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Citation for published version:

Amorim, IS, Lach, G & Gkogkas, CG 2018, 'The Role of the Eukaryotic Translation Initiation Factor 4E (eIF4E) in Neuropsychiatric Disorders' *Frontiers in genetics*, vol. 9, 561. DOI: 10.3389/fgene.2018.00561

Digital Object Identifier (DOI):

[10.3389/fgene.2018.00561](https://doi.org/10.3389/fgene.2018.00561)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Frontiers in genetics

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The Role of the Eukaryotic Translation Initiation Factor 4E (eIF4E) in Neuropsychiatric Disorders

Inês S. Amorim¹, Gilliard Lach¹ and Christos G. Gkogkas^{1,2*}

¹ Centre for Discovery Brain Sciences, The University of Edinburgh, Edinburgh, United Kingdom, ² The Patrick Wild Centre, The University of Edinburgh, Edinburgh, United Kingdom

Protein synthesis in eukaryotic cells is a complex, multi-step and tightly regulated process. Translation initiation, the rate limiting step in protein synthesis, is dependent on the activity of eukaryotic translation Initiation Factor 4E (eIF4E). eIF4E is the cap-binding protein which, in synergy with proteins such as the helicase eIF4A and the scaffolding protein eIF4G, binds to mRNA, allowing the recruitment of ribosomes and translation initiation. The function of eIF4E is tightly regulated in cells under normal physiological conditions and can be controlled by post-translational modifications, such as phosphorylation, and by the binding of inhibitory proteins, including eIF4E binding proteins (4E-BPs) and CYFIP1. Recent studies have highlighted the importance of eIF4E in normal or aberrant function of the nervous system. In this mini-review, we will highlight the role of eIF4E function and regulation in the pathophysiology of neurodevelopmental and neuropsychiatric disorders.

Keywords: eIF4E, neurodevelopmental/neuropsychiatric disorders, anxiety, depression, protein synthesis, translation, Autism Spectrum Disorders, Fragile X Syndrome

OPEN ACCESS

Edited by:

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RIKEN, Japan

*Correspondence:

Christos G. Gkogkas
christos.gkogkas@ed.ac.uk

Specialty section:

This article was submitted to
RNA,
a section of the journal
Frontiers in Genetics

Received: 14 September 2018

Accepted: 06 November 2018

Published: 23 November 2018

Citation:

Amorim IS, Lach G and
Gkogkas CG (2018) The Role of the
Eukaryotic Translation Initiation Factor
4E (eIF4E) in Neuropsychiatric
Disorders. *Front. Genet.* 9:561.
doi: 10.3389/fgene.2018.00561

INTRODUCTION

In Archaea and Bacteria, the mRNA Shine-Dalgarno sequence promotes binding of the ribosome to mRNA and thus translation initiates (Shine and Dalgarno, 1975). Contrary to that, the majority of eukaryotic precursor mRNAs harbor a 5' end cap, a 7 methylguanosine triphosphate (m⁷GpppG) structure, which serves as a docking point for eukaryotic translation initiation factors (eIFs) (Furuichi and Miura, 1975; Shatkin, 1976; Furuichi et al., 1977; Sonenberg et al., 1979). eIF4E directly binds the mRNA 5' cap (Sonenberg et al., 1979) and interacts with the scaffolding protein eIF4G, which in turn binds the helicase eIF4A to form the eIF4F complex and allow the recruitment of ribosomes to initiate the predominant form of eukaryotic translation: cap-dependent translation (Gingras et al., 1999). eIF4G provides the backbone of the eIF4F complex. In addition, it helps to circularize mRNAs through its interaction with poly(A) binding proteins (PABPs) and provides a binding site for other regulatory factors, such as MAP kinase-interacting serine/threonine-protein kinases 1/2 (MNK1/2) and eukaryotic Initiation Factor 3 (eIF3). The eIF4A helicase unwinds secondary structures present in the mRNA 5' Untranslated Regions (UTRs) to facilitate translation. eIF4A helicase activity is promoted by eIF4G and eIF4B (Gingras et al., 1999), as well as eIF4E (Feoktistova et al., 2013).

Cap-dependent translation is responsible for the bulk of protein synthesis in eukaryotic cells, and is the rate limiting step in protein synthesis. Crucially, eIF4E and the eIF4F complex carry a well-conserved function in eukaryotes, where they preferentially regulate the synthesis of a subset of proteins, by controlling mRNA translation initiation (Pelletier and Sonenberg, 1987; Sonenberg and Hinnebusch, 2007, 2009; Hinnebusch et al., 2016). Thus, the term “eIF4E/eIF4F-sensitive” mRNAs has emerged (Hinnebusch et al., 2016). Consequently, eIF4E activity is tightly regulated by a variety of factors such as hormones, growth factors, cytokines and other extracellular stimuli, which converge on two major signaling cascades: MAPK/ERK and PI3K/mTOR pathways (Joshi and Platanias, 2014; Saxton and Sabatini, 2017; Figure 1).

The PI3K/mTOR pathway regulates eIF4E function via the action of eIF4E-binding proteins (4E-BPs) (Pause et al., 1994). 4E-BPs compete with eIF4G for binding on the dorsal surface of eIF4E, hence disrupting the formation of the eIF4F complex (Pause et al., 1994). Hypo-phosphorylated 4E-BPs have a higher affinity for eIF4E and thus repress translation initiation (Gingras et al., 2001). Conversely, activation of PI3K/mTOR signaling

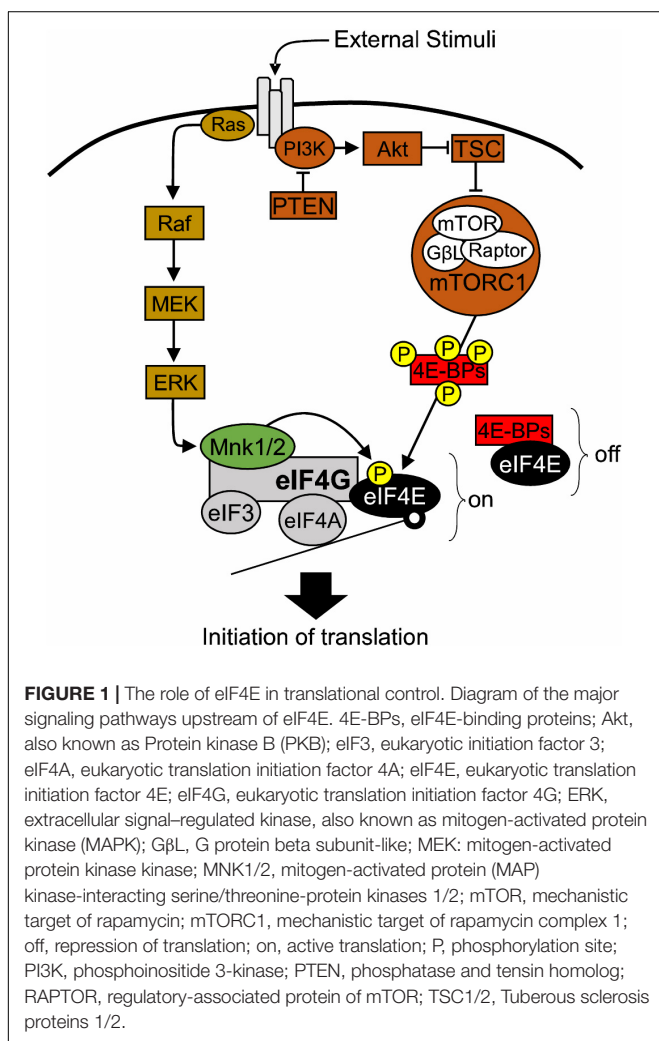
leading to downstream phosphorylation of 4E-BPs by mTORC1, triggers the release of 4E-BPs from eIF4E. As a result, the availability of eIF4E for initiation increases (Haghighat et al., 1995; Richter and Sonenberg, 2005).

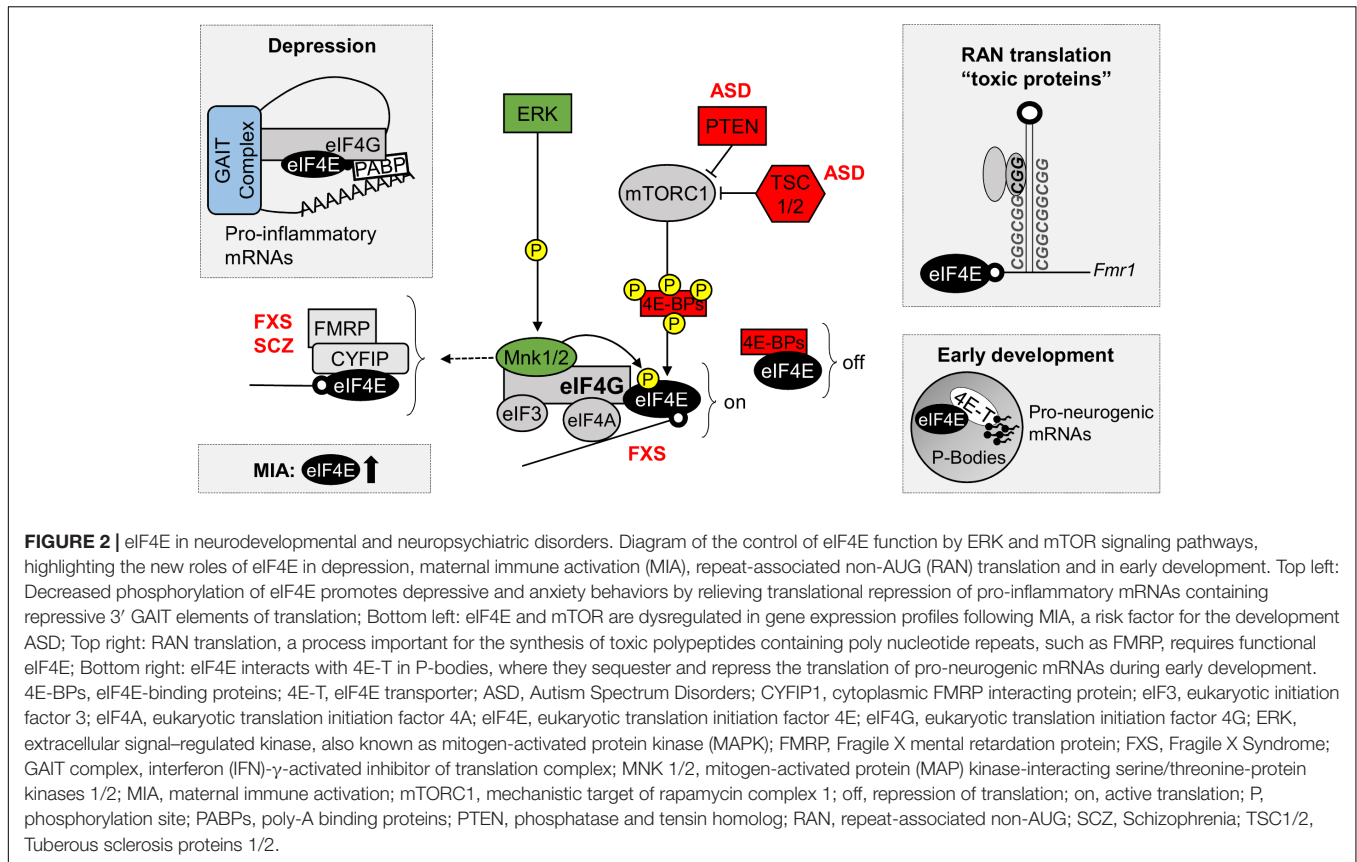
Activation of MAPK/ERK pathway leads to phosphorylation of eIF4E at the Serine 209 residue by MNK1/2 (Joshi et al., 1995; Ueda et al., 2004). MNK1/2 are recruited to the eIF4F complex by binding to the c-terminal domain of eIF4G, where they promote the phosphorylation of eIF4E (Pyronnet et al., 1999; Shveygert et al., 2010). While two studies suggested that eIF4E phosphorylation is either not required for translation (McKendrick et al., 2001) or that it decreases cap-dependent translation (Knauf et al., 2001), the majority of the literature suggests that eIF4E phosphorylation promotes initiation (Pyronnet et al., 1999; Lachance et al., 2002; Panja et al., 2014; Bramham et al., 2016). Moreover, several studies have identified phospho-eIF4E-sensitive mRNAs in cancer (Furic et al., 2010; Grzmiel et al., 2011; Konicek et al., 2011; Robichaud et al., 2015) and in the nervous system (Gkogkas et al., 2014; Cao et al., 2015; Amorim et al., 2018). eIF4F complex formation is also affected by sequestering eIF4E in a repressive complex with the Fragile X Mental Retardation Protein (FMRP) and the Cytoplasmic FMRP Interacting Protein (CYFIP1) (Napoli et al., 2008). The eIF4E-CYFIP complex is sensitive to MNK1/2 activity and precludes eIF4E-eIF4G binding, thus hindering translation initiation (Napoli et al., 2008; Panja et al., 2014; Genheden et al., 2015; Bramham et al., 2016).

eIF4E-dependent translational control is linked to several cellular processes, including cell cycle progression, cell survival, cell motility and tumorigenesis (Rhoads et al., 1993; Malka-Mahieu et al., 2017; Steinberger et al., 2017), as well as inflammation, immunity and viral infection (Jan et al., 2016; Hoang et al., 2018). Nevertheless, a growing body of evidence indicates eIF4E-dependent translation is important for neuronal cell function and implicates its aberrant function in nervous system disorders (Figure 2), such as neurodevelopmental and neuropsychiatric conditions (Costa-Mattioli and Monteggia, 2013; Santini and Klann, 2014; St Clair and Johnstone, 2018).

AUTISM SPECTRUM DISORDERS (ASD) AND FRAGILE X SYNDROME (FXS)

Autism Spectrum Disorders are a group of heterogeneous neurodevelopmental conditions characterized by persistent deficits in sociability, impaired communication, and the presence of restricted or repetitive stereotypical behaviors (Elsabbagh et al., 2012). ASDs are amongst the most common neurodevelopmental disorders, with an estimated prevalence of 16:1000 in children aged 8 years in the United States and high heritability (Sandin et al., 2017; Baio et al., 2018). ASDs have been linked to a variety of genetic mutations and risk factors, including genetic variants in conditions such as Rett syndrome, Tuberous Sclerosis and FXS (Carter and Scherer, 2013). FXS is one of the most common inherited forms of intellectual disability and is the leading genetic cause of ASDs (Gabis et al., 2011; McCary and Roberts, 2013). FXS is caused by a mutation (CGG nucleotide repeats) in the 5'





UTR of the *FMR1* gene, leading to transcriptional silencing of *FMR1* and subsequent loss of FMRP expression (Santoro et al., 2012). FMRP is a translational repressor, thus its loss engenders an across the board increase in protein synthesis (Li et al., 2001). Protein synthesis-linked hyperactivation of type I metabotropic glutamate receptors (mGluRs), leading to synaptic dysfunction, constitutes the predominant mechanistic theory aiming to explain the diverse pathophysiology of FXS (Bear, 2005).

Likewise, ASD is believed to arise from common downstream defects in synaptic function and brain connectivity (Abrahams and Geschwind, 2008). A leading hypothesis posits that downstream defects in mRNA translation lead to aberrant local protein synthesis, which results in altered synaptic development and plasticity (Kelleher and Bear, 2008; Gkogkas and Sonenberg, 2013). In accordance, patients and animal models of ASD and FXS show widespread alterations in synaptic plasticity and dysregulated mRNA translation (Kelleher and Bear, 2008; Jung et al., 2014; Contractor et al., 2015; Dahlhaus, 2018). Altered translation in ASD and FXS results not only from mutations in genes that directly impact on translational control mechanisms, but also from altered signaling, upstream of translation (MAPK/ERK and PI3K/mTOR) (Costa-Mattoli and Monteggia, 2013). A pivotal convergence point of these pathways is the control of cap-dependent translation, particularly through the function of the eIF4F complex.

Abnormalities in the *EIF4E* locus have been identified in genetic studies of autistic patients (Yonan et al., 2003;

Neves-Pereira et al., 2009; Waltes et al., 2014). Moreover, a comparison of gene-expression in rodent models of maternal immune activation (MIA) with ASD patient cortical gene-expression revealed a strong involvement of the *Tsc2*/mTOR/eIF4E axis (Lombardo et al., 2018). MIA during the first trimester of pregnancy increases the risk for ASD most likely by affecting fetal brain development. Notwithstanding some epidemiological evidence, there is no compelling, direct link of *EIF4E* to ASDs. Nonetheless, several reports from animal models of ASD provide strong evidence for a key role of *Eif4e* in ASD. Deletion of *Eif4ebp2* (the predominant 4E-BP in the brain) or overexpression of *Eif4e* in mice lead to altered synaptic excitation/inhibition balance and altered behaviors, such as social interaction deficits, altered ultrasonic vocalizations, and repetitive/stereotyped behaviors (Gkogkas et al., 2013; Santini et al., 2013). Molecular, electrophysiological and behavioral defects in mice, which are reminiscent of ASD phenotypes diagnosed in patients, could be normalized by inhibition of cap-dependent translation using 4EGI-1 (Gkogkas et al., 2013; Santini et al., 2013), a small molecule developed as an eIF4E-eIF4G interaction inhibitor (Moerke et al., 2007). Recent work revealed that type I mGluR agonists, which were proposed as FXS therapeutics, also rescue phenotypes reminiscent of ASD in *Eif4ebp2* knockout mice (Aguilar-Valles et al., 2015). Furthermore, 4EGI-1 has shown beneficial effects in *Fmr1*^{-/-} mice, a model of FXS, where it reversed contextual memory deficits

and normalized altered dendritic morphology, dysregulated actin dynamics and exaggerated mGluR-dependent LTD (Santini et al., 2017). Interestingly, crossing *Fmr1*^{-/y} mice with *Eif4e* overexpressing mice engenders cognitive impairments in addition to ASD-like phenotypes (Huynh et al., 2015).

Regulation of eIF4E by phosphorylation is associated with FXS. Patients and animal models of FXS show increased levels of phosphorylated eIF4E (Hoeffler et al., 2012; Gkogkas et al., 2014; Sidhu et al., 2014). Moreover, genetic deletion of the MNK1/2 kinases, which phosphorylate eIF4E, administration of the MNK1/2 inhibitor cercosporamide, or substitution of the eIF4E phosphorylation site for a non-phosphorylatable residue (*Eif4e*^{ki/ki} mice; Ser209Ala), ameliorated FXS phenotypes in *Fmr1*^{-/y} mice (Gkogkas et al., 2014).

In addition to eIF4E phosphorylation, a new translational control mechanism was found where FMRP interacts with eIF4E through CYFIP1 to prevent eIF4E-eIF4G binding, thereby hindering translation initiation (Napoli et al., 2008). The FMRP-CYFIP1-eIF4E complex is present in dendritic spines and actively participates in the local control of protein synthesis during synaptic activity. Synaptic activation by BDNF or mGluR stimulates the release of FMRP and CYFIP1 from eIF4E and promotes local translation (Napoli et al., 2008; Genheden et al., 2015). In fact, the levels of CYFIP1 have been shown to influence the maturation of dendritic spines (Pathania et al., 2014; Oguro-Ando et al., 2015), whereas *Cyfp1*^{+/-} mice show some phenotypes similar to *Fmr1*^{-/y} mice, such as exaggerated mGluR-LTD (Bozdagi et al., 2012).

One avenue through which aberrant eIF4E-dependent translation may lead to the manifestation of ASDs is through the translational control of specific subsets of mRNAs. eIF4E was shown to regulate the translation of mRNAs with 5' UTRs that are highly structured (Feoktistova et al., 2013; Hinnebusch et al., 2016) or that contain CERT (cytosine-enriched regulator of translation) motifs (Truitt et al., 2015). Furthermore, phosphorylation of eIF4E has been proposed to affect the translation of mRNAs containing 3' GAIT (interferon (IFN)- γ -activated inhibitor of translation) elements (Amorim et al., 2018). Subsets of mRNAs controlled by eIF4E perform a variety of functions, such as promoting tumorigenesis or participating in the control of the circadian rhythm and serotonin pathways (Furic et al., 2010; Cao et al., 2015; Amorim et al., 2018). In addition, eIF4E-sensitive mRNAs encode scaffolding proteins such as neuroligins (Gkogkas et al., 2013; Pettem et al., 2013; Rothwell et al., 2014) and extracellular matrix components (Gkogkas et al., 2014; Amorim et al., 2018). Mutations in several neuroligin isoforms are present in ASD patients (Jamain et al., 2003). In addition, overproduction of neuroligins was shown to modulate synaptic function and behavior in animal models of ASD and FXS (Hines et al., 2008; Dahlhaus and El-Husseini, 2010; Dahlhaus et al., 2010; Gkogkas et al., 2013). Extracellular matrix metalloproteinase 9 (MMP-9) regulates spine morphology, synaptic plasticity, learning and memory (Huntley, 2012), and is implicated in phenotypes in rodent models of ASD and FXS (Bilousova et al., 2009; Rotschafer et al., 2012; Dziembowska et al., 2013; Sidhu et al., 2014).

Translation of MMP-9 is stimulated by eIF4E phosphorylation, the levels of which are increased in FXS patients and *Fmr1*^{-/y} mice (Hoeffler et al., 2012; Gkogkas et al., 2014; Sidhu et al., 2014). In addition, modulation of MMP-9 expression in rodents modulates FXS phenotypes associated with increased eIF4E phosphorylation (Gkogkas et al., 2014; Gantois et al., 2017). Finally, a recent study proposes a novel mechanism, whereby eIF4E is required for repeat-associated non-AUG (RAN) translation of the *FMR1* gene (Kearse et al., 2016). CGG repeats in the *FMR1* gene stimulate RAN translation, which leads to the synthesis of toxic polypeptides (Todd et al., 2013).

Apart from direct translational control, eIF4E may be linked to ASD pathophysiology via a role in early neuronal development through its interaction with the eIF4E-Transporter (4E-T) in processing bodies (P-bodies), which are cytoplasmic granules involved in mRNA degradation (Eulalio et al., 2007). Here, eIF4E and 4E-T cooperate to sequester and repress the translation of pro-neurogenic mRNAs, such as transcription factors and neuronal differentiation-related mRNAs (Yang et al., 2014). In addition, recent work revealed that 4E-T also binds to Pumilio2 and that this complex ensures neuronal specification of deep and superficial layer murine cortical neurons (Zahr et al., 2018).

DEPRESSION AND ANXIETY DISORDERS

Depressive and anxiety disorders are often comorbid and represent the most common causes of disability worldwide (Zhou et al., 2017). In addition, these psychiatric conditions are commonly present in people suffering from ASDs (Magnuson and Constantino, 2011). mTOR signaling is affected in patients with major depressive disorder as well as animal models of depression and anxiety (Jernigan et al., 2011; Chandran et al., 2013; Ignacio et al., 2016). Furthermore, treatment with selective serotonin reuptake inhibitors or other anti-depressant drugs, such as ketamine, were shown to affect mTOR and its downstream targets p70S6K and 4E-BP1 (Jernigan et al., 2011; Park et al., 2014; Liu et al., 2015; Zhuang et al., 2016; Abelaira et al., 2017). MAPK/ERK signaling is also altered in patients and animal models of depressive disorders (Dwivedi et al., 2001; Rao et al., 2007; Dwivedi and Zhang, 2016). Given the convergence of these two pathways in the control of translation initiation, the question arises of how eIF4E function may affect or be affected by depression and anxiety disorders.

Two recent studies revealed that mice with defective eIF4E phosphorylation (*Mnk1/2*^{-/-} or *Eif4e*^{ki/ki} mice) show behaviors reminiscent of depression and anxiety, concomitant with increased inflammatory responses. *Mnk1/2*^{-/-} and *Eif4e*^{ki/ki} mice displayed increased immobility in the force-swimming and tail suspension tests, increased latency to feed in a novelty suppressed feeding assay, and anxiety behaviors in the open-field and elevated plus maze tests (Aguilar-Valles et al., 2018; Amorim et al., 2018). Translational profiling in brain tissue from *Eif4e*^{ki/ki} mice revealed increased translation of genes involved in serotonin pathways concomitantly with reduced levels of serotonin in the

brain (Amorim et al., 2018). Aguilar-Valles et al. (2018) further report impaired serotonin transmission in the prefrontal cortex and reduced firing of serotonergic neurons in the dorsal raphe of *Eif4e*^{ki/ki} and *Mnk1/2*^{-/-} mice. Moreover, loss of eIF4E phosphorylation resulted in elevated levels of key inflammatory cytokines, including TNF α , IFN γ , and IL-2, in addition to an exaggerated response to lipopolysaccharide-induced microglial activation and cytokine production (Aguilar-Valles et al., 2018; Amorim et al., 2018). Interestingly, administration of a dominant negative form of TNF α rescued the behavioral and electrophysiological abnormalities in *Eif4e*^{ki/ki} mice (Aguilar-Valles et al., 2018).

The connection between depression and inflammation has received increased attention (Miller and Raison, 2016). There is an elevated comorbidity between depression and chronic inflammatory conditions (Abbott et al., 2015; Euesden et al., 2017), and while several studies have found increased levels of pro-inflammatory cytokines in patients with anxiety and major depressive disorder (Dowlati et al., 2010; Shelton et al., 2011; Mostafavi et al., 2014; Michopoulos et al., 2015), anti-inflammatory drugs are effective in the treatment of depression (Müller, 2018; Wiedlocha et al., 2018). The new evidence from Amorim et al. (2018) suggests an important mechanism through which impaired translation control via dysregulated eIF4E phosphorylation downstream of the MAPK/ERK pathway affects the translation of specific mRNAs to directly influence the inflammatory response and impact on depression and anxiety-like behaviors. Amorim et al. (2018) propose that eIF4E phosphorylation may control inflammatory responses in depression by regulating binding of the 3' UTR element (GAIT) onto the 5' eIF4F complex in circularized pro-inflammatory mRNAs. The GAIT complex acts as a translational repression mechanism that controls the translation of pro-inflammatory mRNAs (Mukhopadhyay et al., 2009). Loss of eIF4E phosphorylation may decrease the affinity of the GAIT complex to eIF4E, thus allowing excessive translation of pro-inflammatory mRNAs.

SCHIZOPHRENIA (SCZ)

SCZ is a neuropsychiatric disorder characterized by a combination of positive, negative and cognitive symptoms, including hallucinations and delusions, apathy and social withdrawal, and attention, memory and executive thinking deficits, respectively. SCZ is a highly disabling condition, affecting around 1% of the population, and it has high heritability rates (Kahn et al., 2015). The etiology of SCZ is not fully understood and is associated with a variety of genetic and environmental risk factors. Even though *DISC1* is one of the better characterized genes regarding its association with SCZ (Roberts, 2007; Bradshaw and Porteous, 2012), several studies have additionally identified *de novo* copy number variants (CNVs) as conferring high risk for the development of the disease (Xu et al., 2008; Malhotra et al., 2011). Interestingly, these CNVs are often associated risk factors for other neurodevelopmental disorders, such as ASD, mental retardation and epilepsy (Sullivan

et al., 2012). In addition, network analysis has suggested they affect neurodevelopmental, synaptic function and post-synaptic signaling pathways (Walsh et al., 2008; Kirov et al., 2012; Brennand et al., 2015).

One recurrent CNV associated with SCZ, as well as with cognitive and behavioral abnormalities, is the 15q11.2 microdeletion (Stefansson et al., 2008; Kirov et al., 2009; De Wolf et al., 2013). The 15q11.2 locus includes four genes – *CYFIP1*, *TUBGCP5*, *NIPA1*, and *NIPA2*. Of particular interest is the *CYFIP1* gene, which has emerged as an important player in ASD and FXS and participates in the control of protein synthesis and dendritic spine maturation. Furthermore, *CYFIP1* is also part of the WAVE regulatory complex, which is involved in the control of actin polymerization and lamellipodia formation (Chen et al., 2010; Abekhoukh et al., 2017). The functioning of this complex and of *CYFIP1* contribute to the correct formation of adherens junctions and cell polarity in patient-derived induced pluripotent stem cells (iPSCs) neuroprogenitor cells (Yoon et al., 2014). Other studies have used iPSCs-derived neuronal populations to address SCZ-related impairments in cell migration, cytoskeletal remodeling and protein synthesis (Brennand et al., 2015; Topol et al., 2015). Interestingly, by using olfactory neurosphere-derived cells, a model that was shown to replicate some of the molecular phenotypes of SCZ (Mackay-Sim, 2012), English et al. (2015) identified, both at the level of the transcriptome and proteome, significant changes in signaling pathways key to the control of mRNA translation, including eIF2, eIF4 and mTOR signaling. Although the role of mTOR in SCZ has not been well established, various studies have noted the presence of altered mTOR signaling, particularly in the context of *DISC1* animal models (Kim et al., 2009; Zhou et al., 2013; Gururajan and van den Buuse, 2014). Exploring the relationship between mTOR and SCZ will be particularly interesting in terms of its connection to eIF4E, given the ability of this initiation factor to interact with *CYFIP1* and to influence crucial mechanisms to SCZ, such as dendritic spine morphology and neurodevelopment.

CONCLUSION – OUTLOOK

The genomic and gene-expression “boom” of the early 00's, bolstered by the advent of technologies to measure transcriptional changes (micro-array, RNA/exome/whole genome next generation sequencing) has placed a focus on transcription as the key step in the gene-expression pathway underlying the pathophysiology of neuropsychiatric disorders (Kelsoe, 2004; Kavanagh et al., 2013; Nievergelt et al., 2018). Thus, the regulatory mechanisms of protein synthesis have not received much attention, while translational control and investigation of the translome has not become part of large consortia mainly due to the lack of accessible genome-wide methodologies. The onset of translome profiling will change this trend and important mechanistic data will surface in the coming years (Ingolia et al., 2009, 2018). Thirty-nine years after its discovery, eIF4E still poses an enigma as to the identity of the mRNAs it controls and the precise regulatory mechanisms it participates in during different stages of development and in

different cell-types of the brain. Understanding the role of cap-dependent translation in the brain will facilitate the adaptation of the already existing compendium of biochemical/genetic models and pharmacological approaches to modulate translation (Sonenberg and Hinnebusch, 2007; Malina et al., 2011, 2012), for the treatment of neuropsychiatric disorders.

AUTHOR CONTRIBUTIONS

All authors contributed to writing the manuscript. All authors read and approved the submitted version.

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FUNDING

This work was supported by grants to CG: Sir Henry Dale Fellowship from the Wellcome Trust and Royal Society (107687/Z/15/Z) and a NARSAD Young Investigator grant from the Brain and Behavior Research Foundation (24968).

ACKNOWLEDGMENTS

We sincerely apologize to colleagues whose work was not cited due to space considerations.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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