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The role of the m6A pathway in the regulation and disorders of cognitive functions

Úloha m6A dráhy v regulaci a poruchách kognitivních funkcí

Bachelor´s thesis

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Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Podpis

Abstract

N6-methyladenosine (m6A) methylation is a dynamic and reversible modification, marking RNA molecules. The modifications are executed by methyltransferases (writers), erased by demethylases (erasers), and recognised by effector proteins (readers). This modification influences mRNA stability, transcription, splicing, transport, and translation, adding layers of complexity to cellular communication. Recently, the role of m6A was discovered in synaptic plasticity and learning. This modification is essential in transferring information from short-term to long-term memory, establishing or strengthening existing neuron connections. Dysregulation of m6A is implicated in neurological disorders, affecting the ability of the organism to memorise and learn new information. Understanding this epitranscriptomic code will be helpful for therapeutic exploration, promising a more complete comprehension of cellular biology.

Keywords: m6A methylation, synaptic plasticity, cognitive dysfunctions, Alzheimer's disease, Parkinson's disease, METTL3, FTO

Abstrakt

N6-methyladenosin (m6A) metylace je dynamická a reverzibilní modifikace, která označuje molekuly RNA. Modifikace jsou umisťovány metyltransferázami (writers), vymazány demetylázami (erasers) a rozpoznány efektorovými proteiny (readers). Tato modifikace ovlivňuje stabilitu mRNA, splicing, transkripci, transport a translaci, čimž zesložituje komplexitu buněčné komunikace. Recentně byla objevena role m6A v synaptické plasticitě a učení. Tato modifikace hraje klíčovou roli při přenosu informace z krátkodobé do dlouhodobé paměti, ustanovování nebo posilování existujících spojů mezi neurony. Dysregulace m6A je spojována s neurologickými poruchami, ovlivňující schopnost organismu zapamatovat si a naučit se nové informace. Porozumění tomuto epitranskripčnímu kódu bude užitečné pro terapeutický výzkum, umožňující kompletnější pochopení buněčné biologie.

Klíčová slova: m6A metylace, synaptická plasticita, kognitivní poruchy, Alzheimerova choroba, Parkinsonova choroba, METTL3, FTO

Abbreviations

5xFAD: 6-month-old familial Alzheimer's disease mice model

6-OHDA: 6-hydroxydopamine

Aβ: amyloid-beta

ACSL4: acyl-CoA synthetase long-chain family member 4

AD: Alzheimer's disease

ADHD: attention deficit hyperactivity disorder

ADRB2: adrenoreceptor beta 2

ALKBH5: AlkB homolog 5

AMPA: receptor: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

APOE: apolipoprotein E

APP: amyloid precursor protein

APP/PS1: mouse model: amyloid precursor protein/presenilin 1 mouse model

ATAT1: alpha-tubulin acetyltransferase 1

ATM: ataxia telangiectasia mutated

ARC: activity-regulated cytoskeleton-associated protein

BDNF: brain-derived neurotrophic factor

CaMKII: Ca2+/calmodulin-dependent protein kinase II alpha

carRNA: chromatin-associated regulatory RNA

CBLL1: Cbl-proto-oncogene-like protein 1

CCR4-NOT: Carbon Catabolite Repression-Negative On TATA-less

CDC5L: cell division cycle 5-like

CDS: coding sequence

circRNA: circular RNA

CNOT1: CCR4-NOT Transcription Complex Subunit 1

CNS: central nervous system

CP: ceruloplasmin

CPSF: cleavage and polyadenylation specificity factor

CREB: cAMP response element-binding protein

CRM1: Chromosome region maintenance 1

CRY: cryptochrome

CSF: cerebrospinal fluid

CTD: carboxy-terminal domain

DG: dentate gyrus

DGCR8: DiGeorge syndrome critical region 8

DGK: diacylglycerol kinase

DNMT3A: DNA methyltransferase 3A

DR: dopamine receptor

eIF: eukaryotic initiation factor

ELAV1: ELAV-like RNA-binding protein 1

ERK: extracellular signal-regulated kinase

EZH2: Enhancer of Zeste homolog 2

FIS1: Fission 1

FMRP: fragile X mental retardation protein

FTO: fat mass and obesity-associated

GAB1: GRB2-associated binding protein 1

GABA: gamma-aminobutyric acid

GBP11: guanylate binding protein 11

GFAP: glial fibrillary acidic protein

GIRK channel: G protein-coupled inwardly-rectifying potassium channel

GLRX: glutaredoxin-1

GNG4: G-protein subunit gamma-4

GPR17: G protein-coupled receptor 17

HD: Huntington's disease

HNRNP: heterogeneous nuclear ribonucleoprotein

hp1: hairpin 1

HPA axis: hypothalamic-pituitary-adrenal axis

HRSP12: heat-responsive protein 12

HuR: human antigen R

IEG: immediate early gene

IGF2BP: insulin-like growth factor 2 mRNA-binding protein

KDM: lysine demethylase

KEGG: Kyoto Encyclopedia of Genes and Genomes

KH domain: K-Homology domain

KO, **cKO**: knockout, conditional knockout

LC-MS/MS: liquid chromatography-tandem mass spectrometry

LINE-1: long interspersed element-1

lncRNA: long non-coding RNA

LPS: lipopolysaccharide

LRPPRC: leucine-rich pentatricopeptide repeat containing

LTD: long-term depression

LTP: long-term potentiation

M1/M2: microglia type 1/2

m1A: N1-methyladenosine

m5C: 5-methylcystonine

m6A: N6-methyladenosine

m6Am: N6,2'-O-dimethyladenosine

MAPK: mitogen-activated protein kinase

MAT2A: methionine adenosyltransferase 2A

MATR3: matrin 3

MBP: myelin basic protein

MCI: mild cognitive impairment

MDD: major depressive disorder

mEPSC: miniature excitatory postsynaptic current

MeRIP-seq: methylated RNA immunoprecipitation sequencing

mESC: mouse embryonic stem cell

METTL: methyltransferase-like

mGluR: metabotropic glutamate receptor

mPFC: medial prefrontal cortex

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

mTOR: mammalian target of rapamycin

ncRNA: non-coding RNA

NFT: neurofibrillary tangle

NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells

NG2: neural/glial antigen 2

NMDA receptor: N-methyl-D-aspartate receptor

NRF2: nuclear factor erythroid 2-related factor-2

NRIP1: nuclear receptor-interacting protein 1

NSC, **aNSC**: neuronal stem cell, adult neuronal stem cell

NSUN2: NOP2/Sun RNA methyltransferase 2

NXF1: nuclear mRNA export factor 1

NXT1: nuclear transport factor 2 (NTF2)-like export factor 1

OPC: oligodendrocyte progenitor cell

PABP: poly-A binding protein

PABPC1: poly-A-binding protein cytoplasmic 1

P-bodies: processing bodies

PCIF1: Phosphorylated CTD Interacting Factor 1

PD: Parkinson's disease

PDGFRA: platelet-derived growth factor receptor A

PET: positron emission tomography

PI3K: phosphoinositide-3-kinase

PIKE: phosphoinositide-3-kinase (PI3K) enhancer

PKC-α: protein kinase C alpha

PMS: progressive multiple sclerosis

POCD: postoperative cognitive dysfunction

PPP2CA: serine/threonine-protein phosphatase 2A catalytic subunit alpha

PQ: paraquat

PRRC2A: proline-rich coiled-coil 2A

PSD95: postsynaptic density-95

PTEN: phosphatase and tensin homolog

RBM15/15B: RNA-binding motif protein 15/15B

RBMX: RNA-binding motif protein X-linked

RBP: RNA-binding protein

RGG: domain: arginine/glycine-rich domain

RNAPII: RNA polymerase II

RNase P/MRP: ribonuclease P/MRP

ROBO3.1: Roundabout3.1

ROS: reactive oxygen species

RRM: RNA recognition motif

RRMS: relapsing-remitting multiple sclerosis

rRNA: ribosomal RNA

SAM: S-adenosylmethionine

SETD2: SET domain-containing 2

SGZ: subgranular zone

SH: domain: Src Homology domain

SIRT1: sirtuin 1

SNP: single nucleotide polymorphism

snRNA: small nuclear RNA

SNRP: small nuclear ribonucleoprotein polypeptide

SOCS5: suppressor of cytokine signalling 5

SOX2: Sex-determining region Y-box-2

SRSF: serine/arginine-rich splicing factor

STAT3: signal transducer and activator of transcription 3

STUB1: STIP1 homology and U-box containing protein 1

STZ: streptozocin

SVZ: subventricular zone

TCA: tricyclic antidepressant

TGF-β: transforming growth factor beta

TRAF6: tumour necrosis factor receptor (TNFR)-associated factor 6

TREX: complex: TRanscription-EXport complex

TRMT112: tRNA methyltransferase activator subunit 11-2

tRNA: transfer RNA

TrκB: tropomyosin receptor kinase B

TSC1: tuberous sclerosis 1

TYROB: TYRO protein tyrosine kinase-binding protein

UBC: ubiquitin C

UBE2A: ubiquitin-conjugating enzyme E2 A

UTR: untranslated region

VIRMA: vir-like m6A methyltransferase associated

VTA: ventral tegmental area

WT: wild-type

WTAP: Wilm's tumour 1-associated protein

Xist: X-inactive specific transcript

XRN1: 5'→3' exoribonuclease 1

YTH: YT521-B homology

YTHDC: YTH N6-methyladenosine RNA-binding protein C

YTHDF: YTH domain-containing family protein

ZC3H13: Zinc finger CCCH-type containing 13

ZCCHC4: Zinc finger CCHC-type containing 4

(pre)-mRNA: (precursor) messenger RNA

(pri)-miRNA: (primary) microRNA

Contents

1. Introduction

In recent years, significant biological milestones such as the central dogma, histone modifications and DNA epigenetics have paved the way for the discovery of RNA modifications. The identification of m6A dates back to the 1970s, marking the dawn of epitranscriptomics (Desrosiers et al., 1974; Perry et al., 1974). Initial studies revealed m6A as a prevalent modification in eukaryotic mRNA, and subsequent research expanded its presence to other types of RNAs (Berulava et al., 2015; Chen et al., 2020; Dominissini et al., 2012; Hess et al., 2013; Liu et al., 2017). The discovery of methyltransferases ("writers"), demethylases ("erasers"), and m6A-binding proteins ("readers") showcased the dynamic nature of m6A modification. Dysregulation in any of those proteins can be implicated in numerous diseases, while their normal functioning dynamically regulates many biological processes. The identification of m6A modification posed a significant challenge due to the limitations of available techniques. Classical methods relied on biophysical and biochemical approaches unsuited to detect specific modifications like m6A methylation. The breakthrough came with the development of innovative techniques such as MeRIP-seq, which utilises m6A-specific antibodies to enrich and map m6A-modified RNA molecules (Dominissini et al., 2012; Meyer et al., 2012). This technique revolutionised the field of RNA epitranscriptomics by allowing researchers to study m6A at a transcriptome-wide level with higher resolution and sensitivity.

M6A RNA modification has garnered increasing attention in the field of neuroscience. The methylation dynamically regulates gene expression, protein translation, and various aspects of RNA metabolism (discussed below). It was discovered that m6A plays a pivotal role in modulating synaptic plasticity in the brain, the cellular basis of learning and memory (Koranda et al., 2018; Shi et al., 2018; Widagdo et al., 2016; Z. Zhang et al., 2018). M6A sites were found at the genes involved in neuronal communication, neuronal stem cells (NSCs) self-renewal, synaptic strength, and axonal growth (Chang et al., 2017; J. Chen et al., 2019; L. Li, S. Sultan et al., 2017; Merkurjev et al., 2018; Yoon et al., 2017; Zhao et al., 2021). Neurological disorders like Alzheimer's disease (AD), depression, glioma, fragile X syndrome, Parkinson's disease (PD), and others are associated with dysfunctions in m6A regulation, making m6A modification an important regulator of cognitive processes and brain function (Chai et al., 2021; Niu et al., 2022; Westmark et al., 2020; Z. Yu et al., 2022).

In this work, I aim to explore current studies on the role of m6A in memory and learning regulation and its implications for cognitive disorders.

2. Regulation of RNA metabolism by m6A epitranscriptome

2.1 Distribution and Frequency

Modifications are added to RNA molecules by the m6A-methyltransferase writer complex at specific adenosine-containing motifs, DR[A]CH (D = A, G or U; R = A or G; H = A, C or U). M6A sites can be found in regions like 3'UTRs, unusually long internal exons, 5'UTRs, and near stop codons (Dominissini et al., 2012; Meyer et al., 2012). Methylation at the N6 position of adenosine makes up approximately 0.1-0.4% of total adenosine residues in RNA (Dubin & Taylor, 1975; Wei et al., 1975). In the brain, however, its numbers are much higher, emphasizing its significance in this region (Chang et al., 2017).

M6A modifications are regulated spatiotemporally with different methylation patterns across brain regions, cell types, and mRNAs. Adolescent mice had the lowest levels of m6A compared to young and aged mice, with more hypomethylated genes than hypermethylated. Hypermethylation in early and late stages correlated with upregulated gene expression. M6A modifications significantly affected steady-state mRNA levels during adolescence and adulthood, ensuring proper neurodevelopment. Additionally, m6A methylation plays a role in the development of specific tissues by marking and upregulating tissue-specific mRNAs. These effects are even more pronounced in humans (Shafik et al., 2021). Notably, the cerebellum exhibited the highest m6A methylation rate compared to the cerebral cortex (Chang et al., 2017).

2.2.Writers and erasers

The deposition of m6A in neurons is facilitated by RNA-binding proteins (RBPs). The methyltransferase-like 3 (METTL3), part of a **writer** complex, contains an S-adenosylmethionine (SAM) domain and catalyses methyl transfer on RNA (Bokar et al., 1997). SUMOylation of lysine residues in METTL3 weakens its methyltransferase activity (Du et al., 2018). The complex includes the METTL3/METTL14 heterodimer in the cytoplasm, with METTL14 enhancing the catalytic activity of METTL3 (Liu et al., 2014). The core heterodimer interacts with other adaptor and auxiliary proteins. Wilm's tumour 1-associated protein (WTAP) localises the heterodimer to nuclear speckles, where m6A is installed on newly synthesised mRNAs (Ping et al., 2014). KIAA1429, also known as vir-like m6A methyltransferase associated (VIRMA), promotes preferential methylation in the 3'UTR and near stop codons (Yue et al., 2018). Cbl-proto-oncogene-like protein 1 (CBLL1), or HAKAI, stabilises the components of the complex (Bawankar et al., 2021). RNA-binding motif protein 15/15B (RBM15/15B) interacts with WTAP via Zinc finger CCCH-type containing 13 (ZC3H13) and ensures the recruitment of the complex to the U-rich sequences on the mRNA (Knuckles et al., 2018; Patil et al., 2016). ZC3H13 transfers the complex into the nucleus (Wen et al., 2018). Phosphorylated carboxy-terminal domain (CTD) Interacting Factor 1 (PCIF1) is the only known human 5'UTR N6,2'-O-dimethyladenosine (5'm6Am) methyltransferase (Akichika et al., 2019; Boulias et al., 2019; Sendinc et al., 2019). METTL16 and METTL4 are involved in methylating U6 snRNA and U2 snRNA, respectively, further affecting pre-mRNA splicing (Chen et

al., 2020; Pendleton et al., 2017). METTL16 is part of a feedback loop that regulates SAM production by regulating the splicing of Mat2a mRNA, which encodes SAM synthetase expressed in most cells (Pendleton et al., 2017). Furthermore, ZCCHC4 and METTL5 are the writers that methylate 28S rRNA and 18S rRNA, respectively (Ma et al., 2019; Van Tran et al., 2019; L. Wang et al., 2022).

The opposite function of methyltransferases is carried out by m6A demethylating enzymes, **erasers**, such as the fat mass and obesity-associated (FTO) and AlkB homolog 5 (ALKBH5) proteins (Jia et al., 2011; Zheng et al., 2013). Both proteins are in the alpha-ketoglutarate-dependent dioxygenase B (ALKB) subfamily of the Fe(II)/α-ketoglutarate-dependent dioxygenases (Gerken et al., 2007; Zheng et al., 2013). FTO was the first identified RNA demethylase; it can be found in the nucleus and cytoplasm (Gulati et al., 2014; Jia et al., 2011). It was reported that FTO preferentially demethylates the 5'm6Am of the target mRNAs (Mauer et al., 2017). Further findings expanded its substrate specificity to N1-methyladenosine (m1A) in some tRNAs, cap-m6Am in mRNA, and m6A and m6Am in some snRNAs (Mauer et al., 2019; Wei et al., 2018). ALKBH5's erasing function is specifically important in spermatogenesis in the testis, while FTO is highly enriched in neurons in the brain (McTaggart et al., 2011; Zheng et al., 2013). Interestingly, demethylases do not require a consensus motif; m6A itself functions as a "conformational marker," crucial for substrate specificity (Zou et al., 2016).

2.3 Readers

M6A marks are then recognised by another group of methylation-binding proteins known as **readers**. The proteins interact with other RBPs and signalling molecules, influencing the fate of the transcript. Readers' ability to bind to a specific site depends on the presence of different binding domains within a reader and the specific cell-type context.

The first discovered readers were cytoplasmic YTH domain-containing family proteins 1-3 (YTHDF1-3), YTH N6-methyladenosine RNA-binding protein C2 (YTHDC2) with domains different from other family members, and one nuclear protein, YTHDC1 (Li et al., 2014; Roundtree et al., 2017; Xu et al., 2014; Zaccara & Jaffrey, 2020; Zhang et al., 2010). The proline-rich coiled-coil 2A (PRRC2A) reader competes with YTHDF2 for binding to a GGACU consensus motif in the coding sequence (CDS) of Olig2 in an m6A-dependent manner. However, the specific molecular mechanism is not known yet (R. Wu et al., 2018).

The second m6A-binding family utilises four K-Homology (KH) domains and two RNA recognition motifs (RRMs) for binding. The insulin-like growth factor 2 mRNA-binding proteins 1-3 (IGF2BP1-3) recruit mRNA stabilisers like ELAV-like RNA-binding protein 1 (ELAV1), or human antigen R (HuR), matrin 3 (MATR3), and poly-A-binding protein cytoplasmic 1 (PABPC1) to facilitate mRNA stability and translocation (Behm-Ansmant et al., 2007; Fan & Steitz, 1998; Nielsen et al., 1999; Salton et al., 2011;). Fragile X mental retardation protein (FMRP) binds to m6A-containing RNAs in a context-dependent manner through its three KH domains, two Agenet motifs, and one arginine/glycine-rich (RGG) domain (Ashley et al., 1993; Edupuganti et al., 2017;

Myrick et al., 2015). FMRP was suggested to be an essential reader in the synapse, as its target mRNAs were hypermethylated in the CDS region (Chang et al., 2017).

The heterogeneous nuclear ribonucleoprotein (HNRNP) superfamily members, including HNRNPA2B1, HNRNPC, and HNRNPG, use a distinct indirect RNA-binding profile named "m6A-switch". Each member of the superfamily contains at least one of the following RNA-binding domains: RRM, KH, or RGG (Burd et al., 1994; Dreyfuss et al., 1993). The presence of m6A and the binding domain regulates the RNA structure-dependent accessibility of mRNA and lncRNA for binding by some members of the superfamily (**Fig. 1**) (Liu et al., 2015, 2017; Sun et al., 2019). IGF2BP3 *in vitro* may also bind to m6A in a switch-dependent manner (Sun et al., 2019).

2.4 Downstream regulation of the m6A-methylated RNA

2.4.1 M6A in alternative splicing

Early co-transcriptional deposition at 5'- or 3'-splice junctions fastens splicing, while m6A deposition in intronic regions slows down intron processing and alternative splicing events, highlighting the importance of m6A in splicing kinetics (Louloupi et al., 2018). YTHDC1 reader in a complex with a trans-acting serine/arginine-rich splicing factor 3 (SRSF3) promotes exon inclusion. On the other hand, the SR factor SRSF10 has an opposing role as it competes with SRSF3 for binding to the reader or pre-mRNA. SRSF3 abundance in a cell is much higher, suggesting that exon inclusion is the predominant pattern under normal physiological conditions and may serve a protective role against exon skipping (Xiao et al., 2016). Approximately 10% of all m6A peaks in mouse embryonic stem cells (mESCs) were located in introns closer to 5'-splice sites. Most of these peaks were found to overlap with RBM15 binding sites and H3K36me3 histone marks, suggesting their involvement in intron/exon inclusion (Huang et al., 2019; Patil et al., 2016; Wei et al., 2021). *Fmr1* loss in the hippocampal tissue led to a reduced ribosomal stalling on specific mRNAs, one of which is Setd2 (H3K36me3 methyltransferase), leading to aberrant alternative splicing in transcripts associated with neuronal function and autism spectrum disorders (Shah et al., 2020). Upon depletion of HNRNPA2B1 and METTL3, similar alternative splicing patterns were observed. HNRNPA2B1 is involved in miRNA processing, either in a similar manner as METTL3 or alongside METTL3, by recruiting the microprocessor complex subunit DGCR8 to primary miRNAs (pri-miRNAs) (Alarcón, Goodarzi, et al., 2015; Alarcón, Lee, et al., 2015). HNRNPG binds to near-m6A splice sites of pre-mRNA and the phosphorylated CTD of RNA polymerase II (RNAPII) through its RGG motifs, resulting in the regulation of RNAPII occupancy pattern and promotion of exon inclusion (Liu et al., 2017; Zhou et al., 2019). HNRNPC binding to alternative exons results in their silencing, while binding to the preceding intron enhances the inclusion of alternative exons (König et al., 2010). Depletion of HNRNPC and METTL3/14 together has been observed to inhibit exon inclusion, consequently affecting cell proliferation and other biological processes (König et al., 2010; Liu et al., 2015). FTO binds to intron regions near alternative exons and

poly-A tails, and its knockout (KO) favours exon-skipping events (Bartosovic et al., 2017). In contradiction, in adipocyte cells, FTO depletion promoted SRSF2 binding and increased exon inclusion (Zhao et al., 2014). ALKBH5 is essential for the correct splicing and production of longer 3'UTRs in mRNAs in spermatogenic cells (Tang et al., 2017). Interestingly, in neurons, polyadenylated transcripts that undergo the intron inclusion process remain in the nucleus instead of being degraded in the cytoplasm, awaiting neuronal activity impulses (Mauger et al., 2016). Whether m6A is involved in intron inclusion is unknown but may be demonstrated in the future.

2.4.2 M6A in RNA stability

The presence of m6A residues has been linked to the reduced half-life of mRNA transcripts (Ke et al., 2015; Wang et al., 2014). YTHDC2 functions as a 3'→5' RNA helicase and recruits 5'→3' exoribonuclease XRN1 through the Ankyrin repeats located between in the helicase domain of YTHDC2, facilitating germline development (Kretschmer et al., 2018; Wojtas et al., 2017). YTHDC2 is abundant in the spleen and brain, prompting future studies to focus on its role in these regions (Hsu et al., 2017). All YTHDF proteins are associated with transcript degradation (Lasman et al., 2020; Zaccara & Jaffrey, 2020). YTHDF2 is co-localised with deadenylation and decapping enzyme complexes in cytoplasmic processing bodies (P-bodies), affecting mRNA and ncRNA half-life, and is involved in stress granule formation (Fu & Zhuang, 2020; Wang et al., 2014). YTHDF2 recruits the CCR4-NOT deadenylase complex to the 3'poly-A methylated tail by binding to the CNOT1 subunit (Du et al., 2016). CNOT7 subunit of the deadenylase complex is downregulated in the hippocampus following synaptic activity, impairing dendritic transcript transport, synaptic plasticity, and cognition (McFleder et al., 2017). Endoribonucleotic m6A-dependent RNA degradation occurs through the interaction between YTHDF2 and RNase P/MRP, bridged by HRSP12 adaptor protein (Park et al., 2019).

On the other hand, transcript stabilisation occurs through the IGF2BP in interaction with stabilising proteins HuR and MATR3 (Huang et al., 2018). FMRP reader can also play a role in transcript stabilisation (Edupuganti et al., 2017; Shu et al., 2020). FMRP competes with YTHDF2 for the m6A binding sites or directly regulates YTHDF2 in an RNA-independent manner, thus affecting mRNA fate (F. Zhang et al., 2018). *In vivo*, postsynaptic density-95 (Psd95) mRNA is stabilised through FMRP binding to its 3'UTR (G-quadruplex), and metabotropic glutamate receptor (mGluR) activation further increases the stabilisation of this synaptic signalling regulator (Zalfa et al., 2007).

2.4.3 M6A in transcription

Alterations on the transcriptional level shape long-term cell response to the impulse, which is important for memory and learning formation. In mESCs, METTL3 facilitates the nuclear degradation of chromatin-associated regulatory RNAs (carRNAs), such as LINE-1, in a YTHDC1-dependent manner. Depletion of METTL3 leads to reduced m6A methylation, resulting in increased carRNAs and active histone marks at H3K4me3 and

H3K27ac, thereby activating transcription (Liu et al., 2020). YTHDC1 recruits H3K9me2 demethylase, KDM3B, to m6A-associated chromatin, promoting gene expression (Li et al., 2020). The absence of METTL14 has an impact on the self-renewal of embryonic NSCs. This leads to a reduction in radial glial cells, disturbances in gene expression related to cell proliferation, promotion of genes associated with cell differentiation, and destabilization (Wang et al., 2018). In *Drosophila* cells, the m6A methyltransferase complex and YTHDC1 increased RNAPII pause release at gene promoters (Akhtar et al., 2021).

2.4.4 M6A in translocation

FMRP interacts with the nuclear export protein CRM1 for the export of methylated transcripts. Nuclear retention and impaired neural differentiation were observed in *Fmr1* KO mice and *Mettl14* conditional KO (cKO) mice (Edens et al., 2019). FMRP binds to the 3'UTR G-quadruplex in transcripts via its RGG domain and regulates efficient transport to neurites (Goering et al., 2020). The TREX complex recruits the NXF1:NXT1 heterodimer to the mRNAs. Additionally, TREX interacts with the WTAP/VIRMA complex and recruits YTHDC1 associated with SRSF3 to interact with the NXF1, mediating nuclear export (Lesbirel et al., 2018; Roundtree et al., 2017). The regulation of translocation is also facilitated by the selective inclusion of alternative last exons through alternative polyadenylation. Upon increased synaptic activity, various transcripts undergo 3'UTR shortening and intronic alternative polyadenylation, including Notch and Creb1, known for their function during LTP (Fontes et al., 2017; Tushev et al., 2018). M6A peaks are dense at distal poly-A sites and in the proximal area of the last exons within the transcripts in the brain (Ke et al., 2015). Deletion of *Alkbh5*, *Virma*, and *Mettl3* altered the length of the 3'UTR (Ke et al., 2015; Yue et al., 2018; Tang et al., 2017).

2.4.5 M6A in translation

YTHDC2 facilitates the translation of m6A-modified transcripts by interacting with the small ribosomal subunit in close proximity (Kretschmer et al., 2018). YTHDF1 enhances translation by interacting with the preinitiation complex proteins through the formation of a closed loop (**Fig. 1**) (Wang et al., 2015). YTHDF3, in cooperation with YTHDF1, associates with ribosomal proteins of the 40S/60S subunits, regulating m6A-modified transcript translation (A. Li et al., 2017). YTHDF3 also cooperates with YTHDF2 to regulate mRNA decay (Shi et al., 2017). Upon exposure to heat shock, transcripts show increased methylation at the 5'UTR. YTHDF2 protects these sites from FTO-mediated demethylation, which allows for cap-independent translation (Meyer et al., 2015; Zhou et al., 2015). FMRP inhibits the translation of plasticity-related transcripts by pausing ribosomal translocation during elongation (Darnell et al., 2011). In *Drosophila*, the loss of m6A impairs fly behaviour. YTHDF interacts with FMRP to repress the translation of transcripts essential for axonal growth regulation. Dysregulation of the m6A pathway causes axonal overgrowth and misguidance at larval neuromuscular junctions and in the adult mushroom bodies (Worpenberg et al., 2021). YTHDF in the mushroom

bodies potentiated the translation of transcripts with lower translational efficiency (Kan et al., 2021). In spinal commissural neurons of mice, cKO of *Ythdf1* impaired the translation of the axon guidance receptor Robo3.1, resulting in pre-crossing axon guidance defects in the spinal cord (Zhuang et al., 2019).

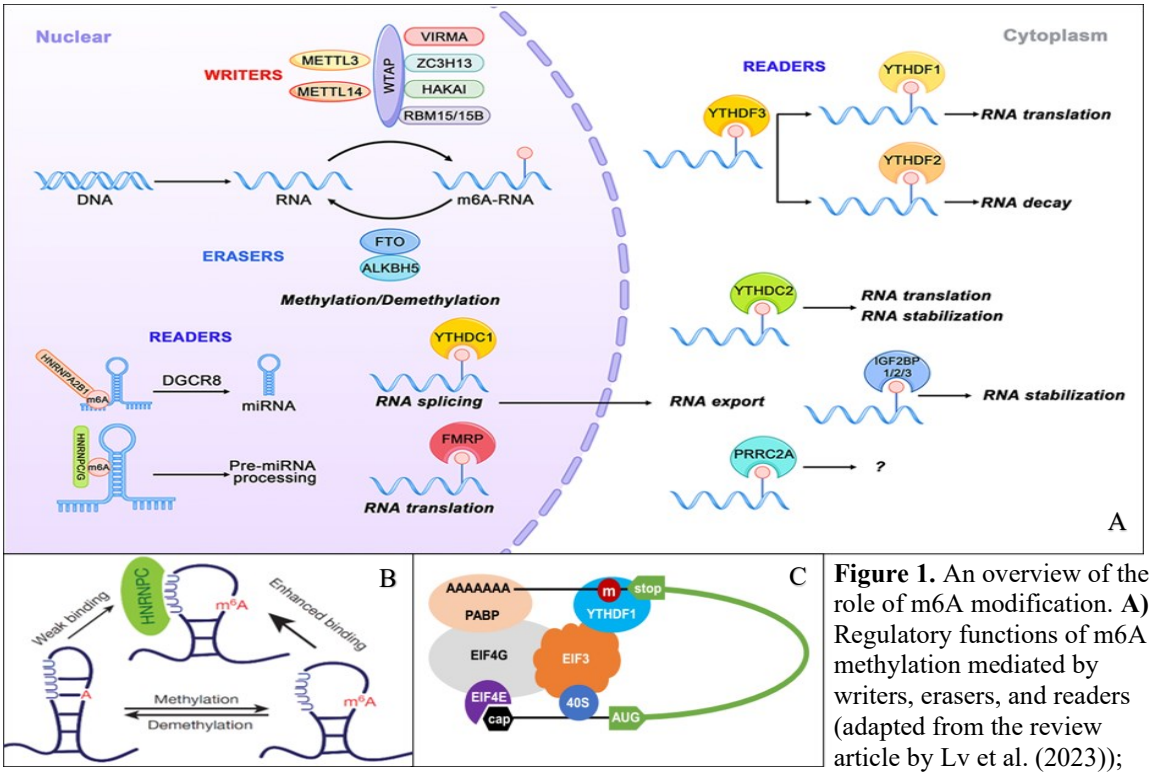

Figure 1. An overview of the role of m6A modification. **A)** Regulatory functions of m6A methylation mediated by writers, erasers, and readers (adapted from the review article by Lv et al. (2023)); **B)** The presence of m6A alters the structure of RNA and lncRNA, leading to the formation of an "m6A switch". These structural changes enhance the binding of the HNRNPC reader through its RRM motif to the RRACH-U sequence on RNAs (adapted from Liu et al. (2015)); **C)** YTHDF1 interacts with preinitiation complex proteins, eIF3, to enhance the translation of the transcript. The authors have suggested a closed-loop model in which YTHDF1 binds to m6A residues in the 3'UTRanrecruits eIF3 to the 5'UTR, with eIF4G facilitating the interaction of eIF4E and PABP to bring both ends into close proximity (adapted from Wang et al. (2015)).

3. The role of m6A signalling in the regulation of learning and memory

3.1. Learning and memory in the hippocampus

The hippocampus is involved in memory formation, pattern separation, pattern completion, imagining the future and recalling the past. LTP in the hippocampus has been extensively studied and is considered a cellular mechanism underlying learning and memory (Abraham & Williams, 2003). Upregulation of immediate early genes (IEGs) such as *Arc*, *Egr1*, *c-Fos*, *Zif268*, *Npas4*, and *Nr4a1* following a stimulus is crucial for the formation of long-term memories (Chen et al., 2014; Jones et al., 2001; Plath et al., 2006; Ramamoorthi et al., 2011; Sun & Lin, 2016). In just 30 minutes, fear conditioning training led to a twofold increase in the expression of IEGs

and a significant upregulation of m6A modification sites on the transcripts (Chang et al., 2022). METTL3 abundance correlated with the mice's ability for contextual fear discrimination and learning, potentially contributing to individual variations (Chang et al., 2022; Z. Zhang et al., 2018). *Mettl3* cKO mice had impaired learning and long-term memory consolidation ability, which was compensated by repeated training (Z. Zhang et al., 2018). FTO was transiently decreased near the synapses in response to fear conditioning. Loss of *Fto* in the dorsal hippocampus enhanced contextual fear memory. The authors suggest that FTO might have a role in preventing memory generalisation in hippocampus-dependent memory formation and interfering with neuronal incorporation into a new engram (Walters et al., 2017). The *Ythdf1* KO mice were normally developed up to the end of the experiment (4 months), had normal cortical morphology and adult neurogenesis, normal gross hippocampal histology, unchanged motor abilities or general emotional state, and acquired procedural learning without a problem. However, contextual fear memory was impaired after performing classical fear conditioning tests. In the KO mice, protein translation promoted by synapse activation is attenuated, leading to lower efficiency of synaptic strengthening and a decreased probability of memory formation. YTHDF1 in CA1 neurons maintains the amplitude and frequency of the spontaneous miniature excitatory postsynaptic currents (mEPSCs), basal synaptic transmission, LTP, and dendritic spine density. After the acute depletion of YTHDF1 and METTL3 in the adult mice's hippocampus, mice showed impaired contextual fear and spatial memory. However, their emotional state, auditory fear memory, and locomotor activity remained unchanged (Shi et al., 2018). In glutamatergic postsynapses, YTHDF1, YTHDF3, and ALKBH5 were co-localised with m6A-methylated mRNAs and had similar spatio-temporal expression patterns during synapse development. However, ALKBH5 is present at active synaptic ribosomes only during short-term plasticity. RNA-YTHDF complexes are suggested to play a role in forming post- and presynaptic nanodomains. FMRP is also co-localised with modified transcripts at postsynaptic sites upon NMDA activation, emphasising its role in short-term plasticity at glutamatergic synapses. M6A modifications affected the expression levels of Camk2b and all NMDA receptor subunits and transcripts associated with cell-cell communication, such as cadherin (De La Cruz et al., 2021). Nevertheless, a new study refutes that YTHDF1 is the reader that controls learning and memory in the hippocampus. The YTHDF2 reader is believed to have a crucial role in stabilizing protein transcripts and controlling the growth of axons in the dentate gyrus (DG). *Ythdf2* cKO in this specific region of the hippocampus led to excessive growth of mossy fibres, the axons of granule cells. This, in turn, disrupted the formation of excitatory synapses between the mossy fibres and the CA3 region (Zhuang et al., 2023).

3.2 Learning and memory in the cortex

The neocortex is responsible for higher cognitive functions. Synaptic plasticity in the cortex plays a role in integrating sensory information, forming complex associations, and encoding fear memory (Chau et al., 2014; Widagdo et al., 2016). The levels of m6A in the medial prefrontal cortex (mPFC) after the behavioural training

were upregulated, which was in correlation with the downregulated expression of FTO and upregulated METTL3. Knockdown of *Fto* in the adult mPFC increased total m6A levels and resulted in an enhanced consolidation of cued fear memory. The genes affected by the methylation had functional involvement in dendritic and postsynaptic regulation, synaptic transmission, and transmembrane transport regulation (Widagdo et al., 2016).

3.3 Learning and memory in the striatum reward circuit

The striatum has a key role in regulating procedural and motor learning as well as reward-related behaviours. Plasticity in the striatum influences the synaptic connections within its neural circuits, which are essential for adaptive behaviours. The striatum's role in learning involves receiving and filtering cortical inputs while promoting specific responses and inhibiting irrelevant ones.(Kiyatkin & Rebec, 1996). The medium spiny neurons in the striatum can be divided into two categories: with D1-like receptors (dopamine receptors, including D1R and D5R) or with D2-like receptors (D2R, D3R, D4R) making up to 95% of striatal neurons, while the cholinergic and GABAergic neurons account for other 5% (Kreitzer, 2009). The lack of FTO in a mouse model results in the excessive methylation of many transcripts in the dopaminergic midbrain circuitry. This affects pathways involved in neuronal signalling, and dopamine signalling specifically, leading to reduced dopamine levels in the presynaptic sites and attenuated inhibitory cell signalling of the D2R-D3R-GIRK (G protein-coupled inwardly-rectifying potassium) channel. Conditional *Fto* depletion has effects similar to the lack of D2 presynaptic autoreceptors in mice. These effects include inhibiting quinpirole-mediated downregulation of dopamine firing and locomotor activity and enhancing cocaine-induced locomotor activity and place preference (Hess et al., 2013). The *Metll4* cKO in the striatum led to a downregulation of the neuron- and synapse-specific transcripts, whereas the amount of the normal cell metabolism and translation regulatory transcripts was increased. No changes were found in the overall striatal cell number, axonal projections, or dendritic morphology. It was suggested that m6A modification maintains the identity of neuronal cells in the brain. Most changed transcripts after *Mettl14* deletion were common to both striatonigral and striatopallidal cell populations. However, few transcripts were downregulated explicitly in striatonigral (Tac1 and Pdyn) or striatopallidal (Penk and Drd2) cells, depending on a specific reader context in a cell. Thus, they observed increased neuronal excitability in striatonigral neurons, which supposedly impaired spike frequency adaptation and striatal-dependent behaviours. The deletion was carried out in the striatum of adult mice, as deleting *Mettl14* early in life is incompatible with survival (Koranda et al., 2018). The downregulation of METTL14 leads to the whole genome changes in histone modifications (H3K27me3, H3K27ac, H3K4me3), which affects gene expression, NSC proliferation and differentiation (Wang et al., 2018).

3.4 The impact of stress on memory

Moderate acute stress improves the adaptive response of the cognitive functions, represented by associative learning and working memory. However, chronic stress is involved in the impairment of PFC-dependent cognitive functions due to impaired glutamate cycling and loss of glutamate receptors (Popoli et al., 2011). In response to fear memory, the abundance of m6A methylation sites correlated with the ability to discriminate threats (Chang et al., 2022). Area-specific methylation after stress was detected in two stress-related brain structures: PFC was globally hypomethylated, and the amygdala was globally hypermethylated. Deletion of *Mettl3* in cortical adult excitatory neurons reduced m6A levels, whereas *Fto* cKO mice had m6A peaks without any change, but m6Am peaks were increased. *Mettl3* cKO and *Fto* cKO brain tissue had very different epitranscriptomic and transcriptomic profiles; however, behavioural alterations were quite similar in both cKO mice. Both mice models had no change in anxiety-like behaviour, memory across time, fear extinction, and general condition but had an increased cued fear memory. Additionally, synaptic plasticity was altered in the CA1 region of *Fto* cKO mice, reflecting the correlation with enhanced contextual fear memory observed in this model (Engel et al., 2018). However, Spychala and Rüther (2019) reported that loss of *Fto* increased stress-related parameters like corticosterone in the blood, resulting in hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and a processing defect of BDNF via reduced expression of matrix MMP-9. The mice with an FTO deficiency exhibited anxiety-like behaviour, compromised working memory, and reduced hippocampal neuron differentiation (Spychala & Rüther, 2019). Methyltransferase PCIF1 could be one of the targets for manipulation in the follow-up studies about stress-related plasticity and major depressive disorder (MDD) pathophysiology.

3.5 Adult neurogenesis regulated by m6A methylation

In adult neurogenesis, newly created neurons are integrated into already existing neural circuits of the mammalian brain – the subgranular zone (SGZ) in the DG and the subventricular zone (SVZ) lining the lateral ventricles. The cells produced in adult neurogenesis show increased intrinsic excitability, strong responsiveness to external inputs, and enhanced synaptic plasticity (Dieni et al., 2016; L. Li, S. Sultan, et al., 2017). *In vivo,* proliferation and differentiation of adult NSCs (aNSCs) are significantly reduced in *Fto* KO adult mice due to the altered expression of several critical components of the BDNF signalling pathway (L. Li, Zang, et al., 2017). Expanding this finding, both *in vitro* and *in vivo*, *Fto* cKO in aNSCs transiently enhanced the proliferation and promoted differentiation of aNSCs. However, long-term FTO deficiency resulted in the inhibition of adult neurogenesis and differentiation. Hypermethylation decreased Pdgfra and increased Socs5 expression. These alterations in transcript expression jointly contributed to the phosphorylation of Stat3, which subsequently regulates neurogenesis (Cao et al., 2020). Depletion of METTL3 significantly reduced methylation and protein

expression levels of the histone methyltransferase EZH2, leading to decreased H3K27me3 modifications. On a cellular level, neuronal development in aNSCs was impaired, the cells were more prompt to differentiate into glial cells, and morphological maturation was inhibited both *in vitro* and *in vivo* (J. Chen et al., 2019). Discoveries in adult neurogenesis could be implicated in treating psychiatric disorders, neurodegenerative diseases, and recovery from brain injuries.

3.6 Myelination regulated by m6A methylation

Myelination is essential for synchronising neural activity within the circuits and integrating different inputs. Oligodendrogenesis and *de novo* myelination are important for memory formation and spatial learning through activated circuit tuning and hippocampal ripple-cortical spindle coupling (Pajevic et al., 2014; Steadman et al., 2020). In parahippocampal tissue, m6A sites are distinct in white and grey matter. In the grey matter, modified transcripts are involved in neuronal and synaptic function, protein binding, cell junctions, cell adhesion, and post-translational modification (De La Cruz et al., 2021). METTL14 downregulation did not affect the number of oligodendrocyte progenitor cells (OPCs) but impaired the ability of the progenitor cells to mature into MBP-positive oligodendrocytes *in vitro*. The deactivation of *Mettl4* in the later stages of oligodendrocyte cell development did not affect their transformation into mature cells, indicating m6A regulation importance in early stages. The authors suggest that interactions with other cells in the CNS *in vivo* may lessen the negative effects on postmitotic oligodendrocyte differentiation compared to *in vitro* conditions. RNA-seq and m6A-seq analyses of transcripts showed that m6A methylation influences the expression of transcriptional regulators, DNA epigenetic modifiers, and signalling pathways crucial for oligodendrocyte lineage development. Loss of *Mettl4* in OPCs and oligodendrocytes led to aberrant splicing of many transcripts (Ptprz1, Gsn, Map2, Nfasc). One of the isoforms of the neurofascin protein, NF155, encoded by *Nfasc155*, was downregulated in *Mettl14* cKO mice, resulting in abnormalities in the nodes of the Ranvier domain (Xu et al., 2020). PRRC2A stabilises the methylated Olig2 transcript, responsible for oligodendrocyte differentiation and myelination. *Prrc2A* deletion or FTO-induced demethylation destabilises the transcripts, leading to severe hypomethylation, locomotive and cognitive deficits, or even decreased life span in a mouse model (R. Wu et al., 2018). A depletion of METTL5 in mESCs led to craniofacial and neural development defects, corresponding to the symptoms observed in human patients with mutated *Mettl5*. In *in vivo* tests, *Mettl5* KO mice exhibited smaller size and impaired learning and memory abilities. RNA-seq analysis showed a downregulation of genes associated with neuron ensheathment, myelination, and neuron transmission (L.Wang et al., 2022).

4. Neurological disorders associated with cognitive impairments

4.1 Alzheimer's disease

Alzheimer's disease (AD) is the most well-known form of dementia. The risk of developing Alzheimer's increases with age, as well as other factors such as genetics, lifestyle, and environment. Individuals with AD experience a decline in several cognitive functions and changes in behaviour. The occurrence of this disease is detected by PET or through analysis of cerebrospinal fluid (CSF) when the disease has already progressed to a chronic stage. Mild cognitive impairment (MCI) is a transitional and also reversible stage. Finding biomarkers at the MCI stage might help with an early diagnosis and intervention. METTL3 and METTL14 were downregulated in the brains of MCI patients. The expression level of other regulators was unchanged, suggesting that METTL3 plays an important role in the early stages of AD (Zhao et al., 2021). Other m6A regulators, members of the small nuclear ribonucleoprotein polypeptide family, SNRPG and SNRPD2, were decreased in correlation to the transformation from MCI to AD (Du et al., 2021). Multiple studies have reported conflicting findings on whether m6A sites are decreased or increased in AD pathology, as reviewed in **Table 1**.

4.1.1 Aβ deposition as a hallmark of Alzheimer's disease pathogenesis

The protein Aβ binds to NMDA receptors, blocking the influx of Ca^{2+} ions. This process promotes long-term depression (LTD) and activates a Ca^{2+}/calmodulin-dependent protein phosphatase, calcineurin, enhancing the internalization of AMPA and NMDA receptors (Snyder et al., 2005; Wu et al., 2010). Changes in mRNA caused by m6A are linked to glutamatergic synapses, axon guidance, LTP, and Ca^{2+} signalling in the AD brain (Han et al., 2020). The upregulation of the amyloid precursor protein (APP) is caused by the downregulation of FMRP and upregulation of HNRNPC, which competitively bind to App mRNA, thus promoting its translation in the AD brain (Borreca et al., 2016). In a high-IGF2BP2 subgroup in the human AD brain, m6A-modified genes are enriched in cytokine-cytokine receptor interaction, focal adhesion, ECM receptor interaction, and TGF-β signalling pathways, with abnormally low levels of Aβ and tau protein expression (Deng et al., 2021).

4.1.2 The role of m6A in tau phosphorylation and neurotoxicity

Hyperphosphorylation of tau protein results in the intracellular accumulation of NFTs, and AD was the first neurodegenerative disease where NFTs were identified (Morris et al., 2011). Hyperphosphorylated tau protein disrupts axon transport, including the trafficking of glutamate receptor subunits and mitochondria (Terwel et al., 2002). In 3xTg AD mice, *Fto* cKO in neurons partially improved the cognitive impairment symptoms. FTO induces tau phosphorylation by increasing the levels of TSC1, an inhibitor of the mTOR (Li et al., 2018).

Table 1. An overview of the conflicting findings regarding m6A methylation levels and their regulators in Alzheimer's disease.

m6A levels	Materials	Localisation	m6A regulators	Functions	References
Decreased	Postmortem human AD brain; mouse N2a cells	Hippocampus	METTL3 ↓	*In vitro*, *Mettl3* knockdown induced PSD95 loss and cyclin D2 mRNA upregulation, leading to significant synaptic abnormalities and aberrant cell cycle events. *In vivo*, METTL3 depletion disrupted pyramidal cell physiology by reducing caspase 3 and 9 expression, inducing oxidative stress, DNA damage and enhanced neuronal death. METTL3 overexpression rescued soluble Aβ-oligomers-induced cognitive deficits and neurodegeneration.	(Zhao et al., 2021)
	Postmortem human AD brain	Hippocampus	Soluble fraction: METTL3 ↓, RBM15 ↑; Insoluble fraction: METTL3 ↑	The insoluble form of METTL3 showed a positive correlation with the presence of tau aggregates in the insoluble fraction.	(Huang et al., 2020)
	Tyrobp$^{-/-}$ mouse model	Hippocampus	METTL3 ↓ METTL14 ↓ WTAP ↓	M6A levels were decreased in astrocytes, microglia, and neurons, leading to aberrant regulation of genes linked to cancer, various signalling pathways and cell adhesion.	(Lv et al., 2022)
	Postmortem human AD brain; Aβ-induced cells	Hippocampus	METTL3 ↓	M6A levels on Arc were decreased, which reduced ARC protein expression. METTL3 rescued Aβ-induced ARC downregulation in a YTHDF1-mediated manner.	(Xu et al., 2022)
	5xFAD mouse model	Cerebral cortex, cerebellum, hypothalamus, hippocampus	METTL3 ↓ FTO ↑	The expression levels of AD-related transcripts increased. During normal ageing (1.5 vs. 13-month-old mice), global m6A methylation increased as the mice aged.	(Shafik et al., 2021)
	Mouse model of cognitive decline; postmortem human AD brain	Mouse hippocampus and ACC; human CC	METTL3 ↓	The aged mouse models and AD patients exhibited differentially methylated transcripts associated with synaptic function (Camk2, Glua1). M6A levels were reduced in the aged mouse models (3 vs 16-month-old mice) and AD patients.	(Castro-Hernández et al., 2023)
Increased	APP/PS1 mouse model	Cerebral cortex, hippocampus, cerebellum	METTL3 ↑ FTO ↓	M6A levels were higher in the hippocampus and cortex but not in the cerebellum. Differentially methylated transcripts were associated with the presynaptic, postsynaptic membrane, and synaptic growth.	(Han et al., 2020)
	Mettl3$^{fl/fl}$*Lyz2*$^{Cre/-}$ aged mice model, Aβ-induced AD mice model, HEK293T cells	Cortex	METTL3 ↑	METTL3 downregulation enhanced the migration of monocyte-derived macrophages and Aβ clearance through the attenuated m6A-modification of Dnmt3a mRNA and YTHDF1-mediated translation of this protein. DNMT3A binds to the promoter of *Atat1* and promotes its expression, leading to reduced acetylation of α-tubulin in bone-derived macrophages and improved symptoms of AD.	(Yin et al., 2023)

HNRNPA2B1, m6A and oligomeric tau levels are up to 5-fold higher in AD brain and P301S mice model. HNRNPA2B1 functions as a linker between m6A-modified transcripts and oligomeric tau, mediating translational stress response upon oligomeric tau induction. Phosphorylation is more important in accelerating the oligomer formation rather than in HNRNPA2B1 binding. Knockdown of *Mettl3* lowered m6A methylation and impaired tau-dependent cytoplasmic translocation of HNRNPA2B1, preventing neurodegeneration (Jiang et al., 2021). *Mettl3*, *Mettl14*, and *Ythdf* deletion lead to decreased m6A sites and aggravation of tau toxicity and locomotive defects in the *Drosophila* transgenic AD model (Shafik et al., 2021). In contradiction, lysine

demethylase KDM1A binds to the promoter of *Mettl3* and enhances its expression, which then stabilises Stub1 transcript in an IGF2BP1-dependent manner, improving symptoms of AD by promoting autophagic clearance of the phosphorylated tau in $A\beta_{1-42}$-treated cells (Tang et al., 2023). NSUN2 is an m5C methyltransferase found in the nucleus of hippocampal and PFC neurons. It also serves as an m6A regulator of miRNAs. Upon NSUN2 downregulation, miR-125b is dysregulated, promoting tau hyperphosphorylation. This, in turn, induces tau toxicity in both *Drosophila* and mouse models, as well as in human induced pluripotent stem cells (Hussain et al., 2013; Kim et al., 2023).

4.1.3 M6A regulators in association with apolipoprotein E in the pathogenesis of AD

The ε4 allele of apolipoprotein E (APOE) is a risk factor for developing AD. Moreover, all ApoE RNA types are elevated in the AD brain (Lee et al., 2020). Using bioinformatics tools, it was found that APOE ε4 was associated with METTL3, METTL16, YTHDC2, RBMX, and LRPPRC, connecting this risk factor to the m6A regulation (Du et al., 2021). The occurrence of both *Fto* AA (rs9939609) and *ApoE* ε4 alleles increases the risk of dementia/AD onset (Keller et al., 2011).

4.1.4 Inflammation regulated by m6A in the pathogenesis of AD

Microglia. Microglia cells can be in two well-defined stages and transitional stages between them: M1 phenotype is involved in inflammatory processes and neurotoxicity, and M2 in tissue reparations and brain homeostasis (Prinz & Priller, 2014). KEGG analysis revealed that differentially m6A methylated mRNAs in M1 microglia were associated with pathways like immune system modulation, signal transduction, and ubiquitin-mediated proteolysis. M2 microglia had altered m6A modifications in mRNAs involved in genetic information processing, metabolism, cellular processes, and neurodegenerative disease-related pathways. In M1 microglia, the methylation of lncRNAs was elevated, both compared to M0 and M2 phenotypes, suggesting the role of lncRNAs in inflammatory response (Li et al., 2021). Lipopolysaccharide (LPS)-induced m6A signature alterations and mRNA transcript switch in microglia were found to be regulated by IGF2BP1 stabilisation of Gbp11 and Cp mRNAs (Ding et al., 2022). CP enzyme plays a role in iron homeostasis and inflammation in microglia (Lee et al., 2007; Y. Wu et al., 2018). GBP11 is elevated in the lungs and liver upon pro-inflammatory exposure (Al-Quraishy et al., 2018; Mao et al, 2020). Upon LPS exposure, METTL3 binds to TRAF6, thus promoting the activation of the TRAF6-NFκB pathway, which increases inflammatory cytokine production (Wen et al., 2022). M1 polarisation in retinal microglia was found to be regulated by YTHDC1-mediated stabilisation of histone deacetylase, Sirt1, mRNA (Zhou et al., 2021). M6A modifications were elevated in microglia and astrocytes in the hippocampus and cortex area of the AD brain, which they speculate might be the reason for the discovered overall unchanged levels of m6A measured by LC-MS/MS (Zhao et al., 2021).

CircRNA. CircRNAs play a role in Aβ clearance, neuroinflammation, oxidative stress and autophagy through their interaction with neurodegenerative disease-related miRNAs. M6A sites, mediated by METTL3 writer and YTHDF1/2 readers, are present in circRNAs (Zhou et al., 2017). CircRNA ciRS-7 acts as a "sponge" for miRNA-7, leading to downregulation of AD-associated targets such as UBE2A, essential for clearing amyloid oligomers (Akhter, 2018).

Glial cells. White matter degeneration is identified in AD patients. Myelination and demyelination can be monitored by neuroimaging, and any disbalance can be detected earlier than other biomarkers become more apparent (Nasrabady et al., 2018). In the AD brain, OPCs expressed Aβ plaque-associated OLIG2 and NG2 proteins, exhibited senescence-like phenotype and upregulated transcripts involved in OPC function, cell senescence, and inflammation. The senolytic treatment relieved OPC-related dysfunctions and cognitive deficits (Zhang et al., 2019). Streptozocin (STZ)-caused apoptosis, oxidative stress, upregulated GFAP, and mitochondrial dysfunction in the human astrocytoma CCF-STTG1 cell line of the AD model was reduced by MO-I-500 inhibitor of FTO. Overall, levels of FTO and YTHDF1 were higher in STZ-treated astrocytes, indicating the role of m6A in glial cell inflammation for the onset of AD (Cockova et al., 2021).

4.2 Parkinson's disease

PD is the second most common neurodegenerative disease that predominately affects dopaminergic neurons in the substantia nigra and, consequently, leads to dopamine deficiency in the striatum (Vallone et al., 2000). The disease's symptoms can be divided into two categories: motor (resting tremor, muscle rigidity, bradykinesia, postural instability) and non-motor (cognitive impairment, mood disorders, sleep disturbances, autonomic dysfunction).

4.2.1 The role of m6A erasers in PD pathology

Five m6A-related single nucleotide polymorphisms (SNPs), three of which are located on *Alkbh5*, are potentially associated with the risk of PD (Qiu et al., 2020). FTO deficiency in the midbrain and striatum of mice impaired D2R and D3R-dependent neuronal activity and led to the m6A methylation of the transcripts linked to synaptic transmission and cell-cell signalling (Hess et al., 2013). ALKBH5 levels are significantly elevated in the substantia nigra upon MPTP administration. In contrast, the expression levels of FTO are not changed both in the substantia nigra and striatum (Yu et al., 2022). This contradicts a study by X. Chen et al. (2019), claiming that the increased FTO leads to elevated expression of NMDA receptor 1, oxidative stress, Ca^{2+} influx, and eventually induces dopaminergic neuron apoptosis. In the 6-OHDA-treated PD rat model, ALKBH5 levels are elevated in the striatum, while FTO levels are unchanged, whereas in the midbrain, FTO increases, and ALKBH5 is not changed. However, the FTO expression level increases in the PD cellular model, but there is no difference

in ALKBH5 expression. Geng et al. (2023) discovered that FTO expression was increased in PD models both *in vitro* and *in vivo*, promoting the expression of the pro-apoptotic factor ATM and, consequently, the death of dopaminergic neurons. Knockdown of *Fto* in mice's striatum alleviates upregulation of α-synuclein and downregulation of tyrosine hydroxylase, preventing dopaminergic neuronal death (Geng et al., 2023). Elevated FTO levels reduced stability of Nrf2 mRNA, a crucial component of antioxidant defence (Pang et al., 2024). This transcript instability leads to the exacerbation of ferroptosis, a form of programmed cell death characterised by iron-dependent lipid peroxidation, often associated with neurodegenerative diseases such as PD (Dixon et al., 2012; Pang et al., 2024).

4.2.2 The role of m6A writers and readers in PD pathology

Levels of Mettl3, Mettl14, and Ythdf2 mRNAs are significantly lower in PD patients. METTL14 abundance is negatively associated with α-synuclein levels and disease severity. Elevated levels of METTL14 inhibited the expression of α-synuclein in an m6A-YTHDF2-dependent manner (He et al., 2023). Meanwhile, cKO of *Mettl14* in the substantia nigra significantly reduced total m6A levels and decreased tyrosine hydroxylase expression and dopamine synthesis while microglia and astrocytes activation was enhanced. M6A sites are abundant in the 3'UTR of transcription factors essential for tyrosine hydroxylase regulation (Nurr1, Pitx3, and En1) Motor function and locomotor activity also decreased upon METTL14 downregulation (Teng et al., 2021). GLRX, NRF1, and METTL3 levels are low in MPTP-induced mice. NRF1 binds to the *Mettl3* promotor, inducing its expression and promoting m6A modification of Glrx mRNA, stabilised in an IGF2BP2-dependent manner. GLRX downregulation then enhances motor dysfunction and dopamine neuron degeneration (Gong et al., 2024). METTL3 and RBM15 are decreased while the levels of CBLL1 are increased in the striatum region after a mouse model's MPTP injection (Yu et al., 2022). CBLL1 might be associated with neuronal apoptosis upon LPS administration; however, studies on its function in the nervous system are limited (Cao et al., 2013). Additionally, in the substantia nigra of PD mice, YTHDF1, HNRNPC, and FMRP readers were lowered, while the expression of IGF2BP1 increased. In the striatum, HNRNPC and IGF2BP3 levels were downregulated, and FMRP expression levels increased. This article has limitations, and some findings require further investigation (Yu et al., 2022). According to Qin et al. (2020), there is no significant association between 10 m6A-related regulatory proteins (METTL3, METTL14, WTAP, FTO, ALKBH5, YTHDF1-3, HNRNPC, and ELAV1) and the risk of sporadic PD. Nevertheless, the implications of their findings are limited since the experiment was done on the peripheral blood of patients and controls only of Han Chinese origin. In PC12 cells, overexpression of HNRNPC promoted the proliferation of dopaminergic nerve cells and inhibited apoptosis and immune inflammation by reducing the expression of IFN-β, IL-6, and TNF-α. However, the authors warned about several limitations in the interpretation of their findings (Quan et al., 2021). Soot nanoparticles are black carbon particles produced by

engines. Exposure to the particles increased METTL3-mediated methylation in the 5'UTR of Acsl4, upregulating its protein expression via YTHDF1-binding. The increased expression of ACSL4 contributes to the acceleration of ferroptosis in dopaminergic neurons by increasing ROS and iron levels while reducing glutathione levels and mitochondrial membrane potential. These changes worsen the motor and cognitive impairments in PD (Feng et al., 2024).

4.2.3 The role of m6A-modified ncRNAs in PD pathology

Dysregulated lncRNAs upregulate the *Lrrk2* gene, which is associated with PD onset (Wang et al., 2017). In paraquat (PQ)-induced Neuro-2a cells, the m6A abundance on lncRNAs (lncRNA CDC5L and lncRNA STAT3) is higher due to the upregulated expression of methyltransferases and the downregulated expression of demethylases, which affects neurodegenerative processes. (Su et al., 2022). Using a similar approach, it was identified that m6A alterations on circRNAs also result in disrupted oxidative stress regulation through dysregulated expression of UBC and PPP2CA upon PQ exposure (N. Chen et al., 2021).

4.3 Depression

4.3.1 The role of m6A erasers in depression

Depression is a mood disorder that can impair the executive and cognitive functions of a patient. An rs9939609 SNP in *Fto* is considered to have a protective function against depression (Samaan et al., 2013). An rs12936694 SNP in *Alkbh5* is closely associated with MDD in the Chinese Han population (Du et al., 2015). In MDD patients, glucocorticoid stimulation in the blood and blood cells shows a deregulated m6A/m response. The authors proposed that m6A/m stress response evaluation in the blood could be a potential biomarker of MDD (Engel et al., 2018). Upregulation of FTO in the hippocampus has a reversing effect on the depressive behaviour induced by chronic restraint stress. This was evidenced by the heightened dendritic spine density and branch numbers, elevated synaptic plasticity-related proteins (including synaptophysin and PSD95), and thickening of postsynaptic density. Additionally, FTO overexpression led to the activation of the CaMKII/CREB signalling pathway (Shen et al., 2021). FTO overexpression has similar effects to antidepressants by reducing methylation levels on Adrb2 transcript, leading to its increased protein expression. The receptor upregulation further promotes downstream c-MYC expression, which binds to the hippocampal *Sirt1* promoter, increasing the expression of deacetylase SIRT1 (Liu et al., 2021). Tricyclic antidepressants (TCAs) enhance FTO expression in the ventral tegmental area (VTA), leading to reduced transcription of stress-related neuropeptides (Wu et al., 2021).

4.3.2 The role of m6A writers and readers in depression

In a rat model of depression treated with chronic unpredictable mild stress, elevated levels of METTL3 stimulate the generation of mature miRNAs by strengthening the interaction between DGCR8 and pri-miR-221. This results in increased production of miR-221-3p, which, in turn, suppresses the expression of GAB1, exacerbating cognitive impairment (Niu et al., 2022). Hypericin treatment demonstrated antidepressant effects in a mouse model of depression subjected to unpredictable chronic mild stress. It resulted in the upregulation of METTL3 and WTAP expression in the hippocampus via the neurotrophin signalling pathway (Lei et al., 2023). Treatment with chronic unpredictable stress led to increased expression of circHECW2 in the blood plasma of patients with MDD, as well as in a mouse model. Decreasing the expression of circHECW2 led to higher levels of WTAP expression, subsequently increasing GNG4 expression levels. This in turn helped alleviate astrocyte dysfunction and depression-like behaviours (Bai et al., 2024). Through PPI network analysis and functional enrichment, 12 hub genes were identified as potential diagnostic biomarkers in depression's inflammatory infiltration (Wang et al., 2022). ELAV1 (associated with comorbid anxiety) and YTHDFC2 were found to be closely associated with MDD. The authors claim that the proteins had an almost opposite correlation with 23 types of immune cells in MDD patients (Li et al., 2024). A bioinformatics analysis showed the elevated expression of METTL16, YTHDC1, and YTHDC2 in the PFC and low expression of IGF2BP1/2 in both normal and MD patients. Expression levels of the m6A regulators differ in the dorsolateral PFC of depressed patients in a sex-dependent manner (Joshi et al., 2022).

4.4 Other examples of m6A regulation of cognitive impairments

4.4.1 Diabetes mellitus

Diabetes mellitus is a common chronic disease related to metabolism dysregulation, with reported higher cases of cognitive disorders, depression and anxiety in affected patients. STZ-induced diabetes mellitus in rats leads to damage to hippocampal neurons. Differentially methylated 4890 m6A peaks (3110 downregulated peaks) were associated with endoplasmic reticulum dysfunction and axon-related alterations. Inconsistent with other studies on FTO function in diabetes mellitus, FTO expression was found to be decreased in the hippocampus. METTL3 levels are significantly elevated both in the hippocampus of diabetic rats and in *in vitro* cells (Song et al., 2020). High glucose has been identified as a risk factor for tau hyperphosphorylation and subsequent cognitive impairments in hippocampal neurons of diabetic patients (Wu et al., 2017). ALKBH5 is downregulated in diabetic rats and high-glucose-stimulated cells. ALKBH5 targets Dgkh, leading to tau hyperphosphorylation via PKC-α activation (Qu et al., 2023). YTHDF1 overexpression reversed cognitive impairment but not diabetic symptoms in the hippocampus of the STZ-induced type 1 diabetic mouse model. Western blot analysis identified that YTHDC2 and ALKBH5 were upregulated, while YTHDF1, YTHDF3 and WTAP were downregulated in the STZ-treated group (Li et al., 2022).

4.4.2 Huntington's disease

Huntington's disease is characterised by changes in associative learning, spatial short-term memory, spatial working memory, recognition memory, and motor dysfunctions in patients (Lemiere et al., 2004). Transcripts associated with the disease pathophysiology and synapse regulation were hypermethylated in the hippocampus of the Huntington's disease mice model. After spatial learning, m6A methylation levels of several synaptic genes essential for learning did not increase in $Hdh^{+/Q111}$ mice compared to WT mice. However, both WT and $Hdh^{+/Q111}$ mice showed similar methylation in IEGs and some synaptic genes (Pupak et al., 2022). Among the modified transcripts in $Hdh^{+/Q111}$ mice, there was a scaffolding protein of the postsynaptic density, Shank1, and Neurexin1, a protein important for enhancing NMDA receptor-mediated synaptic responses (Dai et al., 2019). In the activated neurons, METTL14 levels are increased in the nucleus, while FTO nuclear levels are decreased and increased in postsynaptic fractions in WT mice. In contrast, FTO levels in $Hdh^{+/Q111}$ mice remained unchanged (Pupak et al., 2022). Exploration and novelty are affected by dopamine circuitry neurotransmission modulated by FTO (Hess et al., 2013). Before training, *Fto* knockdown in the CA1 region enhanced spatial and recognition memory and improved exploratory behaviour (Pupak et al., 2022).

4.4.3 Brain-damaging compounds

Long-term Cd exposure causes neurotoxicity and impairs cognitive functions by promoting ROS production, disrupting mitochondrial membrane potential, and reducing ATP. In Neuro-2a cells, exposure to $CdCl_2$ increases the expression of lnc-Gm10532, leading to the recruitment of METTL14. The enhanced methylation of Fis1 mRNA promotes its expression, ultimately promoting mitochondrial fission. In a rodent model, Cd exposure resulted in observed mitochondrial dysfunction and memory deficits (P. Deng et al., 2023). FTO deficits impact dopamine neurotransmission upon arsenite exposure. This results in elevated methylation levels and disrupted expressions of tyrosine hydroxylase, dopamine transporter, catechol-O-methyltransferase, DRD1, and DRD2, leading to impaired learning and memory, changes in conditioned avoidance, escape responses, and anxiety-like behaviour (Bai et al., 2018). Prolonged exposure to constant light is associated with cognitive impairments due to activation of circadian regulators CRY1 and CRY2, leading to a reduction in FTO and an increase in METTL3, METTL14, and WTAP. Consequently, m6A levels on the 3'UTR of various mRNAs are increased, resulting in reduced expression of proteins, including TrκB protein (a BDNF/TrκB/ERK pathway component) in the hippocampus in a YTHDF2-dependent manner (Yang et al., 2021).

Postoperative cognitive dysfunction (POCD) is affected by anaesthesia, mostly in elderly patients, and sevoflurane is one of the most widely used anaesthetics. Sevoflurane disrupts METTL3-mediated methylation in the hippocampus of mice. Hypomethylation was detected in 1244 genes, whereas hypermethylation in 56 genes (He & Wang, 2021). METTL3 downregulation leads to a decrease of transcript expression of Sox2,

impacting cell proliferation and apoptosis in the LPS and sevoflurane-treated cells (Wang & Yang, 2023). YTHDF1 overexpression improved sevoflurane-mediated neuronal damage and cognitive dysfunction in the POCD brain through interaction with Creb mRNA and activation of the CREB/BDNF pathway in the hippocampus, which then represses inflammasome activation-mediated pyroptosis (Huang et al., 2023). *Ythdf1* reintroduction increased translation of multiple transcripts, including the presynaptic protein synaptophysin. It restored impairments in fine motor control skills and cognition in the cortical neurons of a young mouse affected by multiple sevoflurane anaesthesia exposures (L. Zhang et al., 2022). Sevoflurane exposure in the PFC of infant rhesus monkeys decreased both YTHDF1 and YTHDF3 levels and resulted in sex-specific hypermethylation of several transcripts related to synaptic plasticity, affecting neurodevelopment (Chen et al., 2022).

4.4.4 Brain injury/damage

Traumatic brain injury of the rat cerebral cortex led to decreased levels of METTL14 and FTO. Inhibiting FTO with FB23-2 impaired neurological damage repair but not spatial learning and memory abilities (Yu et al., 2020). However, a study on mouse hippocampus showed that the expression of METTL3 decreased, but the expression of other enzymes (METTL14, FTO, WTAP, and ALKBH5) was not significantly altered after traumatic brain injury (Wang et al., 2019). Hypoxic ischemia results in delayed neurite outgrowth and synaptogenesis, impacting LTP and often leading to neonatal brain damage and death (X. Chen et al., 2021). In neonatal rats, FTO was downregulated, resulting in elevated levels of PTEN, a tumour suppressor that negatively modulates the AKT/mTOR pathway, thereby enhancing autophagy in a model of hypoxic-ischemic brain damage (J. Deng et al., 2023). Weng et al. (2018) highlighted the role of METT14, YTHDF1, and PTEN in axon regeneration after injury in the adult nervous system.

4.4.5 The effects of normal physiological processes on cognitive dysfunctions

During pregnancy and post-delivery, there is a higher occurrence of mental disorders, such as depression and anxiety. Pregnant rats that experienced stress displayed symptoms of mental disorders. The reduced level of FTO in the fear-stressed rats impacted the regulation of four genes (Antgpt2, Fgf10, Rpl21, and Adcy7), which may be involved in the pathogenesis of mental disorders (Jiang et al., 2023).

Aging is inevitably associated with a decline in many body functions, including cognitive function, making us vulnerable to neurodegenerative disorders. In the aged hippocampus of the 20-month-old mice, 426 genes were hypermethylated, and 102 genes were hypomethylated. Moreover, lowered m6A sites in the 3'UTR of a Gpr17 reduced its translation efficiency, affecting. active myelination in CNS (Huang et al., 2023). There is also a correlation between m6A modification and cell senescence through methylation of several transcripts involved

in the cell cycle (p21, p53, p27, Ago2), implying a possible connection between brain development and ageing (Lewinska et al., 2017; Q. Li et al., 2017; Min et al., 2018).

4.4.6 Down syndrome

Down syndrome is an intellectual disability caused by an extra copy of chromosome 21. The overexpression of NRIP1 in the fetal brain cortex tissue of individuals with Down syndrome is attributed to a reduction in m6A mRNA modifications caused by downregulated METTL3. This leads to mitochondrial dysfunction in the brain tissue (Shi et al., 2021).

4.4.7 Fragile X syndrome

Reduced FMRP is responsible for causing fragile X syndrome, a hereditary intellectual disability characterised by developmental delays, autism-like behaviour, and an average IQ of around 40. Loss of *Fmr1* significantly altered m6A epitranscriptome in mRNAs associated with transcription and synapses. Reverse regulation of FMRP (degradation in P-bodies) and HNRNPC (translation promotion) on APP's expression was previously discussed in the chapter on AD (Lee et al., 2010). However, FMRP is not associated with the nuclear export of App mRNA, but it does play a role in the cleavage of App by facilitating the nuclear export of APP's secretases Adam9 and Psen1, encoding for an α-secretase and γ-secretase, respectively. Other FMRP targets did not change their nuclear/cytoplasmic distribution after the KO of *Fmr1*, except for Agap2 mRNA, which encodes for PIKE protein. This protein serves as a regulator of group 1 mGluR-dependent PI3K activity (Westmark et al., 2020).

4.4.8 Vitamin B_{12} deficiency

Vitamin B_{12} is a cofactor for methionine synthase (Stubbe, 1994). Methionine is a direct precursor of SAM. Vitamin B_{12} deficiency leads to a widespread decrease in m6A methylation sites caused by the dysregulation of SAM and/or the observed overexpression of FTO in two cellular models. However, no changes in FTO expression were noted in the hippocampus and hypothalamus of the mice model, suggesting that SAM alone can regulate m6A methylation in those areas. Despite the decrease in m6A levels, Prkca mRNA was hypermethylated, resulting in increased PKCα expression, which then affects various cell pathways in the brain, such as dopaminergic, GABAergic, serotonergic, or glutamatergic synapse activity, LTD, and the WNT or sphingolipid signalling pathways. The local hypermethylation may serve to preserve essential cell functions (Mosca et al., 2021).

5 Conclusion and future perspectives

Despite being discovered in the 1970s, the first mentions of m6A's role in regulating various functions are very recent. This highlights the limited time for a comprehensive study of m6A regulatory pathways in the brain. The highly specific and dynamic m6A mark further challenges the long-standing "nature vs nurture" debate. Researchers have long acknowledged the intricately controlled nature of synaptic function, yet the exact mechanism has been elusive. Identifying m6A regulation has shed light on the connection between phenotypic changes and gene expression. This epitranscriptomic mark is pivotal in neuronal function and plasticity, and its impact on gene expression is closely associated with the observable traits of neurological disorders. Single-cell profiling of the heterogeneous population of neurons under resting and stimulating conditions is critical for delineating the fine-tuning activity of the m6A pathway (a short overview of m6A-detecting methods can be found in a review by Capitanchik et al. (2020)). The MeRIP-seq mapping technique, which paved the way for the discovery of m6A at the time, should be noted for its lack of quantitativeness and reproducibility, along with its limited ability to confidently detect changes in m6Am (McIntyre et al., 2020). In recent years, there have been numerous efforts to identify therapeutic targets and agents for treating neurological diseases. These efforts have focused on various inhibitors, activators, and ncRNAs, which show promise in disease prevention. Further research is needed to explore new targeting compounds of the m6A pathway. Future studies might focus on reconciling conflicting findings on m6A and m6A regulator levels in different disorders and improving techniques for distinguishing between m6A and m6Am sites. This could help to identify specific regulatory pathways for m6Am in the brain.

It is important to mention that the information above provides a glimpse into the various regulatory functions of m6A in RNA metabolism. The field of m6A research is expanding, revealing additional roles and contributing to a deeper understanding of co-transcriptional and post-transcriptional gene regulation. Nevertheless, we can already state that m6A modification ensures a rapid and dynamic response to the stimulus based on the current needs of the cell and organism.

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