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Neuromodulation for restoring and amplifying brain function

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Shrey Grover [1], Wen Wen [1] & Robert M. G. Reinhart [1,2,3,4,5]

Neuromodulation aims to improve brain function by altering neural activity. While many rehabilitation strategies seek to restore normal, healthy-like dynamics, some adopt a complementary strategy, using neuromodulation to strengthen repurposed processes that support function. Here we formalize these approaches as 'restorative normalization' (RN) and 'compensatory amplification' (CA), respectively. Drawing on cognitive neurophysiology, we evaluate the following four factors that enable CA to be effective: multiple realizability, multiscale neuroplasticity, precision readiness and activity selectivity. We analyze the interplay between RN and CA across clinical goals, such as stroke rehabilitation, and identify opportunities in neurodegeneration, psychiatry and aging where CA could delay decline, facilitate remission or increase neural processing capacity. We propose that positioning CA alongside RN as a core design principle can sharpen target selection, guide stratified treatments and translate known compensatory signatures into testable neuromodulation protocols.

Addressing the global mental health crisis demands strategies that can reliably improve brain function. One set of strategies gaining interest is neuromodulation or manipulation of brain activity through external stimulation. Many such methods, including noninvasive approaches such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), are being explored to mitigate memory decline, regulate mood and treat psychiatric illness[1–4]. Many protocols share a common assumption—impairments should be minimized and the impaired brain driven back toward healthy patterns. But in doing so, it can be argued that we risk disregarding the brain's compensatory adaptations[5,6], which may be as important for recovery as restoring healthy patterns. Here we promote the long-standing neurorehabilitation principles of restoration and compensation as design rules for neuromodulation. We formalize two complementary design strategies for neuromodulation—restorative normalization (RN) and compensatory amplification (CA; Fig. 1a). RN targets neural abnormalities to reexpress healthy-like dynamics. CA, by contrast, leverages and strengthens compensatory adaptations that already support behavior in the impaired system. We emphasize the mechanistic basis of CA-driven approaches and draw comparisons with RN, illustrating how each maps onto distinct neural substrates and yields differing models for achieving physiologically grounded cognitive enhancement. We highlight emerging opportunities for CA-based interventions to delay disease progression, improve cognition and prevent the reemergence of cognitive abnormalities. By formalizing these two approaches as explicit alternatives, we motivate direct comparisons of the strengths and limitations of RN-driven and CA-driven neural targets for cognitive enhancement across neurology, psychiatry and aging.

Promise and limits of RN

The goal of RN is to reduce the influence of neurological abnormalities on cognitive function by restoring activity patterns associated with a normal, functional state. For example, in obsessive-compulsive pathology, corticostriatal network abnormalities can be normalized through deep brain stimulation (DBS)[7,8], transcranial alternating current stimulation (tACS)[9] and TMS[10], resulting in the restoration of both local activity and broader connectivity to patterns observed in healthy individuals[7,8]. This 'restoration' principle has also been applied across

[1]Department of Psychological and Brain Sciences, Boston University, Boston, MA, USA. [2]Department of Biomedical Engineering, Boston University, Boston, MA, USA. [3]Center for Systems Neuroscience, Boston University, Boston, MA, USA. [4]Cognitive Neuroimaging Center, Boston University, Boston, MA, USA. [5]Center for Research in Sensory Communication and Emerging Neural Technology, Boston University, Boston, MA, USA. e-mail: rmgr@bu.edu

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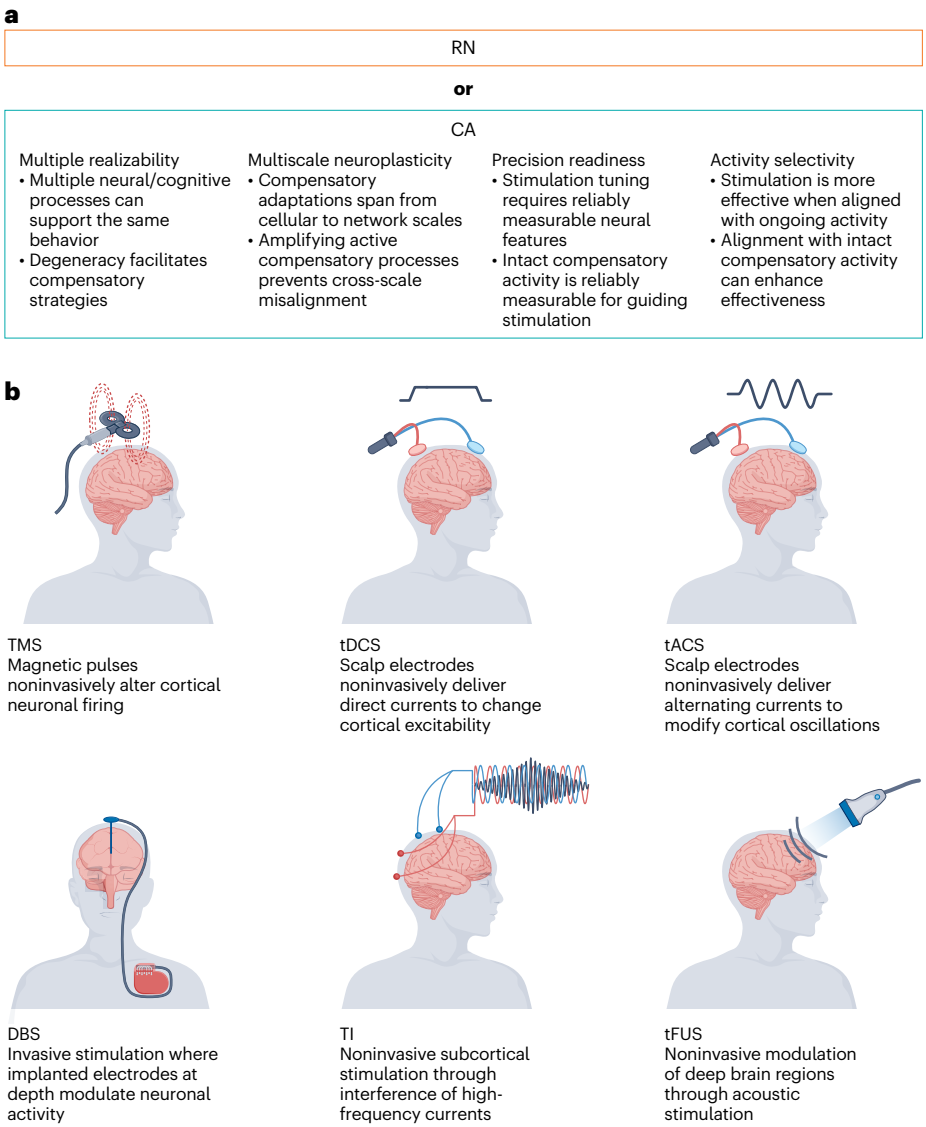

Fig. 1 | RN and CA, and ways to achieve them. a, RN and CA are complementary strategies. RN aims to restore normative brain activity to mitigate impairment; CA strengthens repurposed processes that support function despite deficits. The following four attributes make CA feasible and potentially effective: multiple realizability (distinct processes can support the same function, for example, allocentric and egocentric navigation), multiscale neuroplasticity (adaptations across molecular, circuit and network levels), precision readiness (reliable, measurable features suitable for closed-loop control) and activity selectivity (subthreshold neuromodulation is most effective when matched to ongoing activity[89]). **b**, Common neuromodulation methods. Manipulation of brain activity for both RN and CA can be achieved through, among other approaches, noninvasive methods such as TMS, tDCS, tACS, temporal interference (TI) and transcranial focused ultrasound stimulation (tFUS). Invasive DBS can also be used in severe, treatment-resistant scenarios. Figure created in BioRender; Reinhart, R. https://BioRender.com/4xcn2kb (2026).

other conditions (for example, major depressive disorder[11], Parkinson's disease (PD)[12] and multiple sclerosis (MS)[13]), underscoring the broad utility of RN as a therapeutic strategy.

RN targets can be derived in two ways. First, case–control contrasts (that is, comparisons of a characteristic of interest between individuals with a disease and those without) can identify aberrant neural signatures[14]. Second, brain targets can be selected on the basis of their causal linkage to symptoms; for example, lesion-guided and lesion-network-guided approaches aim to reveal circuits frequently associated with symptoms across individuals, thereby identifying generalizable targets for modulation[15] (although recent work questions whether these methods identify symptom-related networks or simply those with high intrinsic connectivity[16]). In both cases, the aim is to identify maladaptive activity and down-modulate it to restore network function toward normative reference patterns.

Although the RN approach has produced clinically meaningful outcomes across diverse domains, it rests on the important assumption that impaired circuits still have the capacity to reexpress healthy-like dynamics when externally stimulated. If they do not have this capacity, attempts to reinstate those dynamics will fail[17]. For instance, if the neural processes underlying motor function are substantially impaired owing to severe stroke[17], attempts to reinstate them have little likelihood of success. Similarly, if the neural generator of a functionally relevant rhythm is irreparably damaged, as is the case in prefrontal lesions affecting working memory (WM)[18], then RN has little prospect of inducing functional recovery. Indeed, that modulation outcomes depend on the integrity of the targeted regions is a common observation in neuromodulation studies[19–22] and highlights an inherent limitation of RN. Restoration thus cannot be the sole strategy for neuromodulation-based recovery.

RN in stroke recovery and the importance of compensation

Neuromodulation research in stroke rehabilitation highlights the limitations of a purely restorative therapy. The interhemispheric inhibition model[23] is a framework proposing that poststroke motor impairment is caused by imbalanced and/or excessive contralesional inhibition after stroke[24]. According to this model, functional recovery driven by neuromodulation therapies would be achieved by rebalancing activity between the hemispheres, that is, by boosting the lesioned side while dampening the intact side. Early studies bore this out—application of noninvasive tDCS protocols that enhance excitation of the affected cortex[25] (Fig. 2a, left) and repetitive transcranial magnetic stimulation protocols that inhibit activity in the unaffected cortex improved motor function[26]. In short, recovery initially appeared to hinge on restoring interhemispheric balance.

Yet subsequent work revealed a more nuanced reality. Inhibiting the contralesional hemisphere sometimes worsened symptoms in severely impaired patients[27–29], suggesting that 'abnormal' contralesional hemispheric activity was, in some ways, beneficial for recovery. This was consistent with increasingly robust evidence that functional recovery involved recruiting contralesional homologous brain regions to sustain function, that is, compensation[30–34]. This observation resonated with vicariation theories[35,36], which emphasize the brain's capacity to reassign lost functions to intact regions.

Based on these findings, subsequent neuromodulation studies tested an alternative strategy. Instead of attempting to restore interhemispheric balance, they sought to potentiate adaptive reorganization by strengthening, rather than impeding, activity in the unaffected cortex (Fig. 2a, right). Interestingly, these studies found promising motor gains (that is, functional motor recovery) from contralesional excitation through noninvasive neuromodulation[37,38].

These insights gave rise to the bimodal balance-recovery model, which incorporates structural reserve, that is, the amount of intact neural architecture available to support functional recovery[39,40]. In this view, the contralesional cortex supports recovery when ipsilesional integrity is low but, conversely, acts as an inhibitor when integrity is high[39,40]. Notably, side-by-side comparisons of the efficacy of this contralesional excitation approach (or CA) with previous ipsilateral excitation and contralateral inhibition approaches (or RN) confirm that, in severe stroke, the former outperforms the latter[37]. Animal studies echo this pattern, showing that contralesional excitation not only drives the strongest recovery but also upregulates growth factors in the damaged hemisphere[41].

Together, these findings make a simple point—restoration helps some patients but not others, whereas compensation is more effective when damage is extensive. The inclusion of such compensatory principles has broadened neuromodulation strategies for stroke, enabling patient stratification and tailored interventions[4] based on whether RN or CA is more likely to restore functional recovery[42,43].

CA strategy

The complementary approach to RN can be formalized as CA. In contrast to RN-based approaches, which aim to directly reduce abnormality, CA-based approaches work by boosting the brain's own adaptive response to that abnormality[6]. RN and CA reflect different physiological goals—restoring lost function by targeting the affected networks versus strengthening repurposed function by targeting the unaffected networks, respectively. Thus, in stroke recovery, motor function can be restored by reengaging the affected cortex[25] (RN) or compensated for by potentiating the homologous, unaffected cortex that takes over its role (CA)[37,38].

A clear motivating factor for CA is that adaptive circuits are not directly impaired by pathology and are therefore amenable to neuromodulation. Beyond this pragmatic factor, the following four mechanistic factors make CA particularly feasible and effective: multiple realizability, multiscale neuroplasticity, precision readiness and activity selectivity (Fig. 1a).

Multiple realizability

CA fundamentally rests on multiple realizability, or the notion that distinct physiological processes or structures can give rise to the same functional output[44–48] (Fig. 1a). This property, known as degeneracy, is a hallmark of resilient biological systems, allowing structurally different circuits to achieve common goals even in the presence of impairment.

For example, humans can navigate using hippocampal allocentric strategies based on landmarks or striato-parietal egocentric strategies based on self-position[49]. Older adults[50] and patients with Alzheimer's disease[51] (AD) preferentially shift toward egocentric strategies[52], probably owing to hippocampal atrophy[51]. Thus, degeneracy provides a built-in substrate for compensation and an opportunity for CA—when one route is compromised, others can be recruited to sustain function.

Multiscale neuroplasticity

Although multiple realizability provides a foundational architecture for functional recovery, neuroplasticity enables the brain to achieve this by adaptively reorganizing the neurophysiological mechanisms underlying psychological function[5,6,53,54]. This reorganization compensates for impairment[55], providing new substrates for CA-based neuromodulation protocols to target, such as contralesional rather than ipsilesional excitation with tDCS in the case of severe stroke[37]. Adaptive plasticity is evident across a range of conditions, from increased prefrontal recruitment in aging[56–58] to redistribution of processing within the prefrontal cortex in schizophrenia[59,60] and reorganization of language pathways in aphasia[61]. It also underlies the therapeutic effects of interventions such as pharmacotherapy[62] and has a central role in stroke recovery[63].

Adaptive neuroplasticity may give CA an advantage over RN in many conditions. Adaptive changes in the brain are systemic, spanning multiple scales from the molecular to the whole-network level[64] (Fig. 1a). Because efficient function depends on coordination across these levels[65], interventions confined to a single scale may disrupt alignment with the broader physiological architecture. Indeed, the transient effects of some neuromodulation protocols may reflect homeostatic resistance to such perturbations (for example, in DBS[66]). In some cases, compensatory changes following disease or injury may represent attempts to establish a new equilibrium across multiple scales[67]. Supporting endogenous compensatory adjustments, rather than overriding them, could lead to more durable therapeutic outcomes—a hypothesis that merits further investigation.

Precision readiness

Across neurology and psychiatry, there is growing interest in precision medicine approaches to improve modulation outcomes[68–71], driven by extensive evidence of brain state-dependent effects[72–74]. These approaches typically involve two key elements—personalizing treatment to account for individual differences[68,69], including anatomy[75] and physiology[14], and implementing closed-loop modulation by dynamically adjusting parameters in response to ongoing changes in brain state[70,71]. This can range from precisely positioning a TMS coil on the basis of individualized functional connectivity (that is, a personalized connectome)[76] to modulating activity at the specific frequency at which an individual exhibits rhythmic, functionally relevant brain activity[9,14], thereby capturing both interindividual variability and fluctuations over time.

One key limitation of RN-based protocols is that, depending on the severity of damage or the absence of a reliable neural signature, it may be difficult to measure or infer the necessary parameters. For example, although personalized connectome-guided neuromodulation is being increasingly adopted[77,78], loss of functional connectivity in damaged regions means that inferring targets in individuals with brain lesions

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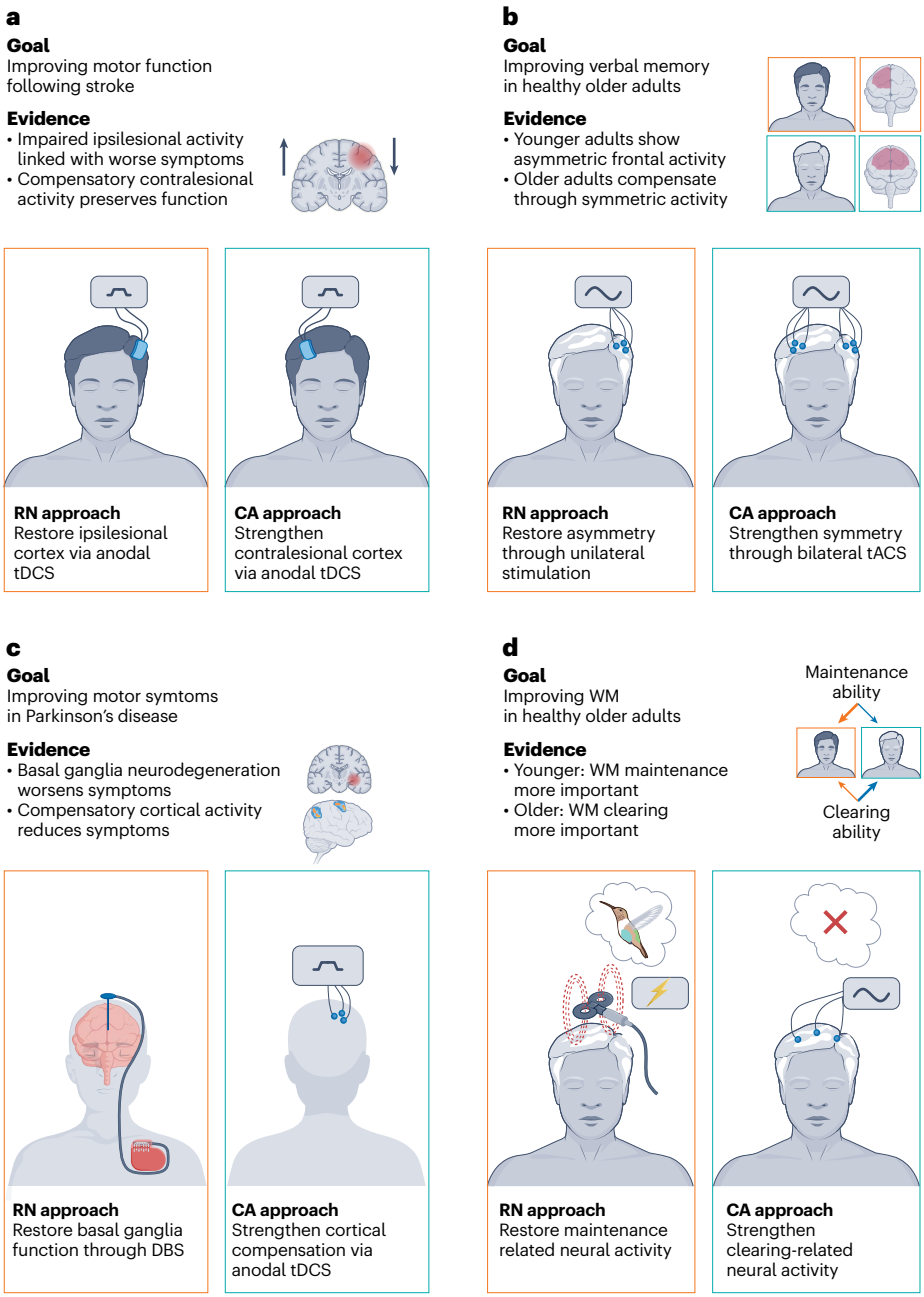

Fig. 2 | Distinct RN-based and CA-based strategies for specific neurocognitive and clinical objectives. RN and CA make distinct, testable predictions about targets. **a**, Stroke recovery. Stroke involves a shift in hemispheric balance, with ipsilesional impairments and contralesional compensation. RN seeks to revive perilesional activity, whereas CA strengthens adaptive contralesional recruitment. **b**, Aging, MCI and AD. Aging involves a reduction in hemispheric asymmetry, whereby bilateral frontal regions are recruited to support deficient unilateral function during verbal WM. RN aims to restore hemispheric asymmetry by reducing bilateral prefrontal recruitment, whereas CA leverages bilateral recruitment when it supports performance. **c**, PD. PD involves basal ganglia neurodegeneration, following which cortical regions are adaptively recruited to support motor function. RN would target normalization of basal ganglia circuits to improve motor function, whereas CA would enhance parieto-premotor compensation to sustain performance[112]. **d**, WM in older adults. Younger and older adults use distinct neurocognitive processes to optimize performance—younger people regulate performance through maintenance-related beta oscillations, whereas performance in older adults is better regulated by memory-clearance (deletion)-related beta oscillations. RN would target younger-like beta dynamics by reducing beta power and variability during maintenance, whereas CA would entrain beta power and variability during postresponse deletion[144]. Figure created in BioRender; Reinhart, R. https://BioRender.com/az2yew8 (2026).

often requires reference to normative connectomes[79]. By contrast, CA-based protocols can bypass this challenge by leveraging preserved, functionally relevant neural activity that remains measurable even in compromised circuits. This enables more consistent personalization and real-time adjustment, positioning CA as particularly well suited to precision medicine applications (Fig. 1a).

Activity selectivity

Although tailoring neuromodulation to brain state is increasingly common[70,72,80], the idea that the mechanics of neuromodulation themselves can inform effective targeting—guiding the design and evaluation of CA-based interventions and generating testable predictions about efficacy—remains underappreciated.

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BOX 1

Side-by-side comparison between RN and CA

CA leverages what is preserved, recruitable or adaptable; RN seeks to reinstate functions that are absent or degraded. Here we provide some examples of how RN and CA can yield different predictions about which neural substrates to target.

Hippocampal atrophy in aging
Hippocampal atrophy causes a shift in the use of spatial navigation strategies, from allocentric to striato-parietal egocentric, in older adults[50]. An RN approach would seek to revive hippocampal allocentric coding, whereas a CA approach would strengthen striato-parietal egocentric strategies.

Bilateral prefrontal recruitment in aging
Aging involves a reduction in hemispheric asymmetry, whereby bilateral frontal regions are recruited to support deficient unilateral function during verbal WM[56,104–106]. RN would attempt to reestablish hemispheric asymmetry, whereas CA would try to potentiate bilateral prefrontal engagement (Fig. 2b).

Parkinson's motor control
PD involves basal ganglia neurodegeneration, following which cortical regions are adaptively recruited to support motor function[112]. RN would seek to normalize impaired basal ganglia loops, whereas CA would enhance parieto-premotor compensation (Fig. 2c).

Absent oscillatory synchrony in damaged circuits
Individuals with frontal lesions can show preserved WM performance by relying on compensatory posterior rhythms[18]. RN would attempt to reestablish the lost rhythm, whereas CA would amplify extant rhythms already engaged (for example, parietal alpha and/or beta), which should improve performance.

Many noninvasive neuromodulation protocols operate in the subthreshold regime by biasing neuronal dynamics without directly inducing action potentials. These include methods that manipulate brain activity through tDCS[81], alternating current such as tACS[82] and transcranial random noise stimulation[83], and transcranial focused ultrasound stimulation[84]. This is consistent with the activity selectivity principle, which holds that subthreshold neuromodulation preferentially influences active rather than inactive neuronal populations[85,86]. This effect has been validated in human electrical neuromodulation studies, although more work is needed to robustly confirm this effect across neuromodulation methods[87,88]. Thus, some level of ongoing neural activity may be required for subthreshold methods to exert measurable effects.

A specific form of activity selectivity relevant to brain rhythm modulation is frequency specificity. Neural systems, like other dynamical systems, exhibit the Arnold tongue phenomenon[89], whereby entrainment is most effective when the modulation frequency matches the system's intrinsic resonance[14,90–93]. This tuning is especially relevant for subthreshold methods such as tACS[14,93], but emerging evidence suggests that it may also apply to higher-intensity approaches such as TMS[94] and DBS[95] when used to modulate oscillatory dynamics. Rhythmic neuromodulation, in short, is most effective when aligned with the frequency characteristics of the target populations.

These principles suggest that subthreshold neuromodulation is most effective when (1) target populations are already active and (2) modulation parameters are matched to the intrinsic dynamics of the system (Fig. 1a). Under conditions such as severe neuronal damage, circuits targeted by RN may lack these prerequisites for subthreshold modulation. By contrast, intact compensatory circuits preserved through degeneracy and plasticity remain measurable and responsive, making them ideal targets for CA-based approaches operating within the subthreshold regime.

CA is therefore a feasible and theoretically sound rehabilitation strategy that, without dismissing RN approaches, deserves recognition as a core component of the neuromodulation toolkit because it supports testable, competing hypotheses and enables direct empirical comparisons (Box 1).

Potential for broader application of CA in pathology

With the mechanistic considerations above in mind, we can now explore whether CA holds broader potential beyond supporting functional recovery following stroke. Although the clearest evidential support for CA-induced functional recovery comes from stroke research, this condition has unique features—it has an abrupt onset[96] and creates a window of heightened plasticity[97], and for motor, visual and language functions, contralateral homologs often remain intact. These factors make compensation approaches especially effective.

The question is whether similar potential exists in neurodegenerative and psychiatric disorders, in which impairments emerge gradually and diffusely. By analogy with stroke, CA may become most useful in more advanced disease stages. However, we argue that the opportunity is broader—CA could be used to slow disease progression, support recovery following symptomatic episodes and boost residual cognitive capacity. Below, we outline these directions as a roadmap for future research.

Delaying disease progression and promoting recovery

Neurodegenerative diseases such as AD and PD unfold over long presymptomatic and prodromal phases[98,99]. During these phases, function is often preserved through compensatory mechanisms[98–103] despite ongoing neurodegeneration. Increasingly, the transition to the symptomatic phase appears to hinge on the collapse of these mechanisms[103]. Enhancing compensation, alongside efforts to slow degeneration, may therefore delay the onset of clinical impairment.

For example, individuals with mild cognitive impairment (MCI), a precursor to AD, exhibit bilateral frontal recruitment during verbal WM, a classic compensatory signature in aging, whereas individuals with AD do not[104–106]. In individuals with MCI, stronger bilateral recruitment is associated with higher levels of cognitive function[107]. This suggests that compensation is not only protective but also measurable and variable across individuals. Accordingly, compensation enhancement has become a promising target for early intervention[108].

Other neural mechanisms under investigation include default mode network rerouting around entorhinal cortex abnormalities during episodic memory[109,110], and prefrontal recruitment helping to offset medial temporal lobe atrophy during visual WM[111]. These signatures offer fertile testing grounds for examining whether strengthening compensation in early AD can mitigate symptomatic progression (Fig. 2b).

In PD, emerging evidence suggests that individuals with milder symptoms show stronger parietal and premotor activation despite comparable basal ganglia dysfunction, and that the loss of this compensatory activity predicts motor decline[112]. Enhancing parieto-premotor function early may therefore slow deterioration[113] (Fig. 2c). Although it has long been suggested that neuromodulation in PD may act by engaging preserved cortical pathways[114], direct targeting of compensatory circuits has yet to be tested[113]. This underscores a key research

opportunity—can CA-based neuromodulation slow progression in PD by reinforcing intact functional pathways?

In relapsing–remitting conditions such as MS, CA may aid both recovery and remission. MS shows widespread functional reorganization[115], where impaired synaptic plasticity after relapse was correlated with poorer recovery outcomes[116]. Specific patterns, such as cerebellar network recruitment, appear especially important for remission[117]. Although their predictive validity requires further study, such signatures could serve as entry points for testing whether CA can improve outcomes and reduce relapse risk.

Improving neural processing capacity

Compensation tends to scale with task demands—as demands increase, additional neural resources are recruited to offset inefficiencies[118]. This process follows an inverted U-shaped function, in which performance improves with compensation up to a point, but eventually compensation fails and the function collapses[118].

These dynamics generate two key hypotheses for how CA might enhance neural processing in neuropsychiatric conditions. First, by reducing the burden on compromised circuits, CA could improve cognitive performance even under lower demands, effectively shifting the curve upward. Second, it may expand overall processing capacity, raising the threshold at which functional breakdown occurs and allowing higher demands to be tolerated. These hypotheses offer complementary paths through which CA could enhance resilience in vulnerable systems.

Although no studies have yet directly tested these processing-capacity hypotheses, it has been proposed that compensatory mechanisms operate not only in stroke and neurodegeneration[119] but also across a range of psychiatric conditions, including schizophrenia[60,120–125], major depressive disorder[126,127], attention-deficit/hyperactivity disorder[128,129], generalized anxiety disorder[130] and OCD[131]. Across many of these disorders, researchers have observed the same inverted U-shaped pattern of compensatory recruitment, from MCI[132] to schizophrenia[133] and OCD[134]. These converging findings suggest that boosting compensatory neural pathways via CA could yield broad therapeutic benefits across neuropsychological disorders and that it could also prevent catastrophic cognitive decline in psychiatric disorders, particularly under conditions of high cognitive demand. Although still speculative, this proposal is grounded in observed neural dynamics and offers testable, mechanism-based predictions for future neuromodulation research. More broadly, it invites exploration of CA not only as a rehabilitative tool but also as a strategy for general cognitive enhancement, including in nonpathological contexts such as healthy aging, a topic we now turn to.

CA for cognitive enhancement in aging

Healthy aging brings changes across multiple cognitive domains[135], accompanied by neural adaptations such as reduced hemispheric asymmetry and posterior-to-anterior shifts whereby bilateral and anterior brain regions are recruited to assist with functions such as memory that typically rely on posterior activity alone in young adults[56,136–139]. These adaptive modifications are not solely a reflection of impairments, as they serve specific goals, including compensating for and preserving an impacted function[56,136–140]. These adaptations in nonpathological contexts open a broader avenue for CA—we can identify and enhance mechanisms unique to, and linked with, better performance in healthy older adults for cognitive benefit.

WM is among the cognitive functions most affected by aging[135]. Efficient WM requires both information maintenance and clearing or deletion as task demands change[141–143]. Individual WM proficiency in older versus younger adults is predicted by different mechanisms—in older adults, performance is better predicted by the ability to delete information via increased prefrontal beta activity, thereby freeing limited cognitive resources; in younger adults, by information maintenance through decreased preresponse beta rhythms[144]. Although both operations hinge on beta activity, they do so distinctly, with decreased beta activity supporting maintenance, whereas increased beta activity enables deletion[145], and their relative contributions shift with age[144].

These age differences have distinct implications for WM-focused neuromodulation. An RN approach would target maintenance deficits by promoting beta suppression during maintenance, potentially achievable through cathodal tDCS or TMS[146,147] (Fig. 2d, left). A CA approach would instead entrain beta during postresponse deletion, readily achievable with tACS[148] or brief, state-targeted rhythmic TMS[149] (Fig. 2d, right). The comparative efficacy of these strategies in older adults is not yet known, but explicitly considering compensatory mechanisms expands the range of testable hypotheses and supports the development of combinatorial neuromodulation strategies.

A second example comes from the posterior-to-anterior shift—older adults often recruit the prefrontal cortex more strongly for tasks that rely on parietal regions in younger adults[57]. In this context, prefrontal engagement appears to be particularly beneficial for older adults, implying that potentiating the frontal cortex could selectively enhance performance in this group. Consistent with this view, excitatory anodal tDCS over the prefrontal cortex strengthened neural signatures and WM performance in older but not younger adults[150]. This illustrates how age-related compensatory changes in circuit engagement can be targeted to produce selective cognitive benefits.

Because compensation is evident in healthy, nonpathological contexts such as aging, CA is relevant beyond clinical populations. With growing interest in neuromodulation for cognitive enhancement in aging[1,14,151–153], future interventions may benefit from explicitly incorporating compensatory strategies and prospectively testing their efficacy.

Challenges for CA

Despite the promise shown by CA as a therapeutic approach, it is a relatively underexplored area. It is therefore pertinent to consider the limitations, challenges and cautions associated with this approach in future studies.

Identifying adaptive, causally relevant brain activity patterns

A central challenge inherent in studying brain activity patterns is distinguishing adaptive from maladaptive activity. Not all additional neuronal recruitment is compensatory. For example, hyperactivity in MCI and/or AD can reflect excitotoxic or otherwise harmful overactivity[154]. Likewise, broader recruitment in healthy aging may indicate nonselective engagement of brain areas and a breakdown of executive control[155]. In other words, plasticity can be maladaptive when beneficial adaptive compensation mechanisms fail to occur[156].

Correlational approaches such as electroencephalography and functional neuroimaging, which measure brain activity during cognitive states, offer one way to distinguish adaptive from maladaptive processes. Activity that positively tracks better performance at both interindividual and intraindividual levels is more likely to be adaptive. Indeed, this type of association has been observed in OCD[131] and schizophrenia[59]. A further marker is functional specificity, whereby overactivity that is more generalized across multiple functional domains is less likely to be compensatory. Even so, correlational evidence is inherently limited[157] and provides only putative guidance.

Stronger evidence requires causal tests. If a process is genuinely compensatory, then temporarily disrupting it should transiently impair function. In PD, for example, pharmacological regulation of dopaminergic processes has provided evidence for compensatory benefits associated with functional reorganization within the basal ganglia[158]. Such tests remain rare and are not always practical.

A promising direction for causal inference is lesion-network mapping[159,160] (Box 2). This approach involves identifying networks that are consistently associated with symptom relief and yields

BOX 2

CA in practice: new methodological avenues

Target selection is the first step in any neuromodulation protocol. Standard approaches rely on correlations between brain activity and symptoms measured with neuroimaging or electrophysiology, but correlation does not establish causation[157]. Multiple realizability further complicates target discovery—patients with similar symptoms can show heterogeneous neural abnormalities.

LNM seeks to address this challenge. LNM identifies hubs that are functionally connected to heterogeneous lesion locations consistently across patients[159,160]. These hubs provide causally informed hypotheses about symptom-generating circuits that can inform the selection of modulation targets[15,157]. Knowledge of these anatomical and functional hubs can be combined with cognitive neurophysiology to design protocols that manipulate function-specific activity in the nominated regions[166,167]. LNM can also highlight symptom-relieving networks. By identifying hubs associated with lower symptom burden or remission, it yields candidate targets for promoting recovery[79,160–162]. Although the algorithms currently used to infer these networks have recently been challenged[16], ongoing methodological refinements and alternative implementations of this general principle may continue to guide CA.

Another consideration is timing—when should neuromodulation be applied relative to disease onset and progression, and does this differ for RN versus CA? Effectiveness likely depends on the integrity of neural structures and disease stage. Early in disease, when substrates remain intact, RN may suffice, although such windows are hard to detect; CA may still slow decline. At intermediate stages, RN and CA may both be beneficial, potentially in combination. With severe impairment, the balance may shift toward CA. Systematic, direct comparisons that vary timing, target and disease severity are needed (Box 1).

mechanistic, causally informed targets for neuromodulation design[161,162]. Lesion-network mapping (LNM) can thus be used to determine beneficial networks for CA. Although the validity of the specific algorithms currently used for LNM has recently been questioned[16], continued methodological refinement and the development of more robust implementations may enable more reliable identification of CA-relevant networks.

An additional complication is that the benefit of a given compensatory change may vary over time. Some changes are adaptive in the short term but maladaptive in the long term[163], and vice versa. CA-based protocols may therefore need to adapt to disease progression, with target identification that is both time-dependent and context-dependent.

Overburdening compensatory mechanisms

A second limitation is suggested by pharmacology. In PD, advances that leverage compensation raise the concern that further strengthening may overburden compensatory circuits and increase their vulnerability[102]. There is no direct neuromodulation evidence for this effect, but it remains a reasonable caution. When considering the 'dose' of CA treatment, consideration should be given to intensity, frequency, spacing and intermittency to balance benefits against potential overload.

Interference and nonuse

A widely recognized challenge, also relevant to CA, is interference introduced by compensation itself[5]. Stroke rehabilitation monitoring has shown learned 'nonuse', in which loss of the ability to move a limb, for example, is accompanied by nonuse of that limb, while increased reliance on compensatory strategies impedes recovery of the affected physiology[164]. To manage the risk of nonuse, a CA-driven strategy for enhancing contralesional cortical activity may still occasionally require an RN-driven strategy for enhancing ipsilesional cortex. Real-world CA may therefore need to be paired with RN rather than positioned against it, with the balance between the two approaches tailored to symptom profile, neural integrity and disease severity (Box 2).

Conclusion

We advocate a broader vision for supporting impaired neuropsychological function with neuromodulation—one that leverages intrinsic plasticity. Beyond attempts to restore an idealized unimpaired state, we encourage enhancing processes that support function in individuals while considering both impairments and adaptations. This dual approach respects both deficits and compensation and opens routes to new interventions. Drawing on decades of stroke rehabilitation, we argue for extending CA strategies to both pathological and nonpathological contexts. We hope that future studies will test these ideas and address their limitations. As noted previously, 'It is an error to only see illness in abnormality'[121,165], a reminder to consider the full spectrum of neural adaptation when designing neuromodulation strategies.

Data availability

No new data have been generated for or reported in this manuscript.

Code availability

No custom code was used for this manuscript.

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Author contributions

S.G., W.W. and R.M.G.R conceptualized the study. S.G. contributed to investigation, methodology, validation and writing of the original draft. S.G. and W.W. visualized the study. S.G., W.W. and R.M.G.R. wrote, reviewed and edited the manuscript. R.M.G.R. was responsible for funding acquisition, project administration, resources and supervision.

Competing interests

All authors declare no competing interests.

Additional information

Correspondence should be addressed to Robert M. G. Reinhart.

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