

RNA editing, DNA recoding and the evolution of human cognition

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RNA editing appears to be the major mechanism by which environmental signals overwrite encoded genetic information to modify gene function and regulation, particularly in the brain. We suggest that the predominance of Alu elements in the human genome is the result of their evolutionary co-adaptation as a modular substrate for RNA editing, driven by selection for higher-order cognitive function. We show that RNA editing alters transcripts from loci encoding proteins involved in neural cell identity, maturation and function, as well as in DNA repair, implying a role for RNA editing not only in neural transmission and network plasticity but also in brain development, and suggesting that communication of productive changes back to the genome might constitute the molecular basis of long-term memory and higher-order cognition.

Introduction

RNA editing is a process through which RNA base sequences are post-transcriptionally altered. RNA editing occurs in most, if not all, tissues but is particularly active in the nervous system, where it has long been known to play an important modulatory role, especially in the modification of transcripts encoding proteins involved in fast neural transmission, such as ion channels and ligand-gated receptors [1–3]. It is clear that RNA editing is a principal means by which environmental information can intersect with genetically and epigenetically encoded information, given that RNA is the product of the first and intimately involved with the second [4]. Although RNA editing has been a well-recognized phenomenon throughout evolution, there has been a dramatic increase in the incidence of RNA editing during vertebrate, mammalian and primate evolution, with humans exhibiting the highest levels of both edited and multi-edited transcripts [1–3].

Several different forms of editing occur in humans catalyzed by two classes of RNA editing enzymes [1–3,5]. The predominant form of RNA editing in mammals is adenosine-to-inosine (A-I) editing which is catalyzed by ADARs (adenosine deaminases acting on RNAs), of which there are three paralogs encoding ADAR1–3, all with preferential expression in the nervous system, with ADAR3 being expressed exclusively in the brain [1,2].

The general substrate for A-I editing appears to be double-stranded regions of RNA, but what determines the site selectivity of RNA editing of specific transcripts in different cells and tissues is not well understood [1–3].

RNA editing and gene–environmental interactions in the brain

There are at least three distinct ways that RNA editing can alter brain function in response to experience (i.e. learning) and contribute to the evolution of higher-order cognitive capacities. First, by selectively editing codons and splicing signals in protein-coding sequences involved in modulating fast neurotransmission and all stages of presynaptic vesicle release [1–3], ADAR enzymes can fine-tune the firing properties of neurons required for appropriate neuronal and neural network output and integration. Second, RNA editing can alter the processing, properties and target specificities of microRNAs (miRNAs) and the regulatory networks in which they participate [6,7] (see also below). Third, RNA editing can modify the sequences and biophysical properties of a vast array of other gene products, notably pre-mRNAs and the large numbers of non-coding RNAs known to be specifically expressed in the brain and to play roles in many functional and regulatory pathways, including epigenetic phenomena associated with learning [8–10].

Within brain, ADARs exhibit complex profiles of spatio-temporal regulation and dynamic changes in subcellular localization [3], and are themselves subject to alternative splicing [11]. Moreover, the activities of ADARs are modulated by environmental cues and modify signaling cues embedded within intracellular transduction pathways containing edited targets as seen in ADAR1/2 editing of the serotonin (5-HT_{2C}) transcript [3]. RNA editing is also modulated by genetic background as well as behavioral state, suggesting that this process might represent a hidden layer of regulatory and functional plasticity mediating gene–environmental interactions during neural state transitions [12]. Analysis of *Caenorhabditis elegans*, *Drosophila* and mouse ADAR mutants demonstrates that RNA editing is critical for the cognitive and behavioral correlates of nervous system function [3], and that loss of RNA editing predisposes to progressive neurodegeneration [3,13]. Furthermore, deregulation of ADAR activity and associated hyper- or hypo-editing of RNA transcripts is

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associated with an increased risk of neurodegenerative diseases and cancer in addition to an elevated occurrence of neurodevelopmental as well as neuropsychiatric diseases [3,14,15].

The link between RNA editing and environmental cues is supported by the observation that inositol hexakisphosphate is complexed within the catalytic core of ADAR2, which strongly implies a connection to cell signaling pathways [16]. Moreover, there are well-characterized iconic examples of neural ligand-gated receptors, particularly glutamate and serotonin receptor subunits, that are edited to alter their coding sequence and splice isoforms, thereby modifying their biochemical and electrophysiological properties, presumably to fine-tune individual synaptic strength and other features of synaptic transmission and neuronal network connectivity [3]. Other molecules are also edited, including miRNAs [17–20] and other non-protein-coding RNAs (ncRNAs) [21–23], which can redirect the miRNAs to silence different targets [20]. Sites of RNA editing might also be sites of small nucleolar RNA-mediated RNA modification [24], suggesting that editing is used not only to alter the biochemical properties of proteins but also genetic and epigenetic regulatory networks, and that such networks could be extraordinarily complicated, especially in the brain.

RNA editing in Alu elements – evolutionary co-adaptation?

Recently, it was reported by several groups that A-I editing is much more abundant in humans than in mice, and that over 90% of this increased editing occurs in head-to-tail Alu elements in (mainly) noncoding regions of RNAs, that is, in UTRs of mRNAs, and in intronic and intergenic transcripts [21–23]. Alu elements represent a subclass of primate-specific SINEs (short interspersed nuclear elements) derived from 7S and tRNA sequences and spread around the genome by retrotransposition [25]. These repetitive elements entered the genome in three successive waves during primate evolution, with massive expansion in hominids to over one million copies that now comprise 10.5% of the human genome [25]. Although Alu elements have been exapted for many different functions [25], the observations that (i) editing is most active in brain and is important to brain function, (ii) humans show two orders of magnitude more editing than mice, (iii) most of the increased editing in humans occurs in Alu elements, which are primate specific and (iv) primates are the lineage which has experienced the highest evolution of cognitive capacities, raise the possibility that the predominance of Alu elements in the human genome might not be simply an accident of history but rather in large part the result of evolutionary co-adaptation of these sequences as a modular substrate for A-I editing, driven by positive selection for increased cognitive capacity.

This proposal is consistent with the observation that Alu elements are enriched in GC-rich regions of the genome (which are gene dense) and that this distribution is most likely because of positive selection [26]. If this is the case, Alu elements might have not only supplied the platform for accelerated penetration of RNA editing in the hominid lineage [27], but might also represent a central

part of the functional programming of the ontogeny of neuronal circuitry, the plasticity of brain function and consequently higher-order cognition. The sheer number of these elements (~1 million) makes it difficult to assign an enriched association to any particular type of locus, and indeed the reprogramming of the editable portion of the genome required to support higher-order cognition might have been considerable, as evidenced by the range of transcripts that exhibit editing (see below).

RNA editing in brain development

If RNA editing represents a major molecular mechanism for mediating the interplay between the brain and the environment, what can we learn from the types of sequences that are edited? First, as noted already, it is evident that editing occurs in noncoding as well as coding sequences, indicating that editing can alter the spatiotemporal profiles of gene expression and functional regulation as well as the biophysical properties of gene products, a huge uncharted world to be explored. Indeed, the predominance of editing in noncoding sequences, not just in UTRs of mRNAs but also in other noncoding transcripts, suggests that Alu-based editing sites have been exapted primarily to alter regulatory networks rather than protein structure. A significant subset of the edited transcripts have been recorded simply as expressed sequence tags, many of which appear not to have any protein-coding capacity and to represent independent transcripts, processed intronic RNAs or antisense RNAs. Although there is only one documented case of RNA editing of a repetitive sequence element that has been shown to influence gene expression [28], many ncRNAs, including intronic and antisense RNAs, show precise expression patterns in the brain [10], suggesting a vast hidden layer of RNA-based regulatory transactions [29]. Moreover, some miRNAs are derived from Alu sequences [30] and are subject to ADAR editing [17–20], and recent results show that miRNA-mediated translational repression can be relieved by another class of editing enzymes, the APOBEC family members [31]. Given the abundance of miRNAs in the nervous system and their central roles in brain development [6,7], as well as the fact that many miRNAs are derived from introns [32] and that many are primate specific [33], RNA editing for regulatory purposes might be widespread, particularly if (as expected) it is the regulatory architecture that controls brain development and plasticity [6].

We analyzed the human RNA edited transcript databases [21–23], as well as an unpublished set (A. Athanasiadis, pers. commun.), and found that transcripts from loci involved in fast neural transmission represent only a small subset of the targets of A-I RNA editing. These targets (of which there are thousands) include many examples of transcripts from gene loci involved in nervous system development (Box 1), encompassing loci encoding proteins that modulate neural induction as well as those involved in three-dimensional patterning of the anterior portion of the evolving neural tube, including the forebrain (Box 1a). Editing is also observed in transcripts from loci involved in neural stem cell self-renewal, asymmetric cell division and modulation of proliferation (Box 1b) as well as those

Box 1. Categories/roles of edited genes involved in nervous system development and function

(a) System-wide adaptations

- i. Neural induction (*SMAD1*; *IFNR1*)
- ii. Anterior (forebrain) neural tube patterning (*FGFR1*; *Formin2*; *HHA1*)

(b) Adaptations of regional neural stem cell functions

- i. Neural stem cell (NSC) self-renewal (*NuMA1*; *CD44*; *SNX1*)
- ii. NSC asymmetric (neurogenic) cell divisions (*Nde1*)
- iii. Modulation of NSC proliferation (*CDC2L5*; *RBBP7*; *PKCD1*; *SYK*)

(c) Adaptations of neuronal precursor (neuroblast) development

- i. Neuronal precursor (neuroblast; NB) migration (*CXCL1*; *Foxp1*)
- ii. NB cell-cycle kinetics (*Par6*; *CDK10*; *CDKL1*; *MCM3*; *DNM2*; *Cullin1*)
- iii. Modulation of NB cell-cycle exit (*Sox13*)

(d) Adaptations of the process of neuronal maturation

- i. Progressive neuronal differentiation (*TLE2*)
- ii. Neuronal morphogenesis (*PAK4*; *SPARC*)
- iii. Neuronal cell polarity/neurite process outgrowth (*Neuron navigator1*)
- iv. Neuronal axon guidance (*Centaurin-γ2*)
- v. Neuronal dendritogenesis (*δ2-Catenin*)
- vi. Neuronal synaptogenesis (*Protocadherin β*)
- vii. Neuronal subtype specification (*Lhx3*)
- viii. Neuronal network connectivity (*Protocadherin α1, 2, 4–6, C1, 2*)

(e) Adaptations of mature neuronal functions

- i. Neuronal viability (*Beclin1*; *Casp9*, 10; *TRAP1*; *STAG-1*; Fas inhibitory molecule 1)
- ii. Neuronal excitability (*Annexin A4*; *AMPA1/GluR1*; *VDCCβ4*; *VDKC*)
- iii. Neuronal cell–cell and cell–environment interactions (*Integrin β4*)
- iv. Cooperative clustering of synaptic neurotransmitter receptors (*VDCCβ2*)
- v. Assembly of multimeric intracellular and cell–cell signaling scaffolds (*Syncoilin*)
- vi. Organization of neuronal somadendritic microdomains (*mGluR1*)
- vii. Neuronal signal transduction (*Src* homology domain containing E, *SHE*)
- viii. Neuronal plasticity (*CaM Kinase II*; *Synaptotagmin 2*; *α1-Adaptin*; *Complexin 1*)
- ix. Neuronal energy metabolism (*CPT1A*, C; *Dynamin1-like*)
- x. Neuronal axodendritic transport (*Kinesin 1B, 2, 3B, 6*; *Dynein 10*)

involved in early neuroblast development including cell-cycle kinetics and migration (Box 1c).

Other loci exhibiting edited transcripts are involved in adaptations of the process of neuronal maturation including differentiation, morphogenesis, polarity, axon guidance, dendritogenesis, synaptogenesis, neural subtype specification and network connectivity (Box 1d). These include transcripts from loci encoding the protocadherin α and protocadherin β subclasses of cell-surface molecules. Genes encoding protocadherins have been strongly implicated in the ontogeny of neural circuitry by encoding an unusually large repertoire of isoforms that appear to provide the cellular address codes for directing appropriate cell–cell interactions during progressive stages of nervous system development [34]. Interestingly, conserved noncoding sequences that show positive selection in humans are disproportionately found near genes involved in neuronal cell adhesion [35].

Loci encompassing edited transcripts also include those whose protein-coding genes play central roles in an extraordinary range of innovations in mature neuronal function including neuronal survival, excitability, signal transduction, plasticity, axodendritic transport, energy metabolism, cell–cell and cell–environmental interactions as well as the organization of neuronal somadendritic microdomains, signaling scaffolds and cooperative clustering of synaptic neural receptor subtypes (Box 1e). Many of these genes are associated with neurodegenerative diseases and brain tumors as well as neurodevelopmental syndromes and neuropsychiatric disorders [3].

These observations clearly imply that not only synaptic strength but also brain development is influenced by environment and experience, an observation which is not surprising but which has not been previously made. Moreover, if such editing is context dependent, as one would expect that it would be, this might explain the trafficking of ncRNAs and mRNA to the periphery of axons and dendrites where editing might be taking place in response to local cues, coincident with activation of RNA regulatory networks and before protein translation, respectively [36,37].

DNA repair – DNA recoding?

An intriguing observation is that transcripts from loci encoding a broad range of DNA surveillance and repair enzymes are also subject to RNA editing. These include loci encoding proteins involved in DNA damage sensing and DNA repair enzymes involved in general component pathways of excision repair (base excision repair, nucleotide excision repair and mismatch repair), recombination repair (homologous recombination and non-homologous end joining) as well as specialized pathways to repair active genes (transcription-coupled repair) and those requiring lesion bypass (trans-lesional synthesis), including DNA polymerase- η (Table 1). The central importance of such enzymes has long been recognized [38–41], as evidenced by the sensitivity of the nervous system as well as the immunological system to mutations in DNA surveillance, repair and editing enzymes [39,42].

Given that a key feature of the immune system is alteration of the DNA sequence to generate receptor diversity, in part catalyzed by the APOBEC family of cytidine deaminases that can catalyze C-U/C-T editing of RNA and DNA [5], the possibility exists that the particular sensitivity of both the immune and nervous systems to mutations in ‘DNA repair’ enzymes, including ‘transcription-coupled repair’ enzymes [40,42], has been misinterpreted and that rather this common sensitivity derives from the fact that DNA recoding is a central feature of both systems. Interestingly, genes encoding APOBEC enzymes show some of the strongest signatures of positive selection in the human genome [43,44]. In the case of the immune system, such recoding requires in part the APOBEC1-like editing enzyme AID, which can act at the level of RNA [45] and appears to be exploratory in nature, with clonal selection subsequently being used to amplify antibody receptor variants that have higher affinity for foreign antigens. Clonal amplification is unlikely to be a feature of mature nerve cells, but there is almost certainly selection

Table 1. Human A-to-I edited DNA repair enzymes: functional roles

Gene name	Comment	Functional categories
<i>BRCA1</i>		DSBR (NHEJ, HR); MMR; TCR
<i>Claspin</i>		DSBR (HR)
<i>DDB2</i> ^a		NER; GGR; MMR
<i>DMC1</i>	Rad51 family	Meiotic HR
<i>FANCC</i> ^a		DSBR (HR); TLS
<i>FANCD2</i>		DSBR (HR); TLS
<i>MSH2</i>	Mismatch repair enzymes	MMR; DSBR (HR)
<i>MSH5</i>	Mismatch repair enzymes	MMR; DSBR (HR)
<i>NCoA6</i> ^a		DSBR (NHEJ)
<i>NEIL1</i>		BER; TCR
<i>POLM</i> ^a	X family DNA polymerases	DSBR (NHEJ); TLS
<i>Rad1</i>		BER; TLS
<i>Rad51</i>		DSBR (HR); TLS
<i>RecQL5</i>		DSBR (HR); NER; TCR
<i>Rev3L</i>	Pol-ζ	TLS
<i>TOP3A</i> ^a		DSBR (HR); NER; MMR
<i>UBE2B</i>	Rad6 homolog; ubiquitin [E2]-conjugating enzyme	TLS
<i>USP1</i> ^a		DSBR (HR); TLS
<i>XPA</i> ^a		NER; GGR; TCR
<i>XPB</i> ^a	ERCC3	NER; GGR; TCR
<i>XPV</i>	Pol-η; Y family DNA polymerases	NER; GGR; TLS
<i>XRCC6</i>	Ku70	DSBR (NHEJ)

Abbreviations: DSBR, double-strand break repair; NHEJ, non-homologous end joining; HR, homologous recombination; NER, nucleotide excision repair; BER, base excision repair; MMR, mismatch repair; GGR, global general repair; TCR, transcription-coupled repair; TLS, trans-lesional synthesis.

^aGene loci specifically verified to have edited transcripts in neural tissues. Supporting information can be found in Refs [38–41].

at the level of neuronal identity and neuronal connectivity during development, ongoing learning and brain regeneration, and it appears that the brain, like the immune system, also evolves *in situ* in response to experience [46]. Interestingly, it has been reported recently that cell-cycle activation is important for DNA repair in post-mitotic neurons [47], indicating both that such processes are relevant to their function and that such neurons are in a more dynamic state than previously thought. Thus, we suggest that the potential recoding of DNA in nerve cells (and similarly in immune cells) might be primarily a mechanism by which productive or learned changes induced by RNA editing are rewritten back to the DNA, via RNA-directed DNA repair pathways, to fix the altered genotype once a particular neural circuitry and epigenetic state has been established.

The suggestion that memory formation involves RNA-directed DNA modifications similar to those involved in the immune system is supported by a range of fascinating, albeit circumstantial, observations over many years. These include the findings that two enzymes involved in generating diversity in the immune system via V(D)J recombination (Rag1 and Rag2) are expressed in the central nervous system and in post-mitotic (olfactory sensory) neurons which are actively involved in experience-mediated neural plasticity [48], and that V(D)J recombination [49], as well as programmed genomic rearrangements in other organisms [50], is RNA directed, although it remains uncertain whether such recombination occurs and is relevant to brain function *in vivo* [51,52]. Other observations pointing to parallels between the brain and immune systems, and the role of RNA, include evidence that members of the DNA polymerase Y family involved in somatic hypermutation of genes encoding immunoglobulins have reverse transcriptase activity [53], one of which (DNA polymerase-ι) is expressed in areas of the brain associated with learning and memory (see <http://brain-map.org> [54]), as is DNA polymerase M, which is

involved in rearrangement of genes encoding immunoglobulins. (The fact that transcripts from loci encoding enzymes putatively involved in DNA recoding are themselves edited suggests that this process is itself subject to contextual control, which might explain why some memories are more vivid and enduring than others.) Moreover, A-to-G mutations correlate with nascent mRNA hairpins at somatic hypermutation hotspots, implying roles for both RNA editing and reverse transcription during somatic hypermutation, interestingly involving mismatch repair enzymes [55] that show expression in the hippocampus. It has also recently been shown that RNA-templated DNA repair can occur in eukaryotic cells [56]. In addition, LINE-1 elements that are active in the human genome encode several proteins, including a reverse transcriptase, and individual SINE elements including active Alu sequences have the capacity to hijack and utilize the LINE-1 reverse transcriptase [57,58]. However, although there have been reports of somatic DNA sequence variation in the brain, these have been confounded by errors introduced by PCR amplification, and the existence of such variation remains very much an open question [59,60].

It is also likely that edited RNAs, especially those that have regulatory functions such as we presume will apply to the majority of such sites in Alu sequences, can also communicate epigenetic changes back to the genome to alter gene expression profiles. Epigenetic changes are known to be important in memory formation [61,62], and it is clear that the modifications to DNA and chromatin that are the molecular basis of epigenetic memory are RNA directed [4].

The suggestion that there might be communication of RNA-encoded information back to the genome at the epigenetic and genetic levels would also potentially explain the hitherto surprising observation that diverse RNA species and associated regulatory signals are not only trafficked to the periphery of the nerve cell [36,37] but

might also undergo retrograde transport back to the nucleus [63], involving neuronal RNA granules that link to cargo-selective kinesin and dynein motors and contain several interesting ribonucleoproteins such as Staufen and FMRPs [64]. Indeed, there is increasing evidence for retrograde transport of RNAs, including small RNAs, to the nucleus in a broad range of organisms [65], as well as for RNA informational exchange between cells through exosome-mediated mechanisms [66], specific RNA receptors (SidT1 and SidT2, which show specific expression patterns in the brain) [66] and the derivation of presynaptic RNA from surrounding glial cells [67].

Moreover, there are clear evolutionary and functional parallels between members of the immunoglobulin (Ig) superfamily and the protocadherins [68], as well as many other subclasses of nervous system-selective Ig superfamily domain-containing proteins involved in neuronal cell identity, connectivity, synaptic plasticity and developmental and adult brain homeostasis [69], which have in common central roles in mediating complex regulatory responses in brain morphogenesis, homeostasis and immune recognition arising from cell–cell interactions [70]. Indeed, the pervasive presence of a broad array of functional subclasses of Ig-like CNS superfamily proteins might not only represent flexible modules for molecular recognition but also particularly amenable targets of APOBEC-mediated editing/mutation, as they are in the *in situ* evolution of the immune system itself, explaining their wide evolutionary success and utilization in both contexts.

APOBEC enzymes themselves, as well as ADARs, also exhibit dynamic environmentally mediated changes in nuclear–cytoplasmic translocation, intranuclear microdomain localization and editing functions through the actions of RNA binding domains, co-chaperones, posttranslational modifications and local translation and editing of nuclear trafficking components [71–75]. The nuclear localization signal of APOBEC1 is linked to RNA binding [72]. In addition, the bidirectional nuclear–cytoplasmic transport and cargo specificity of diverse RNA species and the co-transcriptional assembly of complexes of RNA binding proteins in neuronal RNA transport granules [36,64,65,76] suggest that RNA binding proteins might act as posttranscriptional ‘operons’ that promote the coupling of productive RNA editing to DNA recoding. Interestingly, whereas APOBEC3G is thought to act primarily to protect against retrotransposition events [77], it is in fact restricted to post-mitotic neurons in the human CNS [78], consistent with a potential role in DNA recoding in such neurons. The APOBEC3 subfamily has been vastly expanded in primates [5,79], and the complexes that are formed with APOBEC3 enzymes are recruited into RNA transport granules that contain both Staufen and Alu sequences [77]. Staufen itself has been shown to be required for long-term memory formation in *Drosophila* [80], as has Armitage, a putative RNA helicase that is required for mRNA transport and translation at the synapse [81].

Conclusion

These collective observations provide tantalizing clues about the extraordinarily complex molecular mechanisms

underlying the evolution, development and function of the human brain, particularly the pervasive role of RNA editing and its potential coupling to DNA recoding via RNA trafficking between nucleus and synapse and RNA-templated DNA repair enzymes. We suggest that these concepts not only explain a range of disparate observations but suggest how environmentally induced changes in neural development and evolving brain architecture, cell identity and synaptic connectivity might subsequently be hard-wired in the genome, potentially defining the complex and emergent properties of long-term memories and other structural and functional adaptations – a new paradigm and a plausible general molecular basis for dynamic and novel forms of learning and of potential mechanistic links between ontogeny and cognitive plasticity.

We anticipate that a broad but delimited set of sites will be edited and that the profiles of these recoding events will vary spatially and temporally in response to environmental inputs as well as the corresponding behavioral outputs. Because the biological foundation of memory processing is complex and involves many distinct types of memory (working, episodic, semantic, spatial, procedural, implicit memory) and progressive integration phases (encoding, consolidation, storage, retrieval, reconsolidation) occurring in widely distributed anatomical sites (neuronal microdomains, synaptic domains, local collectives termed ensembles, as well as modifiable neural networks), it is likely that the dynamic molecular signatures of these modifications occur at every level of the nervous system. It also is likely that different types of memory traces change over time in response to dynamic and yoked memory processes as a result of crosstalk mediated by non-neuronal glial and other supporting cells that have direct roles in mediating synaptic plasticity [67]. We also suggest that short-term memory might be encoded in edited RNA transcripts and their modified products, and that other cues are required to convert these changes to permanent changes in the genome itself, which can be thought of as rewriting to disk, and which is the basis of long-term memory. We also suggest that memory consolidation, recall and reconsolidation involve the dynamic interplay between RNA and DNA editing enzymes and RNA-directed ‘repair’ systems, as well as bidirectional transport from the nucleus to discrete axodendritic microdomains, and that these can be coordinated among synapses as well as distributed neurons and neural network connections.

If correct, this hypothesis predicts that individual neural cells will, in fact, have distinctive spatially and temporally defined genomic sequences and chromatin structure. The latter has good evidential support [61,62] whereas the former can be examined by sequencing of genomic DNA from individual cells. Indeed, this might be the source of many variant transcripts currently assumed to be the immediate (as opposed to historical) result of RNA editing. It also predicts that memory consolidation, storage and retrieval and associated long-term adaptations of human brain form and function should be modifiable by the targeted and differential modulation of expression of the genes encoding enzymes involved in RNA editing and DNA recoding.

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