Systematic Review of Neuroimaging Correlates of Executive Functioning: Converging Evidence From Different Clinical Populations

Milap A. Nowrangi, M.D., M.Be.
Constantine Lyketsos, M.D.
Vani Rao, M.D.
Cynthia A. Munro, Ph.D.

Executive functioning (EF) is an important cognitive domain that is negatively affected in a number of neuropsychiatric conditions. Neuroimaging methods have led to insights into the anatomical and functional nature of EF. The authors conducted a systematic review of the recent cognitive and neuroimaging literature to investigate how the neuroimaging correlates of EF compare between different diagnostic groups. The authors found that the frontal, parietal, and cerebellar lobes were most frequently associated with EF when comparing results from different clinical populations; the occipital lobe was not correlated with EF in any group. These findings suggest that individual disease processes affect circuits within an identifiable distributed network rather than isolated regions.

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The study of executive function (EF) has become an area of increasing clinical and research interest over the last decade. EF is typically considered to comprise a broad category of several cognitive skills that are commonly referred to as "higher order" or "supervisory," whose role is to control and coordinate other more basic cognitive functions like language, memory, visuospatial ability, and praxis. Miyake et al. conceptualize EF as "general purpose control mechanisms that modulate the operation of various cognitive subprocesses and thereby regulate the dynamics of human cognition."[1] As such, EFs defy classification into any single function but instead include capacities for planning, initiating, sequencing, and monitoring complex goal-directed behavior. Though recognized and described as a cognitive construct since the 1970s by Luria[2] and others, there continues to be neuropsychological and neurobiological interest in better defining its components and understanding its function in relation to other cognitive skills in normal non-disease as well as disease states.

Neuroimaging has emerged as a powerful tool for understanding both the neural structure and function of cognitive processes. As such, EF has become a fruitful area of investigation using neuroimaging techniques.

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From the Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD. Send correspondence to Dr. Nowrangi; e-mail: mnowran1@jhmi.edu

Functional imaging methods such as functional MRI (fMRI) and positron emission tomography (PET) have shown areas of physiological and metabolic activation during EF tasks. Structural methods such as MRI and diffusion tensor imaging (DTI) have shown localized areas of volume change or loss of white matter integrity in those who have EF deficits.

Whereas individual studies have focused on neuroimaging correlates of EF in specific disorders or populations, there has not been an attempt to compile and compare studies from different patient populations to examine whether the neuroanatomical correlates of EF among those populations are similar. Here, we present the results of a systematic review of the cognitive and neuroimaging literature. Our goal was to investigate whether the neural correlates of EF, as measured by clinical tests of EF, are similar between various diagnostic groups. Our hypothesis was that the same brain regions would be implicated regardless of patient population, pointing toward a consistent and identifiable network of brain regions. The results of this study, we hope, will point to converging evidence of the neuroimaging correlates of EF, further supporting the hypothesis that neuropsychiatric disorders associated with executive dyscontrol reflect impaired circuits as opposed to individual regions where specific diseases impact the functioning of those specific circuits.[3] Further, broad agreement about the correlates of EF among differing groups of patients supports the neural basis of EF as being derived from a distributed network and will hopefully aide in improving diagnostic criteria and forming the biological basis for targets for therapeutic interventions.

METHODS

Search Strategy

A systematic literature search was conducted to identify the relevant studies. Searches were thoroughly carried out in the following databases: PUBMED (MEDLINE), PsycINFO, and EMBASE from January 2002 to January 2012 for English-language articles using the following search terms: ("neuroimaging" or "magnetic resonance" or "MRI" or "positron emission tomography" or "PET" or "fMRI") and ("executive function" or "executive" or "executive control"). Other associated search terms were related to other neuroimaging modalities and tests of executive function. We also searched reference lists of selected articles meeting selection criteria for other relevant studies. Initial search results were subjected to a thorough review (by one of the study's authors, M.N.) of the study's abstract and consequently included or excluded studies based on the following criteria.

Inclusion and Exclusion Criteria

From the search results, we selected articles that described neuroimaging relationships to executive functioning tasks in adult or geriatric subject populations (excluding children or adolescents) without regard for specific diagnosis. We did not exclude studies without a control group so as to avoid missing important hypothesis-generating work. Although a correlation analysis was not required to be included in the selected articles, the study must have asserted positive or negative significant statistical or purported relationships based on presented data between neuroimaging findings, brain regions, and tests of executive functioning. We included articles of any structural or functional neuroimaging modality but excluded modalities such as evoked response potential (ERP) or MR spectroscopy to limit the number of articles to the most widely used imaging methods. We included only studies employing tests of EF that are currently and commonly used clinically. Specifically, we included individual tests traditionally considered to be measures of executive function that are included in (but not limited to) well-validated and commonly used neuropsychological batteries. Specific tasks include Trail Making Test (TMT), verbal fluency (letter fluency), design fluency, card sorting (and similar measures), color-word interference (e.g., Stroop), Twenty Questions Test, tower tests [e.g., Tower of London (ToL)], and proverbs test. We excluded novel functional cognitive paradigms specific to a particular study protocol though we included paradigms adapted from common tests as listed earlier. One study by Ueda et al.[4] met inclusion and exclusion criteria but employed a Clock Drawing Task. Because this was the only study to use this task, the authors omitted it from the analysis.

RESULTS

Patient Groups and Diagnoses

Our systematic search yielded 147 articles meeting general selection criteria. Each of these articles was thoroughly evaluated and specific inclusion and exclusion

criteria were applied. After this, 33 articles from the original group were identified as having met our selection requirements. A summary of these articles' content is found in Table 1. Among these articles an aggregate of 2951 participants were studied with both neuroimaging and executive function testing. Of this pool of study participants, 1131 were normal or healthy controls without disease. Seven papers studied normal adults exclusively and six papers did not compare their test subjects with normal control subjects. All of the articles' non-control participants were diagnosed with either a neurological or psychiatric condition. There were no studies pertaining to other medical diseases that met our selection criteria. All tests of EF reported in these studies were deemed by the authors of this review to be easily accessible and frequently used clinical tests of EF. Five different neuroimaging modalities were employed across the selected studies, all commonly used in research and clinical practice.

All non-control subjects studied carried psychiatric or neurological diagnoses. The most common neurological condition studied was dementia. Ten articles studied patients with dementia [Alzheimer's Dementia (AD), frontotemporal dementia (FTD)] or prodromal dementia [mild cognitive impairment (MCI)]. Three studies included subjects with traumatic brain injury (TBI), one included individuals with carbon monoxide (CO) poisoning, and one study included asymptomatic Huntington's Disease (HD) gene mutation carriers. Other neurological conditions included migraine, stroke, and brain tumor. Psychiatric conditions varied. Three articles studied patients with schizophrenia or those at risk for psychosis and three articles reported studies of patients with substance abuse or dependence (cocaine and methamphetamine). Three studies tested subjects with disorders of mood or personality [major depressive disorder (MDD), bipolar disorder, and borderline personality disorder]. Finally, one article studied patients in the adult autism spectrum.

Neuroimaging

Structural MRI was the most common neuroimaging technique employed in 14 articles, followed by fMRI−10 articles, DTI−four articles, PET−three articles, and SPECT−two articles. Two studies utilized multimodal imaging methods (DTI+MRI or PET+fMRI).[19,36] Imaging protocols, scanning parameters, and image processing methods varied widely among studies. Among articles using MRI, most scans were obtained on 1.5 Tesla MRI scanners. Two studies utilized a 3.0 Tesla scanner.[26,37] Most studies employed voxel-wise analyses of data primarily comparing brain surface morphometry, specifically cortical and subcortical thickness. One study used a region of interest (ROI) approach based on regions that were thought to be involved early in AD pathology,[16] otherwise most other studies utilized whole brain (left and right hemisphere) approaches to analysis. Regions correlated with cognitive measures generally represented areas of relative atrophy where worse performance usually indicated increased atrophy. Studies employing fMRI methods utilized either 3.0 Tesla or 1.5 Tesla scanners but scanning parameters, image processing, and statistical mapping methods varied widely based on task paradigms. Regions of significant positive correlation to cognitive tasks were generally indicated as regions of increased blood-oxygen-level-dependent (BOLD) signal. DTI studies collected fractional anisotropy and/or diffusivity (mean, axial, or radial) measurements. Correlations between these measures and cognitive performance were made based on integrity of white matter where decreasing anisotropy and increasing diffusivity represented decreased integrity of white matter tracts. Molecular imaging methods, PET and SPECT, utilized several different radioligands for quantification of perfusion and metabolism.

EF Measures

Several measures of EF were used. Many studies used a combination of tests or a formal battery though some isolated one test of EF to study. The most common test was the TMT, used in 17/35 studies. The Wisconsin Card Sorting Test (WCST), was used in 7 of the selected studies. The Stroop Color-Word Association Test was used in 11. Other tests included, digit spans backward and forward, ToL task, and tests of verbal fluency. The entire Delis-Kaplan Executive Functioning System (D-KEFS) battery was used in one study. In general, there did not seem to be an association between the type of task used and the primary diagnosis of the subjects. Functional neuroimaging methods (fMRI and PET/SPECT) tended to employ single tests of EF whereas structural methods (MRI, DTI) included multiple tests.

Neural Correlates of EF Measures

To compare brain regions across studies, we first determined the primary results of each study. We then

TABLE 1. Summary of Literature

	1st Author	Year	Imaging	Sample	Test(s) of EF	Associated Region(s)	Conclusions
1	Bergeson[5]	2004	MRI	75 TBI, 75 NC	TMT A and B	Left frontal (r=–0.41, p=0.003)[a] and total frontal (r=–0.37, p=0.008) (Trails B)	Frontal and temporal atrophy correlate with deficits in memory and executive function. No other significant regional correlation with tests of EF
2	Baillieux[6]	2010	SPECT[b]	18 focal cerebellar lesions	WCST, Stroop, TMT (A versus B not specified)	Frontal, right cerebellum	Damage to the cerebellar lobe can cause cognitive and affective disturbances.
3	Chang[7]	2010	MRI	358 MCI, 222 NC	TMT A and B, digit span backward	Bilateral frontal cortex, bilateral posterior cingulate cortex (left r=0.22; right r=0.19)	Reduced thickness in frontal lobes in MCI patients with low EF. Post hoc significant correlations with bilateral middle temporal and left inferior temporal regions.
4	Dickerson[8]	2010	MRI	61 ExMCI, 44 MemMCI, 27 ExAD, 12 MemAD	TMT A and B, BNT, AVLT, discriminability, delayed free recall, Digit symbol, digit span forward and backward	Superior frontal, superior parietal	Prominent cortical thinning in frontoparietal regions demonstrated in executive-predominant AD.
5	Kaller[9]	2011	fMRI	30 NC	ToL	Dorsolateral prefrontal cortex (dlPFC)	Bilateral dlPFC activation in complex tasks may reflect the concomitant operation of specific cognitive process that show opposing lateralization
6	Kinnunen[10]	2011	DTI	28 TBI, 26 NC	TMT A and B, D-KEFS: color-word subtest, letter fluency	Left superior frontal white matter ($R_{partial}$ = 0.75, $p<0.001$), right posterior and medial parietal lobe ($R_{partial}$ = 0.30, $p<0.01$),	Frontal lobe connections showed relationships with executive function between two test groups in elevated mean and radial diffusivity
7	Koutsouleris[11]	2010	MRI	40 ARMS, 30 NC	TMT B	Ventromedial prefrontal cortex, cerebellum, fronto-callosal white matter	Executive deficits in the ARMS for psychosis may reflect structurally altered networks.
8	McDonald[12]	2010	MRI	103 MCI, NC 90	TMT A and B	Bilateral dorsolateral frontal lobe, left medial prefrontal and bilateral ventrolateral prefrontal lobe. Pars orbitalis β (1, 94) = 0.33, $p<0.001$	Regional association with frontal lobe atrophy and TMT-B decline. Pars orbitalis (left frontal lobe) was the only significant lobar predictor.
9	Pa[13]	2009	MRI	26 amnestic MCI, 32 dysexecutive MCI, 36 NC	TMT B, Stroop, letter fluency, abstractions	dlPFC, dorsomedial prefrontal cortex	Dysexecutive MCI had lower EF scores, increased behavioral symptoms. The brain imaging differences suggest that the two MCI subgroups have distinct patterns of brain atrophy.
10	Sasson[14]	2012	DTI	52 Normal	Stroop, Go/no-go	Frontal white matter, superior longitudinal fasciculus	Executive function correlated with DTI parameters in frontal white matter and in the superior longitudinal fasciculus. Information processing speed correlated with cingulum, corona radiata, inferior longitudinal fasciculus, parietal white matter and in the thalamus.
11	Schmitz[15]	2008	MRI	24 migraine, 24 NC	Go/no-go, Stroop, switch task	Middle frontal gyrus, inferior parietal lobe with striatum.	Network of fronto-striatal-parietal brain regions responsible for monitoring EF in migraineurs

TABLE 1. Summary of Literature (Continued)

	1st Author	Year	Imaging	Sample	Test(s) of EF	Associated Region(s)	Conclusions
12	Stricker[16]	2011	MRI	105 AD, 125 NC	TMT A and B, digit span backward	Frontal, parietal lobes	Overlap between normal and AD-related MRI-based morphometric changes is greater in the very old than in the young old.
13	Takahashi[17]	2008	PET[c]	23 Normal	WCST	Prefrontal cortex, hippocampus	Orchestration of prefrontal D1 and hippocampal D2 might be necessary for human executive function as part of a prefrontal-hippocampal pathway. No other regions studied
14	Toepper[18]	2010	fMRI	20 Normal	Corsi Block Tapping test, block suppression Test	Left dlPFC	Left dorsolateral prefrontal cortex plays a crucial role for executive controlled inhibition of spatial distraction.
15	Turken[19]	2009	MRI+DTI	1 TBI, 43 NC	TMT B, Color-word test	Frontal cortex and underlying white matter	Tests of executive function were related to cortical abnormalities in the frontal lobes.
16	Wolf[20]	2011	fMRI	16 pre-HD	WCST	Left dlPFC	Left DLPFC less active during working memory performance cross-sectionally but did not persist over time.
17	Connolly[21]	2012	fMRI	18 cocaine-dependent, 9 NC	Go/no-go task	Prefrontal, cingulate, cerebellar and inferior frontal gyrii	Integrity of prefrontal systems that underlie cognitive control functions may be an important characteristic of successful long-term abstinence
18	Jacobs[22]	2012	MRI	337 MCI	TMT-B, Stroop	Frontal-parietal (B=–0.304, p=0.023); Frontal-parietal-subcortical (B=0.355, p=0.001)	Parietal white matter hyperintensities are a significant contributor to executive decline in MCI over time. Frontal-subcortical networks did not relate significantly to executive function
19	Nestor[23]	2011	fMRI	10 MA[19], 18 NC	Stroop	Right inferior frontal gyrus, supplementary motor cortex/anterior cingulate gyrus and the anterior insular cortex, posterior cingulate cortex	Hypofunction in cortical areas that are important for executive function underlies cognitive control deficits associated with MA dependence
20	Eslinger[37]	2011	MRI	26 FTD	TMT-B, Stroop	Right dlPFC, right parietal regions, and left superior temporal gyrus and temporal pole, subcortical areas of the right amygdala and left caudate	Behavioral variant FTD causes multiple types of breakdown in empathy, social cognition, and executive resources, mediated by frontal and temporal disease.
21	van Tol[24]	2011	fMRI	65 MDD, 82 MDD +anxiety, 63 NC	ToL	Left dlPFC	Prefrontal hyperactivation in MDD but NOT In anxiety.
22	Hunt[25]	2011	PET[26]	10 MCI, 10 AD, 14 NC	TMT A and B	Right middle frontal cortex and the right precentral gyrus (TMT B), left middle frontal cortex (TMT A).	Executive dysfunction in AD as measured by TMT is frontal lobe mediated.
23	Chang[26]	2009	DTI	17 CO poisoning, 34 NC	Digit span backward, design fluency	Left orbitofrontal (r^2 = 0.81, p=0.02), right frontal (r^2 = 0.35, p=0.04)	Reduced connectivity between different cortical regions is a pathophysiologic mechanism in CO poisoning and cognitive performance.

TABLE 1. Summary of Literature (Continued)

	1st Author	Year	Imaging	Sample	Test(s) of EF	Associated Region(s)	Conclusions
24	Fine[27]	2009	MRI	19 AD, 25 FTD, 13 Semantic Dementia, 12 PNFA, 9 PSP, 9 NC	D-KEFS – sorting test	Left frontal lobe	Left frontal lobe significantly predicted performance on the D-KEFS Sorting Test
25	Segarra[28]	2008	MRI	28 Schizophrenia, 28 NC	TMT A and B, digit span, WCST, verbal working memory, letter-number sequencing, Controlled Oral Word Examination	Bilateral cerebellum	Cerebellar gray and white matter volume loss correlates with executive function deficits in schizophrenia.
26	Haldane[29]	2008	MRI	44 Bipolar disorder, I, 44 NC	Stroop	Dorsal and ventral PFC, right parietal (compensatory)	PFC dysfunction in bipolar I with compensatory involvement of the parietal cortices through response inhibition
27	Sim[30]	2007	MRI	40 Cocaine dependent, 41 NC	TMT A and B, Stroop	Bilateral Cerebellum (Pearson: left=–0.70; right=–0.75)[d]	Cerebellum vulnerable to cocaine-associated brain volume changes. Cerebellar and frontal, temporal, and thalamic changes correlate with neuropsychological deficits.
28	Grant[31]	2007	DTI	10 Borderline PD, 10 NC	TMT A and B, Stroop, WCST, Controlled Word Association Test	Posterior white matter	Posterior white matter integrity correlated with measures of executive function.
29	Lie[32]	2006	fMRI	12 Normal	WCST	Rostral and caudal ACC, right dlPFC, cerebellum, superior parietal cortex, retrosplenium	Central role of the right dlPFC in executive working memory and cognitive control. Functional dissociation of the rostral and caudal ACC in the implementation of attentional control.
30	Moll[33]	2002	fMRI	7 Normal	TMT A and B	DlPFC and medial prefrontal cortices, intraparietal sulci	Critical role of the dlPFC and medial prefrontal cortices as well as the intraparietal sulci in the regulation of cognitive flexibility, intention.
31	Wilmsmeier[34]	2010	fMRI	36 schizophrenia, 28 NC	WCST	Rostral and dorsal ACC	Set-shifting is associated with increased activation in the rostral and dorsal ACC
32	Schmitz[35]	2006	fMRI	10 ASD, 12 NC	Stroop, Go/no-go, switch test	Left inferior and orbital frontal gyrus, left insula, parietal lobes	Association between successful completion of EF tasks and increased brain activation in people with ASD
33	Schall[36]	2003	PET[e] + fMRI	6 Normal	ToL	Bilateral dlPFC, inferior parietal cortex, cerebellum	ToL is a useful tool for investigating particularly prefrontal dysfunction in a broad range of neuropsychiatric conditions

ARMS: at-risk mental state; ASD: autism spectrum disorder; ExAD: executive predominant AD; ExMCI: executive predominant MCI; FDG: 18-fluoro-D-deoxy-glucose; MA: methamphetamine abuse; MemAD: memory predominant AD; MemMCI: memory predominant MCI; PNFA: progressive nonfluent aphasia; PSP: progressive supernuclear palsy; TMT: Trail Making Test; ToL: Tower of London

[a] r=Spearman's correlation statistic.

[b] Tc–99m-ECD.

[c] [^{11}C]SCH23390 and [^{11}C]FLB457.

[d] Pearson correlation voxel maxima MNI coordinate.

[e] [^{15}O]H_2O.

TABLE 2. Lobar Relationships to Diagnosis

Dementia	Brain Injury	Other Neurological	Psychosis	Affective and Personality	Substance Use	Normal
Frontal, cingulate cortex[7]	Frontal[5]	Frontal and cerebellum[6]	Frontal, cerebellum[11]	Frontal[24]	Frontal, cerebellar[21]	Frontal, parietal, cerebellar[32]
Frontal, parietal[8]	Frontal, parietal[10]	Frontal, parietal[15]	Cerebellum[28]	Frontal, Parietal[29]	Cingulate[23]	Frontal[9]
Frontal[12]	Frontal[19]	Frontal[20]	Anterior cingulate cortex[34]	"Posterior"[31]	Cerebellar[30]	Anterior cingulate, frontal, cerebellar, parietal[36]
Frontal/prefrontal		Frontal[26]				Frontal[14]
Frontal, parietal[16]		Frontal, parietal[35]				Frontal[17]
Frontal, parietal[22]						Frontal[33]
Frontal, parietal, temporal, amygdala, caudate[37]						Frontal[18]
Frontal						
Frontal[27]						

designated each brain region as a lobe (frontal, temporal, parietal, occipital), and/or cingulate gyrus, which spans frontal and parietal lobes. This procedure resulted in grouping together multiple regions within the same lobe, when present, into a single lobe. We did this to simplify comparisons between studies employing a variety of neuroimaging methodologies to better illustrate broad commonalities in areas of high correlation. Where and when available, we included correlation coefficients and effect sizes to further illustrate strength of relationships as seen in Table 1. To associate significant region to diagnostic group, we combined studies of similar patient groups [e.g., patients with dementia, brain injury (vascular, traumatic, carbon monoxide), psychosis, affective disorders and personality disorders (MDD, bipolar disorder, borderline personality disorder)], substance use disorders, and normal healthy subjects. Table 2 summarizes our findings, which show that EF measures were correlated primarily with measures of the frontal, parietal, and cerebellar lobes. There were fewer correlations to the temporal lobe, and when they did occur, they existed exclusively in the dementia patient group. In studies of patients with brain injury, EF measures were most correlated with measures involving the frontal lobes. Within psychotic and substance use disorders, frontal and cerebellar lobes, and the cingulate gyrus were the most frequently associated with EF deficits. In affective disorders, measures of frontal and parietal lobes were most often correlated with EF measures. In normal healthy individuals, a wider range of lobar correlations to EF was found. These included frontal, parietal, and cerebellar lobes and the cingulate cortex.

To examine the associations between individual tests of EF and associated brain region, we identified studies that utilized a single test and applied our lobar method as described above to associated brain regions (Table 3). The TMT (A or B) was associated most frequently with the frontal lobe but in one study was associated with temporal and cerebellar regions. The WCST was associated with the frontal lobe and the cingulum. The Stroop task was associated with frontal and parietal lobes, and cingulum. The Tower of London task was most commonly associated with the frontal lobe but in one study with the parietal lobe and cerebellum. Letter fluency (including controlled oral word association) was examined in two studies and was associated with frontal, parietal, and cerebellar lobes, and subcortical white matter.

DISCUSSION

Impairment of EF is an important finding in many neurological and psychiatric conditions because it has been linked to numerous functional and behavioral outcomes.[38–41] There remains, however, a lack of agreement about its definition, the tests used to approximate it, and its neurobiological substrates. In an effort to address these questions, there has been rapidly increasing interest in correlating measures of EF with brain regions using neuroimaging. The research that has emerged from this area has focused on studying EF *within* specific clinical populations. There is a need, however, to understand if the findings agree *between* clinical groups to further support generalizing hypotheses about EF. In

TABLE 3. Lobar Relationships to Single-Administered Test of Executive Functioning (EF)

ToL	TMT A or B	WCST	Stroop	D-KEFS Sorting	Go-no-go	Letter Fluency
Frontal[24]	Frontal[25]	Frontal[20]	Frontal, cingulate cortex[23]	Frontal[27]	Frontal, cingulum, cerebellum[21]	Frontal, parietal[10]
Frontal[24]	Frontal[5]	Frontal[17]	Parietal[29]			Frontal[13]
Frontal, parietal, cerebellum[36]	Frontal[33]	ACC, frontal, parietal, cerebellum[32]	Frontal, parietal[8]			Cerebellum[28]
Frontal[9]	Frontal, cerebellum[11]	ACC[34]				Posterior white matter[31]
Frontal[5]	Frontal-parietal-subcortical[22]					
	Frontal, parietal[8]					
	Frontal, parietal[10]					

ACC: Anterior cingulate cortex; D-KEFS: Delis-Kaplan Executive Functioning System; TMT: Trail Making Test; ToL: Tower of London; WCST: Wisconsin Card Sorting Test.

this systematic review, aimed to compare the neuroimaging correlates of EF among various clinical populations, our main finding is that the same brain regions (frontal, parietal, and cerebellar) correlate with performance on tests of EF in different clinical populations as well as in healthy individuals. Although the temporal lobes were least often associated with EF in the articles selected for this review, when correlations did exist, they were in patients with dementia and not in patients with other disorders. The occipital lobes were not found to be related at all.

Because EF is not a unitary concept, researchers (e.g., Royall and colleagues,[42]) have argued that a single measure could not possibly serve as the gold standard in assessing it. Indeed, many factor analytic methods have converged upon three components underlying EF: 1) inhibition and switching,[43,44] 2) working memory,[1,45,46] and 3) attention.[47,48] Although attempts have been made at operationalizing these control processes, there continues to be a lack of agreement for a general model of EF. An incomplete understanding of the neurobiological underpinnings of EF is, in part, a reason for these difficulties. As such, the neuroanatomical and functional correlates of EF have become areas of increasing scientific investigation and the search for neurobiological markers for cognitive abilities has intensified.

In addition to difficulties defining EF, another issue complicating the study of EF concerns its associations with other domains of cognition. Spearman's classic theory[49,50] posits that general ability (referred to as "g") underlies performance on a broad range of cognitive tests, including tests of executive function.[49–51] It has long been recognized that performances on tests of different cognitive abilities are positively correlated, and the concept of "g" has been used to represent the statistical variance among different cognitive tests. An alternative model proposes that overall intelligence (as measured by tests of intelligence; that is, "IQ tests") reflects the combination of various discrete cognitive processes, rather than a single factor that underlies them (e.g., Thompson 1951[52]). Whether EF reflects or contributes to "g" is a matter of continued debate. Regardless, the notion that EF is psychometrically related to other domains of cognition is well established. Isolating this clinically important cognitive domain with the use of neuropsychological tests, and examining its relation to specific brain regions is, therefore, complicated by the statistical correlation of EF test performance to performance on tests of other cognitive domains.

Not only have conceptual and statistical issues complicated the study of EF, the specific brain regions believed to be most principally involved in EF are becoming increasingly expanded. Classically, the frontal lobes (and prefrontal cortex) have been considered sine qua non of executive function. The most recent studies, however, have supported posterior brain region involvement, including the temporal, parietal, and cerebellar regions. Emerging is the assertion that complex higher-order cognition is represented by networks of meaningful and functionally active circuits. For example, working memory, which refers to the capacity to attend to and update information that is available for manipulation and conscious evaluation, is thought to largely depend on an intact dorsolateral prefrontal cortex.[53–55] However, working memory also engages attentional systems based in lateral and superior frontoparietal regions that include the ventrolateral

prefrontal cortex, intraparietal sulcus, and the supramarginal sulcus.[56,57]

In our review, we found that across a variety of neuropsychiatric disorders, frontal, parietal, and cerebellar regions were consistently associated with EF. Interestingly, a meta-analysis by Rottschy et al.[58] uncovered similarly correlated brain regions of increased fMRI activity during a working memory task. Taken together, their findings, similar to ours, might suggest a distributed network of regions involved in executive cognition. For example, information processing that is subserved by the parietal lobes may be required for successful performance of EF tasks. Indeed, lesion studies (e.g., Barbey et al.[59]) have found associations between parietal lobe lesions and EF task performance. In contrast, other studies have found relatively isolated EF task impairment as a result of ventromedial prefrontal and/or dorsolateral lesions.[60,61] Thus, elucidating specific aspects of EF that may require multiple brain areas (and are therefore associated with other cognitive skills) versus those that occur in isolation is an area for future study. Moreover, other brain structures, including the basal ganglia, temporal lobe, and other subcortical structures have also been implicated in EF. These studies continue to fuel further research.

Future studies might utilize other neuroimaging techniques to correlate EF—components within both large- and small-scale networks across diseases and health groups. The cognitive processes emerging from networks, then, span multiple cortical sites connected through afferent and efferent projections to the frontal lobes closely collaborating with each other and having overlapping functions. Complimentary multimodal neuroimaging techniques are set to identify more specific areas that may be part of this large-scale network. DTI and resting state fMRI methods, for example, are beginning to characterize the structural and functional connectivity between brain regions identified by white matter tracts that correlate with EF subdomains.[62–65]

As illustrated in this review, EF impairment has been recognized in a wide variety of neurological and psychiatric disorders. Neurological disease including neurodegenerative processes,[66–69] traumatic brain injury,[10,70] and vascular disease including stroke[71–73] are only some conditions that have reliably reported deficits in EF. Psychiatric disorders such as schizophrenia[74–76] and depression,[77–79] for example, have long noted significant changes in executive cognitive ability through the course of the disease. Changes to EF in these conditions and others have been important clinically because of their association to functional decline and disability. Cognitively engaging in and completing goal-directed tasks such as activities of daily living and complex decision-making tasks are known to be impaired in many of these conditions. Accordingly, an improved understanding of the phenomenology and biology of EF will be helpful in forming better diagnostic, treatment, and management strategies.

This review has several limitations. First, although we identified positive associations between tests of executive functioning and several brain regions, the associations were, by and large, weak to moderate. Some reasons for this may include the inherent limitations of the neuroimaging and neuro-computational methods (still early in development) as well as theoretical and practical limitations of test design and administration. Moreover, we caution interpretation of these studies and the correlations between neuropsychological tests and neuroimaging findings together. Because this was not a meta-analysis, comparing correlations found between different studies (particularly studies employing different neuroimaging methods) may be hazardous because it is still not entirely clear whether metabolic activity and atrophy, for example, can be reliably compared. Second, as we have identified several regions of associations, we note that the cerebellum was found to be related to tests of EF in only six of 36 papers. Although the current literature suggests an important role for the cerebellum in cognitive functioning, the results of this review may suggest caution in over-interpreting the role of this specific region as it relates to EF and other brain regions. Finally, a "network" by definition is interconnected. Even though the studies reviewed here have identified common regions, there is no summative evidence that these regions share common physio-biological "connections" per se. Though it is likely that that these connections do exist, it is the work of future research to identify them and describe their physical characteristics.

CONCLUSIONS

At the core of this review is our suggestion that impaired EF is a manifestation of a distributed network of brain regions that appear to be affected similarly by a variety of different underlying pathologies and identified by

a number of diagnostic modalities (imaging or clinical testing). Various imaging modalities as well as neuropsychological tests of EF have pointed to similar brain regions that may be linked functionally and anatomically. We hope that this study will help point toward different lines of evidence that seem to be converging on a common biological system.

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In a Future Issue

- Toward an Understanding of Decision Making in Severe Mental Illness
- Psychiatric Manifestations as Primary Symptoms of Neurosyphilis Among HIV-Negative Patients
- Association Between Clinical Measures and Florbetapir F18 PET Neuroimaging in Mild or Moderate Alzheimer's Disease Dementia
- Kissing or "Osculation" in Frontotemporal Dementia