i.e., to color), the network needs to overcome the bias to sort the old way. This is made possible by the PFC units that are, by design, capable of biasing activity in the hidden layer in favor of the currently relevant stimulus features. The biasing function of the PFC units, however, is constrained by how well they are able to maintain a representation of the current sorting rule. When recurrent connections that PFC units make to themselves are weak, PFC units

maintain only a weak representation of the current sorting rule and are relatively ineffective at overcoming pre-existing biases. Under these circumstances, the network typically perseverates. However, as recurrent connections become stronger, PFC units maintain a stronger representation of the current sorting rule and are more effective at overcoming bias. Under these circumstances, the network is more likely to correctly switch sorting criteria. Despite its simplicity, the model provides an explicit and mechanistic account of *how* inhibition is achieved and *how* the development of the PFC contributes to age-related advances in cognitive control. Specifically, the model inhibits attention to previously relevant stimulus features by amplifying the activity of those hidden units that support the processing of task-relevant features and helping them to compete against simultaneously active hidden units that support the processing of task-irrelevant features via local inhibitory connections. Although the mechanisms underlying inhibitory control remain contested, this account is consistent with biased-competition models of attention[86] and PFC function,[87] neuroimaging evidence that executive control involves the top-down amplification of task-relevant processing by DLPFC,[88] and highlights the importance of connectivity for the realization of cognitive function. Finally, the model suggests that age-related advances in executive control are associated in part with changes in PFC function by virtue of improvements in the ability to actively maintain task rules and instructions.[81,87]

Another important advantage of formal computational models is that they are quantitative. Quantitative models demand that the architecture, inputs, transformations, and/or outputs of a system be mathematically specified, and therefore yield a far more precise characterization of the structure and function of targeted brain regions than is possible with standard verbal theories. As such, computational models are becoming increasingly used as a powerful tool in cognitive neuroscience research. One important application involves the use of computationally derived quantitative predictors to model experimentally induced changes in brain activity measured using fMRI. In this approach, models that simulate the architecture and/or computational function of a putative system (such as the PFC) are administered experimental tasks, and generate quantitative outputs. These outputs in turn are used as regressors in fMRI analyses to effectively find brain regions whose response to experimental manipulations parallels the behavior of the model.[89–91] By integrating computational modeling and neuroimaging in this way, researchers can gain a more refined understanding of the computational function of particular brain regions, and can understand better *why* particular brain regions become active in response to particular experimental manipulations.

Finally, biologically constrained computational models hold great promise as a tool for integrating our rapidly expanding understanding of various molecular, cellular, systems, and experiential influences on the development of cortical function.[92] One particularly compelling illustration involved simulating the influence of different architectural, input, and developmental timing conditions on emerging cortical representations through the use of a 'cortical matrix' neural network model.[93] The model consisted of a cortical layer of inhibitory and excitatory units, and an input layer of excitatory units. Units in the cortical layer received a fixed number of links from units in the input layer (afferent links) and a fixed number of links from other units in the cortical layer (lateral links). All links were initially labile and propagated activity to other units, but changed with experience, such that functional links increased in strength whereas non-functional links were first stabilized and then subsequently eliminated. Connectivity in the network thus mimicked the initial overabundance and subsequent pruning of synapses that is observed in mammalian cortex over development. The network was trained to form representations in the cortical layer based on patterns of input delivered to the input layer, and the topography and abstractness of these cortical representations was assessed at various points of training. The results of the simulations showed that subtle variations in cortical unit firing thresholds, initial afferent and lateral connectivity, synaptic pruning rate, and training set structure impacted the structure of representations that emerged in the cortical layer over the course of training. To be sure, such models remain quite basic at this point and do not address questions concerning the larger functional implications of variation in representational structure. However, at a minimum, they illustrate how biologically constrained models can serve as a framework for investigating the simultaneous molecular, cellular, systems, and experiential influences on the development of cortical function. Such integrative theories will help to refine the broad picture of development offered by standard information processing accounts[28–31] and should be considered an essential goal of developmental cognitive neuroscientific investigations of EF.[92]

CONCLUSION

One of the most remarkable aspects of human behavior is that it is not tied in an obligatory way to environmental circumstances, but can

be flexibly adapted in view of changing contextual demands. Although a comprehensive understanding of the developmental origins of this ability is currently well beyond our grasp, there are several very promising scientific developments that deserve note. NIMH-sponsored longitudinal studies of normally developing children and twin pairs (see http://intramural.nimh.nih.gov/chp/index.html), for example, allow unprecedented use of converging quantitative genetic, neuroimaging, and cognitive-behavioral research methods in the study of the developing brain. These studies are leading to new insights into the normal trajectory of brain development, and will be instrumental for understanding how genes and experience interact to produce developmental variability in EF. Also noteworthy are advances in quantitative techniques for identifying associations between changes in brain structure and brain function that occur with development. Growing understanding that the development of EF is associated with changes in a distributed cortical network has led to new questions about possible mechanisms underlying developmental changes in the connectivity of this network. One hypothesis is that the transmission of information between spatially segregated brain regions is facilitated by changes in the myelination of white matter fiber tracts connecting these regions. New techniques such as joint-ICA provide powerful means of associating developmental changes in functional connectivity and fiber-tract integrity and linking these to age-related variability in EF.[94]

While these and other advances create an unprecedented opportunity to gain insight into the developmental origins of EF, they also pose sizeable challenges. The foremost, perhaps, is to develop theoretical frameworks that will help integrate genetic, neuroanatomical, neurophysiological, and social levels of analysis. This will involve, as argued in this review, moving away from developmental accounts that are based on apparent parallels between individual and developmental variability toward quantitative theories that are more deeply rooted in developmental principles. Several additional issues also require critical attention. It is unclear, for example, whether EF is itself a unified construct. There is some evidence to suggest that, in adults, EF comprises several distinct processes, such as working memory, inhibition, and mental flexibility,[95] and may be further divisible along 'hot' and 'cold' dimensions insofar as executive control in problems involving motivationally salient stimuli can be distinguished from control in more abstract problems.[96] Current evidence suggests that this factor structure is not evident early in development,[97] but more work is clearly required on this issue. Another important issue concerns lateralization of function in brain regions involved in EF, as well as changes in lateralization of function that occur with development. There is, for example, evidence of lateralization of function in inferior PFC (IPC), with regions within right and left IPC specialized for response inhibition[98] and the selection of information from semantic memory,[99] respectively. Importantly, there is evidence that lateralization within the IPC changes with development,[39] perhaps reflecting greater reliance by children on language-based executive strategies mediated by left IPC than is the case with adults.

In sum, although much remains unclear about the developmental origins of EF, rapid developments in our understanding of the human genome, our capacity to safely image the developing brain *in vivo*, and our capacity to quantitatively identify associations between molecular, neurophysiological, behavioral, and social levels of analysis promise to advance our understanding of these important questions.

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