An emerging role for epigenetic factors in relation to Executive Function

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Key Messages:

- Epigenetic Modification of Executive Function is currently under-studied
- Potential Epigenetic Modifications could act as biomarkers for several disorders
- Only 14 studies have examined this link to date, and larger studies are needed

1: The Genomics Research Centre (GRC) undertakes research on the genetic basis of disease through its unique population resources and the application of genetic studies to common, complex human disorders.

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Abstract

Background: Executive Function (EF) includes a range of decision making and higher order thinking processes. Although the genetic basis of EF has been studied and reviewed, epigenetic factors that influence EF are an emerging field of interest; here we summarise the current research. **Methods:** Work relating to different word combinations of "Executive Function" and "Epigenetic" were identified through three academic search directories. Inclusion criteria were: human populations, EF testing, epigenetic testing or genotyping related to epigenetic regulation. **Results:** To date, fourteen studies have been reported which examined epigenetic variation, in particular DNA methylation, in relation to EF assessments conducted in human subjects, with some positive associations found. Study populations included healthy cohorts, as well as psychiatric and neurological patient cohorts. **Conclusion:** Epigenetics in relation to EF is an emerging area of investigation with relatively few studies to date. Most assay DNA methylation, with some studies suggesting that epigenetic factors can be associated with EF. EF constitutes complex phenotypic and genotypic correlates that differ due to cohort attributes as well as the targeted task examined. Larger studies are required to further elucidate the contribution of epigenetic factors to EF with the identification of epigenetic modifications influencing EF having potential to provide new biomarkers for neuropsychiatric disorders.

Keywords: Executive Function, Working Memory, Epigenetics, Epigenetic Modification, Biomarkers, Cognitive Functions, Neuropsychiatric, Neurodegenerative

INTRODUCTION

Defining Executive Function

Executive Function (EF) includes a range of processes, predominantly cognitive processes leading to response inhibition, error processing, Working Memory (WM), and sustained attention [13, 97]. These functions, enable individuals to process complex decisions throughout their daily activities and operate in a goal-oriented behaviour, and are markedly localised in the frontal lobe [79]. WM is often considered as the accessible information crucial for performing consequent cognitive tasks, mainly originating through the differential roles of the frontal and parietal lobes [24]. The relationship between WM and EF is not an area of consensus, with different models used to define and relate the two in varying lights. Some explain EF to be a set of tasks that contribute to WM [114], whereas other define EF as a broad set of skills, including WM [15]. This review will consider the latter approach when considering what skills encompass EF.

Sustained attention is the ability to remain focused to one-goal in an environment with minimal external distractions [9] and requires the interaction between the frontoparietal and brain stem areas, with a major role played by noradrenaline [23, 32, 111]. Furthermore, as the outside world is constantly shifting and feeding the brain with new input, adapting to such changes in an appropriate manner, while modulating responses to suit the environment is largely dependent on an EF known as response inhibition [17]. Response inhibition is a particularly important EF as it is impaired in several neuropsychiatric disorders, including but not limited to, attention deficit hyperactivity disorder (ADHD), schizophrenia, obsessive compulsive disorder (OCD), and certain dementia subtypes [9, 25, 75, 106]. In dementia, the subset of

frontotemporal dementia (FTD) and particularly behavioural variant FTD is characterized by an executive dysfunction with a major focus on frontal functions [102]. In the Alzheimer's Disease (AD) dementia subtype, executive dysfunction occurs in later phases of development, and while typically the impairment is less than FTD cases, there is still a decrease in function from the general population [54, 115]. Error processing and performance monitoring is another aspect of EF whereby the individual has the capacity to continuously monitor their performance, screen it for errors based on implicit and explicit knowledge, and adjust behaviour accordingly [49, 98]. Acknowledgement and reacting to errors is primarily modulated by the dorsal anterior cingulate cortex (dACC), where individuals with higher activation of the dACC during error detection ultimately commit fewer errors [95, 105]

EF, or the impairment thereof, has been suggested to constitute a major endophenotype in numerous neuropsychiatric disorders, with response inhibition and WM prevalent examples in the literature. Consequently, biomarkers of the various aspects of EF could potentially provide insight into the diagnosis and treatment of EF disorders. In addition, EF testing is also relevant in healthy normal populations, as it can act as an indicator of several capacities including reasoning, higher-order thinking, and decision making and typical aging is accompanied by declines in various cognitive abilities including EF [99, 126].

Genetic Basis of EF

With respect to genetic heritability and its role in EF development, Friedman et al. found that EF development stays largely stable throughout adolescence and is influenced more by genetic than environmental factors [33]. A number of studies aiming to uncover the genetic component of EF have been conducted to date, with 4 major sub-categories of EF identified along with

their genetic markers as summarised in Barnes et al. [8], including a set of monoamine system genes (*DBH, DRD4, DRD2, 5-HTT, DAT1, COMT, MAO-A*) which are suggested to contribute to EF through distinctive pathways. In a genome wide association study (GWAS) for potential genetic variances influencing cognitive traits, two SNPs, rs2467774 and rs723686, located near hairy/enhancer-of-split related with YRPW motif 1 (*HEY1*) were shown to be significantly associated with EF and WM [58]. Mukherjee and colleagues also identified significant associations between resilience as an EF phenotype and two SNPs of *RNASE13* (rs3748346 and rs3748348) [81]. More recently, a GWAS of EF related SNPs found a significant association between the Cell Adhesion Molecule 2 (*CADM2*) gene SNP rs17518584 and EF performance and processing speed [52]. Despite the large sample size of this latter study, few SNPs attained genome-wide significance. While increasing the cohort size may identify further SNPs and gene loci involved in EF, rare variants and epigenetic factors may also contribute.

Epigenetic studies and EF

Epigenetics encompasses factors that influence expression of the genome, but which do not involve changes to the underlying DNA sequence. Epigenetic modifications include covalent modification of either the DNA, or the proteins that compose chromatin. The former includes the addition of methyl groups to cytosine residues in DNA [22, 42], which may also be actively reversed [67, 74], while the latter includes the post-translational modification of histones by acetylation, methylation, ubiquitination, and phosphorylation and histone variants [110]. Other epigenetic mechanisms include non-coding RNAs such as microRNAs and non-coding RNAs which can also regulate gene expression via effects on chromatin modification, transcription and translation [10, 80]. Recently, interest has grown as to whether, in addition to genetic variation, epigenetic factors may contribute to disease susceptibility or expression of traits.

Developmental plasticity, of which neuronal differentiation and cognitive development are crucial aspects, is attuned to the environment and adapts to it [37], with synaptic plasticity in hippocampal neurons of animals suggested to be regulated through DNA methylation [76]. Multiple strands of evidence also suggest that neural plasticity and the formation and maintenance of memory, which in turn impacts on EF, is mediated through various aspects of chromatin regulation [27, 46].

It is therefore reasonable to suggest that epigenetic modifications may play a role in memory traits and psychiatric disorders [108]. For example, DNA methylation contributes to age related cognitive decline in both Alzheimer's disease (AD) and normal aging brains [26, 72]**.** DNA methylation is mostly thought to exert its affect via its capacity to silence gene expression, which can be pathological if the gene is required to be expressed. In other instances methylation-linked silencing may ameliorate phenotypic expression resulting in a gain-of-function toxic RNA such as occurs in *fragile X mental retardation one 1* (*FMR1*) [20]. Interestingly, Halder et al. found changes in both histone modifications and DNA methylation during memory acquisition and learning in mice. In that study, the histone modifications showed global changes, while the changes in DNA methylation were more specific to plasticity-related genes, associated with alterations in gene expression and splicing, and required for the maintenance of memory [46]. Thus, DNA methylation is context-specific and can also affect gene regulation positively as well as negatively, in a gene- and loci-dependent manner [29].

Schizophrenia is a psychiatric disorder that has been studied extensively from a genetic and epigenetic perspective. Schizophrenia [21] and neurodegenerative disorders [40] in humans have been shown to be associated with DNA hypo-methylation and hyper-methylation [42] with polymorphisms in both the methylenetetrahydrofolate reductase (*MTHFR*) and catechol-

O-methyltransferase (*COMT*) genes associated with schizophrenia where epigenetic mechanisms are also postulated to contribute [1, 83, 103]. Specific genotypes of *MTHFR* that lead to lower methylation levels have been found to augment the risk for several neuropsychiatric disorders, some of which include EF impairment in their aetiology [36, 92]. In addition, DNA and histone methylation levels in neurons may be lowered when there is a shortage of methyl donors for methylation reactions, as a result of environmental or life style factors or due to genetic variations in methylating genes, or folate pathway genes [11, 108, 117].

Several studies have also linked methylation and methylation of histone to neuronal gene expression, learning, memory and cognitive functions [39, 43-45, 62, 93]. Some genes, such as *HES1*, have been confirmed to play a crucial role in neuronal differentiation, and subsequent cognitive functions [7, 55]. Studying the epigenetic processes of these genes could provide valuable information regarding the specific mechanisms by which the gene is expressed or silenced in relation to neuropsychological phenotypes. Thus, epigenetics provides another layer of information with respect to genes and their regulation. Consequently, linking phenotypes with factors that influence the expression of a gene of interest may provide more substantial information about its role and clinical significance and may have potential as biomarkers for the identification of risk of disease development [123].

Challenges facing EF epigenetic studies

Gene expression processes cannot be traced in the living human brain. However, advances in brain imaging have allowed researchers to study brain activity while performing tasks (e.g. that require EF), providing information to augment genotyping data and create a more

comprehensive view [104]**.** Complications in interpreting epigenetic studies may include that executive dysfunction can be an endophenotype to the onset of a disorder, and the same phenotype may result via different methylation markers. Epigenetic markers are usually not heritable as a genetic variation, but can change in response to environmental stressors, medications, as well as the onset of other disorders. Further complicating the influence of methylation changes on EF is the fact that DNA global methylation levels change in the brain as an individual ages [47, 89], making it challenging to differentiate between normal changes and those induced by pathology. DNA methylation patterns are also tissue-specific [69], although recent evidence suggests that some methylation patterns are conserved between different tissue varieties [12, 85, 112, 116]. This is particularly relevant to methylation that arises early in development, possibly in response to environmental input [116]. For example, methylation patterns that are identical in brain tissues and peripheral blood cells [34], paired with phenotyping, could be a more accurate way to track the development and treatment of certain neuropsychological disorders.

However, epigenetics in relation to EF is still an emerging area in which few studies have been conducted. One particular theory that has been recently proposed, is the impact of early environmental cues on gene expression of neuropsychological phenotypes, including EF [69]. Little evidence has yet emerged from human studies, but animal models have been useful in exploring epigenetic modifications in relation to EF and related functions.

Epigenetic modifications and EF-related traits in animal models

With regards to WM, training mice on WM tasks has been identified to lead to epigenetic changes (methylation and acetylation) across dorsomedial and dorsomedial thalamus brain

regions in a murine model [16]. Interestingly, this WM model did not induce epigenetic changes in the prefrontal cortex region, despite evidence from other studies indicating regarding its involvement in WM and EF in general [96, 122, 124]. Another study by Jacovcevski and colleagues [53] demonstrated that a mouse model of WM depends on synaptic facilitation and temporal summation plasticity processes and that this plasticity is significantly modulated through histone H3K4 methylation mediated by the *Mll1 gene,* which in turn affects expression at a particular gene loci e.g. the homeodomain transcription factor *Meis2*. In a study by Mitchell et al., occupancy of promoters and enhancers with the transcription factor *Mefc2* was shown to be linked to chromatin modifications, including histone H3K4 methylation, influencing regulation of neuron-specific genes and enhancement of WM in mice, adding further evidence that WM, and thus EF, is dependent on epigenetic changes [78].

To date, the link between environmental factors and epigenetic changes linked to EF has been best studied through animal models, mostly linking diet and early stressors to methylation levels and subsequent EF changes [41, 86]. Interestingly, mouse models have identified obesity to induce memory impairments by inducing alterations in DNA methylation of memory-associated genes such as Sirt1, which can be reversed by a diet supplemented with the SIRT1-activating molecule resveratrol [48]. Moreover, methyl donor supplementation in young mice has been shown to ameliorate EF deficits in offspring exposed to a maternal high fat diet [73], and with exercise shown to modulate the levels of epigenetic changes implicated in EF dysfunction disorders [5]. Similarly, schizophrenia mouse models have shown correlations between early environmental stressors and epigenetic changes in the prefrontal cortex, leading to schizophrenia symptoms [88]. Using an established prenatal immune challenge mouse model Labouesse and colleagues reported hypermethylation of the *GAD1* and *GAD2* promoters which accompanied impairments in WM and social interaction associated with infection [65],

suggesting a mechanism by which maternal infection causes GABAergic impairments and associated behavioural and cognitive abnormalities in offspring.

Aims of the study

In this study, we review the literature from research studies on human populations linking epigenetics to EF through the systematic collation of studies in which assays of EF were correlated with a measure of epigenetic modification at genomic loci.

Methods

This review followed a systematic review analysis procedure**.** The following search terms were entered into PubMed, Scopus, and Web of Science academic search engines: (“Executive Function” AND “Epigenetics), (“Executive Function” AND “Methylation”), (“Frontal Functions” AND “Epigenetics”), (“Frontal Functions” AND “Methylation”). Another search was conducted by EF subtype; (“Sustained Attention” AND “Epigenetics”), (“Response Inhibition” AND “Epigenetics”), (“Error Processing” AND “Epigenetics”), (“Working Memory” AND “Epigenetics”)**.** Then, a search was done by commonly used EF assessments: (“Frontal Assessment Battery” AND Epigenetics), (“CANTAB” AND “Epigenetics”), ("Trail Making Test" AND (epigenetic* OR methylation), ("Wisconsin Card Sorting Test" AND (epigenetic*), (“Executive Function” OR “Working Memory”) AND (“Mouse Model” OR “Animal Model”) AND (“epigenetic*” OR “Methylation”), ("Executive Function" OR "Working Memory" OR "Response Inhibition" OR "Sustained Attention") AND ("Mouse" OR "Mouse Model" OR "Animal Model") AND ("Epigenetic" OR "Methylation").

Inclusion criteria

Every search resulted in a number of articles, the maximum being 48. This number made it possible to manually peruse each article prior to inclusion. The inclusion criteria derived from the aims of the study included were: studies using human population cohorts, EF measures, and an epigenetics assay, or a polymorphism linked to epigenetic regulation. The authors acknowledge that a number of animal studies have been conducted in this area, and these were included in the search terms. However, as animal EF models do not always translate to human cognitive equivalents, they were not systematically reviewed, but are summarised and referenced throughout this review to provide the readers with the broader context. Furthermore, studies that did not consider specific EF or WM measures but rather general psychiatric measures that implicitly indicate EF dysfunction (schizophrenia scales or psychosis episodes) were not included. The rationale behind this exclusion was that such measures do not specify which areas of EF are affected and hence cannot be related to non-clinical populations. Studies included only included those that tested for an association between the measured EF and the proposed epigenetic regulation.

RESULTS

Following the search criteria, a total of 14 studies were included with their parameters summarised in Table 1 with a systematic review summary of the elements from each study outlined below.

Cohorts: age, participants' inclusion criteria

From the studies examined, four consisted of healthy population cohorts [42, 118, 119, 123], while one study consisted of a cohort of healthy monozygotic twins [19]; all of these cohorts excluded individuals with any psychiatric or neurological disorders. The other nine studies included cohorts of specific neuropsychiatric, developmental, or cognitive disorders, with some studies including healthy cohorts as normal controls as summarised in Table 1.

Executive Functions assessed

With regards to EF testing: three studies used the Frontal Assessment Battery (FAB) [3, 59, 87]; four studies used WM tests n-back, digit span and letter numbering of WAIS-III, digit ordering, with one study assessing WM through the Sternberg Item Recognition Paradigm [19, 68, 118, 119]; two studies used the Cambridge Neuropsychological Test Automated battery (CANTAB) which included CANTAB Delayed Matching to Subject (DMS), Intra-Extra Dimensional Set Shift (IED) and Spatial Span (SSP) tests [100, 101]; one study used both the Stroop [121] and concept shifting tests [120]; one used Hayling sequence [14], Excluded Letter Verbal Fluency (ELVF) [63] and Letter Number Sequencing (LNS) [125]; and two used the Antisaccade test [30, 107].

Tissue collection for genetic and epigenetic assessments

With respect to source of DNA, the majority of studies obtained pre-mortem peripheral blood samples to isolate and analyse genomic DNA for methylation assays or genotyping. Levine et al. [68] assessed DNA methylation in anatomical post-mortem brain tissues.

Assessment of epigenetic modifications

1) Gene based DNA methylation.

Two studies [87, 119] examined epigenetic mechanisms related to the Brain-Derived Neurotrophic Factor (*BDNF*) gene. Nagata et al. [87] studied the methylation of one of the promotor regions of the *BDNF* gene, while Ursini et al. [119] studied the methylation specifically at the rs6265 polymorphism of *BDNF*, which is at a CpG dinucleotide.

Three studies [3, 118, 123] examined the correlation between methylation of Catechol-O-methyltransferase (*COMT*) gene and EF. Walton et al. [123] narrowed their search to DNA methylation at the promoter of the Membrane bound isoform (MB) of COMT (MB-COMT), while Ursini et al. [118] focused on methylation at the *COMT* missense variant rs4680, which is also at a CpG dinucleotide. Alelú-Paz et al. [3] studied the DNA methylation of promoter regions of 19 different genes, and concluded that levels of methylation at the *COMT* and *MTHFR* promoters were associated with EF.

Four more studies selected other specific genes and tested for association with EF. Cornish et al [20] studied the association of DNA methylation levels in intron 1 of the *FMR1* gene with EF, while Shelton and colleagues [107] examined the methylation levels at the exon 1/intron 1 boundary of the same gene. Using a genome-wide approach Kobayashi et al. [59] identified significantly differentially methylated CpGs in the Non-SMC Condensin II complex, subunit H2 (*NCAPH2*)/lipase maturation factor 2 (*LMF2*) gene promoter region (Illumina 450K array probe cg25152348), and in the Coenzyme A Synthase (*COASY*) gene (cg01765799), between controls and individuals with amnesic mild cognitive impairment or AD. Using a methylation array targeted at promoter regions, Lillycrop et al. [69] identified the hairy and enhancer of split-1 (*HES1*) promoter as differentially methylated with respect to cognitive performance and

validated 9 CpGs with higher EF memory function in two independent cohorts of children. Finally, Cordova-Palomera et al. [19] studied methylation levels of 248 CpG sites at four regions of the *Insulin Like Growth Factor 2 (IGF2)* and the *IGF2 binding proteins 1-3* (*IGF2BP1, IGF2BP2, IGFBP3)* genes.

2) Global/tissue based methylation

Levine at al. [68] studied global DNA methylation levels, through the epigenetic age, of the Pre-Frontal Cortex (PFC), where some EFs are localized in relation to performance of these functions. The epigenetic age of the PFC is determined by averaging the DNA methylation levels at 353 specific CpGs determined using genome-wide methylation arrays [50]. Groot et al. [42] explored global DNA methylation levels from peripheral blood leucocytes at baseline and their association with EF.

3) Specific SNPs that affect DNA and intracellular methylation

In addition to global methylation levels, Groot et al. [42], and three other studies [61, 103] linked a functional polymorphism of the Methylenetetrahydrofolate reductase *MTHFR* gene to EF. This variant, *MTHFR* SNP rs1801133 (677 C>T) reduces MTHFR protein activity by almost 35%, causing global DNA hypomethylation [35].

Associations of epigenetic modifications and executive functions

As seen in Table 1, the association between the selected epigenetic assays and corresponding EF varied across the studies, with three studies finding significant negative associations and

seven studies identifying positive associations of the epigenetic marker studied with EF traits. Four studies found no significant correlation between the epigenetic modification and the selected EF examined [42, 87, 118, 123].

Inclusion of Covariates in analyses

EF is considered a developmental set of traits, that change with the different stages of lifespan development [51]. Further, age and educational level have been shown to potentially influence EF measures [94, 99]. Another variable that is suggested to influence EF measures is IQ [6]. Hence, exploring the relation between EF and other molecular markers needs to account for these variables. The studies with significant associations seemed to include these relevant covariates in their analyses. Of the negative association studies, Kobayashi and colleagues [59] used age and gender as covariates in their cohorts that encompassed healthy and AD individuals, whereas Lillycrop and colleagues [69] included further covariates as the subjects IQ and BMI, with Groot and colleagues [42] including a range of covariates that related to their cohort, including smoking, alcohol consumption, sociodemographics and physical activity. As for the positive association studies, Cornish and colleagues [20] Urisini and colleagues [119], and Alelu-Paz and colleagues [3] did not include covariates in their analyses, whereas the other studies included covariates that were consistent with their population demographics.

Meta-analysis potential

When we considered the potential for a meta-analysis of markers based on the existing cohorts and the data extracted from the reviewed studies, few studies were identified to have examined

the same markers and phenotypes within the same cohort type, as such, a meta-analysis of the results was not feasible.

DISCUSSION

The majority of the studies included in this study assessed EF as part of either an EF specific battery of tests or as wider-scale cognitive functioning testing. The main epigenetic modification investigated in relation to EF to date is DNA methylation which reflects the relative ease of examination of this epigenetic modification, particularly in stored samples. Furthermore, with the exception of the study by Levine *et al*. on post-mortem brain samples, the majority of studies investigated DNA methylation in blood, due to the difficulty in accessing appropriate tissues for other cell types for human studies. In addition, the majority of studies of epigenetic modifications in relation to EF traits undertaken to date have been on small sample cohorts. The largest was that of Levine *et al.* who assayed PFC age according to DNA methylation from arrays, and related it to WM scores in 700 older individuals, including 300 AD individuals [68].

Following our summary of the reviewed papers (Table 1), we present the following analysis of the most recent literature regarding epigenetics and EF. As the study populations were heterogeneous among the studies, we have divided the cohorts into healthy, neurodegenerative, and psychiatric cohorts for clarity in the discussion.

Healthy populations: Karlsgodt *et al*. suggest that WM is the product of a dynamic interaction between genes and environment with environmental factors resulting in changes in cognitive functions via their impact on DNA methylation, which can be counteracted or compensated for

through other mechanisms [56]. Environmental factors also affect hippocampal plasticity, which in turn influences WM [71]. Cordova-Palomera *et al*. [19] found that WM is negatively influenced by the methylation levels of *IGF2*, which is highly susceptible to developmental and environmental influences, especially early in life [91]. This is similar to the findings of Ursini *et al*. regarding methylation of *COMT* and WM function [118]. COMT is the key enzyme for inactivation of prefrontal dopamine with lower dopamine levels associated with reduced prefrontal efficiency and correlated with poorer WM performance [38]. Barnes *et al.* previously reviewed associations between particular *COMT* genetic variants and EF performance [8]. Walton *et al.* reported that WM is associated with methylation of the *COMT* promoter [123], but cautioning that the relationship between DNA methylation in peripheral tissues and the brain is not yet clearly established. In contrast Ursini *et al.* did not find an association between methylation at the *COMT* promoter and WM, although the study did find that *COMT* methylation at rs4680, a SNP at a CpG dinucleotide which therefore affects methylation, was found to positively influence WM [118]. The rs4680 SNP results in either a Val- or Met-encoded allele, the latter no longer a CpG site and therefore not methylated. The ancestral Val allele is associated with greater enzyme activity and reduced efficiency of prefrontal activity during WM tasks [18, 28]. *Ursini et al.* found that methylation of the high-activity Val allele is inversely related to *COMT* expression and therefore partially compensates its negative effects on prefrontal cognition and activity [118]. Ursini *et al*. also included lifetime stress and its effect on methylation, consistent with the premise that early and later environmental factors affect DNA methylation [77, 84]. The association relates to both the genetic variation and methylation which adds complexity to dissecting the mechanism. A similar interaction between genotype and methylation was observed by Ursini and colleagues [119] in relation to WM and *BDNF* at the rs6265 SNP, where increased methylation in Val/Val individuals correlated with WM accuracy. Further, they explored the impact of hypoxia-related

events on methylation, finding in line with other studies reviewed here, that specific environmental factors or life events influenced methylation levels.

On the same developmental note, the level of *HES1* methylation obtained from perinatal umbilical cord cells is associated with EF later in life for children, contributing to the growing evidence of a role for epigenetics in neural plasticity [69]. Further findings from this study suggest that methylation of different CpGs have different influences on neuropsychological correlates. For example, methylation at CpG5 of *HES1* had the highest association with cognitive functions including executive ones, and was found to block the binding of an ETS transcription factor to the CpG region, suggesting a mechanism through which methylation is exerting its effect [4]. These results suggest that the *HES1* gene, a notch target family gene, could be implicated in EF through interacting with another gene of the same family, *HEY1*, identified by Knowles and colleagues to have a potential role in EF [58]. While the studies of Cordova-Palomera *et al*. and Lillycrop *et al.* describe interactions between perinatal or early childhood influences, epigenetic modifications, and cognitive functions [19, 69], further research is needed to explore the details of such interactions in larger and different populations.

While the studies described above focussed on particular gene loci, some studies investigated the effect of more global changes in DNA methylation. The C667T variant in the *MTHFR* gene reduces its enzymatic activity by almost 35%, causing global DNA methylation reduction [35]. This variant has been found to decrease cognitive function and increase the risk of neuropsychiatric illnesses [36, 92]. In both healthy and schizophrenic populations, Roffman *et al*. [103] implicated epigenetic mechanisms on brain plasticity and specifically error response, as the *MTHFR* C667T allele induces a dose-dependent blunting of activation of the dACC, where the EF of error processing is mainly located. Groot *et al.* [42] studied the impact of the same *MTHFR* variant on global DNA methylation for association with cognitive functions

including EF measured by the STROOP, concept shifting and letter-digit substitution tests, but found no significant results. They suggested that these negative results may reflect the fact that DNA methylation is narrowly distributed among healthy individuals [60], and that focussing on DNA methylation patterns at specific loci might be more relevant [42].

Alzheimer's Disease and Mild Cognitive Impairment Populations: Neurodegenerative disorders, like AD, have been at the forefront of neurological epigenetics research. Recent studies have begun exploring epigenetic modifications, not just with respect to neural differentiation, but also extending it to risk, diagnosis, and clinical presentation of AD. As a previous study showed no alterations in global methylation levels in AD [66], Kobayashi and colleagues [59] explored the utility of methylation levels at specific loci as biomarkers for AD. Their study found an association between both general mental state and EF, which are impaired in AD, with the methylation of the *NCAPH2/LMF2* promoter region and therefore identified a potential biomarker which may be used to assist in detecting disease. Despite previous studies finding no association between global DNA methylation and AD, Levine and colleagues [68] examined methylation of the pre-frontal cortex (PFC) through the epigenetic age determined from multiple loci from Illumina 450K methylation array data sets. This revealed another potential epigenetic-based biomarker for AD through the finding of a significant association between the PFC epigenetic changes related to ageing as measured by levels of DNA methylation at particular sites, with cognitive functions and WM.

Nagata and colleagues [87] examined the epigenetic modification of *BDNF*, a gene crucial to the functioning of neural cells [70]. While they found significantly higher DNA methylation at the CpG4 site in the *BDNF* promoter in AD patients compared to controls, and a significant negative correlation between methylation at this same CpG and the prehension behaviour score

subtest, they did not find a significant correlation of CpG4 methylation levels with the other FAB subtest scores measuring complex EF such as conceptualization, sensitivity to interference and inhibitory control, or the overall FAB score [87].

Women with a premutation of the *FMR1* gene, i.e. an expansion of the CGG repeats in *FMR1* to between 55 and 199, show high rates of dysexecutive symptoms [64]. Cornish et al [20] and Shelton *et al.* [107] studied methylation of regions of *FMR1* and found that, in particular, levels of methylation in intron 1 of *FMR1* could be used to dichotomise permutation women into greater and lower risk categories for impaired EF and downstream psychiatric symptoms, which has implications for risk estimates and early interventions to improve outcomes for these women and their families [20].

Neuropsychiatric Populations: Cognitive functions have been established as endophenotypes of psychiatric disorders, with the majority of studies focussed on schizophrenia. As such it was not surprising to find studies correlating the genetic or epigenetic bases of such functions to schizophrenia risk. Three studies [61, 103, 123] explored common schizophrenia risk genes and their epigenetic modification in relation to EFs in schizophrenic patients. They concluded that similar to the genetic component, the DNA methylation of *COMT* and *MTHFR* can be a predictor of schizophrenia risk. Two isoforms are expressed from the *COMT* locus, a cytosolic soluble isoform (S-COMT) and a membrane-bound form (MB-COMT). Mice generated deficient for MB-COMT were found to be sensitive to pain and have short-term memory defects, and male mice additionally displayed a distinct endophenotype with schizophrenia-related behaviours such as aggressive behaviour and prepulse inhibition [113]. Thus, epigenetic modifications may affect the relative levels of the S-COMT and MB-COMT forms. Walton and colleagues note that understanding epigenetic modifications in light of corresponding brain

functional activation might hold the key to further understanding the specific role of a gene [123], especially if the significance of genetic associations with risk fails to reach consensus, as in the case of *COMT* with schizophrenia [31, 82, 90].

While epigenetic regulation of both *MTHFR* and *COMT* has been implicated in EF performance in both healthy and psychiatric populations detecting changes that could be used to develop specific biomarkers for dysfunction or disease in the studies presented to date is questionable. In a pilot study, Alelú-Paz *et al.* performed a genome-wide analysis of DNA methylation in post-mortem brain samples taken from three regions of the brain (the dorsolateral prefrontal cortex, the hippocampus, and the anterior cingulate cortex) and compared schizophrenic patients with severe cognitive measures with controls [2]. Differentially methylated CpG sites were identified a a number of genes, including some known to be important in neurotransmission and signal transduction, but interestingly these were specific, even to the region of the brain analysed. Furthermore, the sites did not correlate with those previously identified in peripheral blood samples [57], highlighting that epigenetic signatures likely differ depending on the tissue analysed and the level of change. While studies of brain tissues such as that by Alelú-Paz *et al.* will be important for understanding the biology of EF and disorders related to EF impairments [2], developing molecular biomarkers will require minimally invasive methods.

CONCLUSION

We have summarised the relevant literature from the last three years examining the epigenetics of EF, an emerging area of interest in our understanding of the factors regulating cognition. The interest in EF and its regulation may be attributed to the growing interest of the contribution

epigenetic phenomena to the expression of complex traits, as well as the increasing evidence relating EF to psychiatric disorders as endophenotypes. Epigenetics is also a potentially feasible area to explore in treating psychiatric disorders, as epigenetic processes are potentially targetable by interventions [109]. Despite the recent increase in the number of studies combining these areas of investigation, there is still further research needed to develop robust epigenetic biomarkers for EF performance and neurodegenerative and neuropsychiatric disorders.

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