Penrose-Hameroff orchestrated objective-reduction proposal for human consciousness is not biologically feasible

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Penrose and Hameroff have argued that the conventional models of a brain function based on neural networks alone cannot account for human consciousness, claiming that quantum-computation elements are also required. Specifically, in their Orchestrated Objective Reduction (Orch OR) model [R. Penrose and S. R. Hameroff, J. Conscious. Stud. **2**, 99 (1995)], it is postulated that microtubules act as quantum processing units, with individual tubulin dimers forming the computational elements. This model requires that the tubulin is able to switch between alternative conformational states in a coherent manner, and that this process be rapid on the physiological time scale. Here, the biological feasibility of the Orch OR proposal is examined in light of recent experimental studies on microtubule assembly and dynamics. It is shown that the tubulins do not possess essential properties required for the Orch OR proposal, as originally proposed, to hold. Further, we consider also recent progress in the understanding of the long-lived coherent motions in biological systems, a feature critical to Orch OR, and show that no reformation of the proposal based on known physical paradigms could lead to quantum computing within microtubules. Hence, the Orch OR model is not a feasible explanation of the origin of consciousness.

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I. INTRODUCTION

The nature of human consciousness is perhaps the most important of unsolved scientific problems. It is widely accepted that the consciousness is linked to the neural activity in the brain; however, the chemical interactions between neurons have been argued by Penrose [1,2] to set restrictive limits on processing capacity. The most developed extended model of cognitive function is the Penrose-Hameroff orchestrated objective reduction [3–8] (Orch OR) model, which proposes that the quantum computation occurs in microtubule assemblies within the neurons of the brain. Currently, there is great interest in both this and other proposals for nontrivial quantum effects in biology [9–11]. Figure 1 depicts the qubit in the Orch OR model and shows a proposed quantum computational cycle. Coherent superpositions of alternative conformational states of individual tubulins dimers are proposed to form the quantum computational elements (qubits). The coherent oscillation depicted in the figure interconverts the classical chemical conformational states *in situ* to facilitate the resonant superpositions (step 1), with coherence originating as a result of Fröhlich condensation [4,5]. This nuclear motion is then coupled to electronic motion, allowing the qubits to interact with each other while maintaining coherence, thus forming the quantum computer across an extensive network of microtubules. Figure 1 shows the formation of these extended superpositions and their spread to encompass many microtubules (steps 2 and 3) and even spread to include many neurons [7]. Quantum gravitational effects are proposed to decohere the system on the physiological time scale [4,6]. Decoherence causes the quantum state of each tubulin-dimer qubit in each participating microtubule to be reduced to one of its classical forms (step

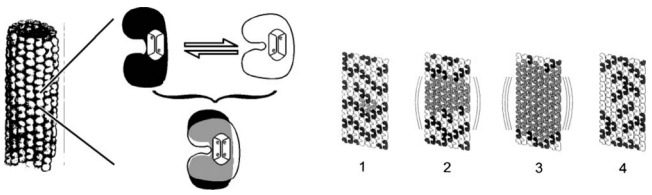

FIG. 1. The physiological elements of a qubit and the operational cycle of the quantum computation within the Penrose-Hameroff model for cognitive function by orchestrated objective reduction, taken from Ref. [8]; reproduced with permission of MIT Press. Left: tubulin dimers within microtubules exist in two conformational states (shown black or white) and it is proposed that resonance coupling between these conformations acts to form qubits from quantum superpositions of the local vibronic wave functions (shown gray). Such superpositions require coherent motion in the vibrational modes, proposed to originate via Fröhlich condensation [4], that interchange the two conformational states and move internal electrons (marked "e"). Right: four steps in the operational cycle starting at (1) superpositions start to appear from among classically localized states in the tubulin-dimer qubits, (2) coherent motions and superpositions grow to encompass large regions of this and neighboring microtubules, (3) superposition reaches critical mass inducing objective reduction to form (4) an ensemble of tubulin dimers throughout many microtubules containing the results of the quantum computation specified through their (classical) conformations.

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4). This classical state then interacts with its chemical environment, possibly through the actin sol-gel cycles that control the microtubule network structure. As microtubules can influence the electrochemical properties of neurons [12], the results of the quantum computation could by this means influence neural processing.

The basic physical principle underlying the resonance-based chemical qubit sketched in Fig. 1 is a widely known motif throughout chemistry and biology. Originally quantum-mechanical "resonance" was conceptualized to describe the "aromatic" nature of benzene compared to the expected properties of its classical form, the hypothetical cyclohexatriene molecule. For benzene, the electron-phonon coupling involving the critical vibrational mode, ν_{14} (see, e.g., [13].), is insufficient to overpower the resonance stabilization and so a fully delocalized structure results [14]. A related problem that is more directly relevant to quantum computing (see, e.g., [15,16]) and Orch OR is the structure and dynamics of ammonia in the gas phase. For ammonia, the electron-phonon coupling in the relevant mode, the umbrella-inversion mode, does overpower the resonance interaction and so two mirror-image pyramidal classical chemical equilibrium structures result [14]. Coherent superpositions of the resulting vibronic states is a known process that in fact leads to the operation of the maser. Also pertinent to the Orch OR proposal are quantum phenomena in the Creutz-Taube ion [17], a mixed valence bisruthenium complex of pyrazine in which charge transport is controlled through coherent motion [18] involving long-range solvent vibrational modes [19]. This system is also very important in that it provided the model through which primary charge separation, quantum coherence, and charge transport was understood in bacterial and plant photosynthetic reaction centers [14,20]. More generally, all biological and chemical charge-transport processes are now known to be controlled by analogous interplays between vibrational motions and resonance couplings [21,22], with a key feature being the time through which coherence is maintained. That such a process might give rise to quantum computation in biological tissues is thus a proposal worth considering. Indeed, a theory describing how resonating classical chemical structures can develop entangled states that function as quantum computer elements has recently been described [15].

Nonetheless, while the Penrose-Hameroff proposal contains many controversial aspects [7,23], the most ambitious requirement is that the tubulin-dimer interconversion oscillation depicted in Fig. 1 remains coherent on a time scale relevant to neural processes [6], 6–9 orders of magnitude longer than that for which any related process has been observed in chemistry or biology [16,18,20,24–26]. If either (i) the envisaged intradimer motion (Fig. 1 left) does not exist, (ii) the intradimer motion is not coherent for long enough, or (iii) if this coherence is not maintained over a network of coupled dimers (Fig. 1 right) sufficiently large to unite individual qubits into a complex quantum computer, then the Orch OR model becomes untenable. Alternatively, if the intradimer motion does exist and is coherent, then most other aspects of the proposal (e.g., the involvement of quantum gravity and the role of sol-gel cycles) could be replaced with other phenomena and the quantum computational element retained [26,27], although its function may manifest differently [4,8]. Here, we concentrate on the intradimer motion: (i) does it exist as envisaged in Fig. 1, and (ii) if it does not exist could any possible alternative process actually maintain coherence on the required time scale. The third critical issue concerning maintenance of coherence over the microtubule network is much more difficult to treat authoritatively and the only issue to have been widely discussed (see, e.g., [6–8,10,23,25,26]); hence, it is not addressed herein.

Specifically, we consider the feasibility of the Orch OR proposal in light of recent developments in the understanding of microtubule structure and function [12,28–45], as well as in regard to the likelihood of extensive coherent oscillations in biology [46–49] and in microtubules [50–53]. We show both that the original biochemical scenario envisaged in Orch OR is incorrect and that no possible modification of this proposal consistent with the biological facts can, using known physical padadigms, produce the required physical properties. Hence, if there are any nonelectrochemical contributions to cognitive function then they must arise by some mechanism other than the Penrose-Hameroff proposal. This gives hope to the vision that digital computing could achieve truly significant levels of artificial intelligence.

II. EXISTENCE OF THE PROPOSED TUBULIN-DIMER VIBRATIONAL MOTION

The observed biochemical dynamics of tubulin dimers and their conformational states within microtubules is depicted in Fig. 2; a review of this dynamics, particularly in regard to microtubules in neurons, has recently been provided by Conde and Cáceres [12]. This figure is presented for comparison with the biochemical processes as envisaged in the Orch OR proposal shown previously in Fig. 1. Microtubules are cylindrical structures formed by the self-association of tubulin heterodimers. Primarily involved are two closely related tubulin isoforms (α and β) that interact to form a stable heterodimer. Each subunit of the heterodimer contains one guanidinium phosphonucleotide (GTP or GDP) binding site [Fig. 2(a)]. The site on the α subunit is nonexchangeable to which GTP is bound constitutively. The site on the β monomer is exchangeable, binding either GTP or GDP [54]. Self-association of tubulin to form microtubules is triggered by the binding of GTP to the β subunit of the free heterodimer (tubulin GTP) [Fig. 2(b)] [33]. The growth of a microtubule involves the initial formation at a centrosome of a 13 membered ring of another tubulin isoform, γ tubulin [12], which then acts as a template for further growth via addition of tubulin GTP. Many slight variations in this process are possible, with the ring size possibly increasing to 17 and the relative orientations of the dimers with respect to each other changing (the so-called "microtubule-*A*" and "microtubule-*B*" structures [28]); such variations affect the rates of subsequent processes and may be important in neurons [28,43], but they do not affect the form of these processes [12,28,29] and hence we do not focus on these features. Other possible variations such as the availability of different types of tubulins (eg., α1, α2, α4, βI, βII, βIII, βIVa, and βIVb) and post-translational modifications to the

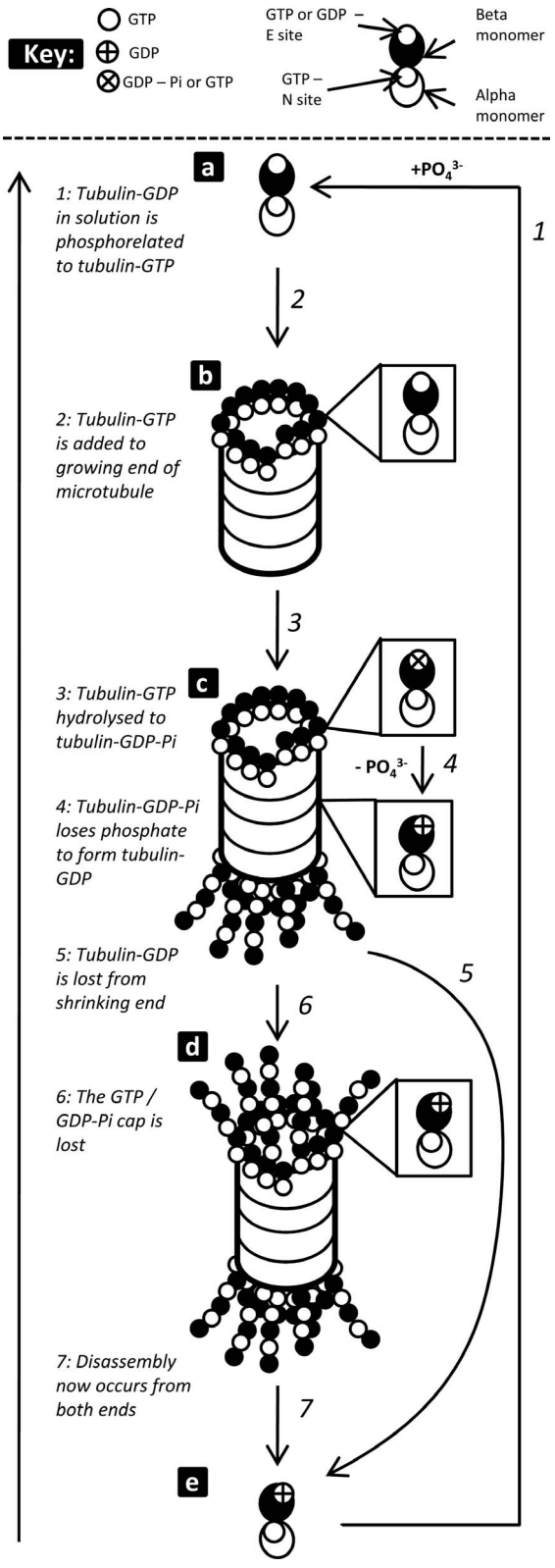

FIG. 2. Current understanding of the biochemical processes that modify the conformational states of tubulin dimmers. A more modern symbol for the dimers is used compared to that used by Penrose and Hameroff (see Fig. 1) to facilitate a more complete description of the biochemical processes; while the microtubule-*B* lattice is shown [28], the depicted processes are lattice independent [12,28–30].

tubulins also preserve the form of the essential dynamical features [12]. Quite generally, some time after incorporation onto the microtubule, the GTP molecule bound to the β subunit is hydrolysed (Step 3, Fig. 2) [33]. Initially, the phosphate ion remains bound to the protein, leading to a metastable intermediate state called tubulin-GDP-Pi [Fig. 2(c)] [31,32,39]. Finally, the phosphate ion is lost (Step 4, Fig. 2) yielding tubulin-GDP.

The essential aspect of the Orch OR proposal depicted in Fig. 1 is that tubulin can adopt more than one conformational state and exist in a coherent quantum superposition of these states. Experimentally, the only identified aspect of the conformation of the tubulin heterodimer inside a microtubule depends on whether GTP or GDP is bound to the β subunit, an aspect that has profound consequences for the formation and function of microtubules. This aspect has been traditionally associated with proposals for computation in microtubules [55] and is the only process to be ascribed to the conformational change depicted in Fig. 1 within the Orch OR proposal [5,45]. Free in solution, the isolated tubulin GTP adopts a straight conformation; in contrast, isolated tubulin GDP adopts a curved conformation [Fig. 2(e)] [36,54]. To be incorporated in a microtubule, a tubulin dimer must be in the straight conformation (tubulin GTP). Even after the hydrolysis of the GTP to GDP (Steps 3 and 4, Fig. 2), tubulin GDP is constrained to remain similar to its original conformation [Fig. 2(c)] [33,36]. This state differs slightly from the tubulin GTP straight structure, however, and involves a 2%–4% reduction in the length of the tubulin dimer [36,38]. It is higher in energy than the curved conformation so that the microtubule as a whole becomes under stress [i.e., in a higher energy state than the tubulin-GDP in solution depicted in Fig. 2(e)] [32,36,40]. As a result, at the trailing end of the microtubule, individual tubulin GDP dimers are lost progressively (step 5, Fig. 2 [33]). Once free in solution the GDP can be exchanged with GTP and the tubulin GTP reattach at the growing end. The growing end is stabilized by a cap of tubulin GTP and tubulin-GDP-Pi [Fig. 2(c)]. Hence, microtubules continuously grow at one end and shrink at the other end, resulting in a treadmill arrangement where individual tubulin dimers move progressively along the microtubule; the length of the microtubule is determined by the kinetics of assembly versus disassembly. However, if GTP is removed from the system the GTP/GDP-Pi cap at the growing end is lost (Step 6, Fig. 2) and the microtubule undergoes a process of rapid and catastrophic disassembly (Steps 5 and 7, Fig. 2), leading to free tubulin GDP. Many factors control the stability of each end and hence the details of the kinetics, including the presence of Microtubule Associated Proteins (MAP) and chemical regulators [12].

There is considerable evidence to support the proposal that any conformational changes associated with the hydrolysis of tubulin GTP to tubulin GDP within the microtubule are small and occur only after the phosphate ion has been released [32,42], i.e., during step 4 rather than step 3 in Fig. 2. The turnover of tubulin heterodimers within a microtubule is slow. The rate of GTP hydrolysis by tubulin-GTP incorporated at the growing end is approximately [56,57] $30-70\ s^{-1}$ per microtubule, while the rate of growth of a microtubule is approximately [58] $0.2-1.2\ \mu m/min$, corre-

sponding to the addition of 5–30 tubulin heterodimers per second (based on a heterodimer length [54] of ca. 80 Å and 13 dimers per layer). This suggests that tubulin-GTP is exclusively found in close proximity to the growing end [56]. Structural studies involving nonhydrolysable GTP analogs support these results [38]. Regardless of when the conformational transition within the microtubule occurs, it is clear that the transition within the microtubule from tubulin GTP to tubulin GDP is for practical purposes irreversible: radioactive labeling studies show that tubulin GDP is not phospho-related back to tubulin GTP inside microtubules [29,30,42].

The core premise of the Penrose-Hameroff Orch OR model, that tubulin within stable microtubules can oscillate between two alternative conformations, as shown in Fig. 1, was postulated before the details of microtubule conformer dynamics was known. According to Orch OR, the quantum superposition of the two states via coherent motion along a specific vibrational mode of the dimer (Fig. 1) acts as a qubit in a quantum processor. However, the basic supposition expounded in Fig. 1, that tubulin repeatedly exchanges between the GTP and GTP bound forms within stable microtubules, is in stark contrast to the physiological description shown in Fig. 2 and is not supported by the available experimental evidence.

III. COULD THE OBSERVED TREADMILLING BE UTILIZED TO FORM A QUANTUM QUBIT?

Next we consider if some revised Orch-OR model based on the known treadmilling microtubule dynamics could be useful as a quantum computer in the brain by considering the inherent time scale of the conformer interconversion cycle. An essential feature of Orch OR is that the tubulin dimer be able to interconvert between the alternative conformations a very large number of times [4,8]: the quantum computational cycle depicted in Fig. 1 must occur at least as fast as does the intrinsic neural processing, of order ms, and the underlying coherent oscillation must be very fast compared to this time scale. However, it is now very clear that each interconversion cycle requires the disassembly and reassembly of the whole microtubule. Exchange of GDP with GTP occurs only in free tubulin and not in the assembled microtubule [29,30,42]. Thus, the system could not interconvert between alternative conformational states, as is required for repeated quantum computation, on a time scale less than that of microtubule assembly. As noted above, the rate of tubulin addition onto a microtubule is approximately $5-30\ s^{-1}$. Given the average length of a microtubule, this means that a tubulin dimer is incorporated at the growth end of the microtubule then released at the other end some seconds to hours later. Furthermore, in neurons, the binding of MAP [42] to microtubules can result in lifetimes of an hour or greater [43]. Clearly, such time scales are too long to be of psychological relevance for oscillatory motions underpinning thought processes.

IV. ALTERNATIVE BIOCHEMICAL MECHANISMS AND THE REQUIREMENT OF COHERENT MOTION

The possibility that a revised biochemical model for Orch OR involving stable microtubules could be developed consistent with the observed biological processes is now considered. Such a revised model could in principle be conceived in many ways, exploiting for example the various forms of the α and β tubulins [12] or post-translational modification effects [12] induced by external protein and chemicals. An essential feature of any such model must be the establishment of coherent motion between the two revised postulated structural forms involved in the qubit. This coherent motion must exist for a very long period of time compared to the sub-ps time scale on which motions associated with conformational change are usually decohered [24,25]. Indeed, consideration of physical mechanisms through which coherence *could* be maintained for the required time scale forms a central element of the original Orch OR proposal [4,5] and of modern discussions [6–8,10,23,26]. One proposal involves the production of mechanical stability through either sol-gel formation, water ordering, and other macroscopic ordering processes [6–8], but such effects could only support intradimer coherence on at most the ps time scale; something more profound is required for which the only proposal to date [4–6,26] is the formation of a Fröhlich condensate [46–48], a pseudo-Bose-Einstein condensate, in the biological medium. This is a critical aspect of the process depicted in Fig. 1 as originally proposed [4]. The core element of this proposal is that incoherent metabolic energy is used to force coherence in much the same way that coherence is induced in lasers. Three possible sources of this metabolic energy have been suggested [6]: GTP-GDP hydrolysis, dephospho-relation of MAPs, and ATP hydrolysis associated with actin polymerization, but of these only the GTP-GDP reaction is inherently associated with the tubulin conformational changes. Numerical simulation of Fröhlich's model has shown that coherence times can be increased by up to 6 orders of magnitude, providing the type of dramatic effect that is critical to Orch OR [59]. We have examined the Fröhlich proposal in detail [49] and identified scenarios under which the coherence requirements of Orch OR could in principle be met. The relevant regime is one in which the supplied energy corresponds to at least 10^{12} GTP-GDP reactions per second per tubulin dimer, ca. 10 orders of magnitude larger than the observed reaction rate.

One necessary consequence of coherent Fröhlich condensation is coherent light emission [60,61]. This would most likely be expected in the terahertz region [62–65] and is a feature observed as a result of similar processes [62–65]. While no such coherent radiation has ever been reported, nonthermal terahertz radiation has been observed from frog muscles [66] and nonthermal radiation at 8.085 MHz has been observed from microtubules [50]. Nonthermal radiation can arise from various sources and does not necessarily imply either the formation of a Fröhlich condensate or the coherence of any formed condensate [50]. The possibility that the observed nonthermal radiation from microtubules arises from Fröhlich condensation has been championed by Pokorný [50–53]. Pokorný estimates that the net energy from GTP hydrolysis within the microtubule available to drive condensation is 1.7 kcal mol^{-1} (0.07 eV). As the conversion of tubulin GTP to tubulin GDP is associated with a large change in net dipole, Pokorný proposed that electrostatic interactions provide the long-range forces that give rise to coherence.

Pokorný's reasoning thus has much in common with aspects of the Orch OR proposal. However, the energy driving Pokorný's proposed condensate is many orders of magnitude less than the energy required for the coherent condensate that is critical to Orch OR [49].

Quantitative analysis of Pokorný's proposed condensation mechanism in terms of the fundamental parameters of Fröhlich's model [46–49] shows that the driving power s/k_B is of the order of 100 Ks^{-1}. Pokorný has argued that the power loss due to frictional forces is quite low [51], with relaxation times extending up to 10^{-5} s. Expressed in terms of Fröhlich's model, this result leads to a power loss of $\phi/k_B=20$ Ks^{-1}. As the formation of a Fröhlich condensate requires $s/\phi \gg 1$, it is thus feasible that the observed nonthermal radiation at 8.085 MHz in microtubules [50] does result from the formation of a Fröhlich condensate. However, Fröhlich condensation does not ensure coherent motion, with *coherent* Fröhlich condensates [49] requiring the power density in the mode to dramatically exceed s/ϕ, a quantity that itself must dramatically exceed 1. The observed [50] excess power density in the 8.085 MHz mode in microtubules is just 5 times the thermal energy, orders of magnitude smaller than that required to produce a coherent Fröhlich condensate. Indeed, thorough analysis [49] of the Fröhlich model indicates that an excess radiative power of a factor of 5 is associated with only a *weak* condensate for which is s/ϕ is actually less than 1. Thus the weak Fröhlich condensate envisaged by Pokorný could not give rise to coherent motion and so contribute to cognitive function. No biologically feasible reformulation of the microtubule-based Orch OR proposal could deliver the essential element of coherent intramolecular vibrational motion via Fröhlich condensation.

V. CONCLUSIONS

We have demonstrated that quantum computation cannot take place as proposed in the Orch OR model using the conformational states of tubulins as qubits. This is because the individual tubulin dimers within the microtubule do not undergo a rapid interconversion between alternative conformational states, the most fundamental assumption used in the Orch OR proposal [8]. Instead, the conformational change that accompanies the self-assembly of tubulin to form a microtubule is essentially irreversible, with the exchange of GDP for GTP occurring only after the tubulin has disassociated from the microtubule. As the cycling of tubulins within a microtubule is on the order of minutes to hours even if it were possible to generate the superposition of states required for quantum calculations, such processes could not occur on a psychologically relevant time scale.

Further, we demonstrate that no alternative biochemical scheme could deliver the essential property of coherent intramolecular motion interchanging two conformers utilizing coherent Fröhich condensation. The available biochemical energy is at least 10 orders of magnitude too small to facilitate coherent Fröhich condensation, and experimentally envisaged possibilities for the involvement of Fröhlich condensates in microtubules do not deliver the essential property of coherent motion. Most significantly, if the proposed mechanism was correct, then one would observe stimulated emission of radiation from all biological tissues. No proposal of how coherence on the required time scale within an Orch-OR qubit has been suggested other than Fröhlich condensation, an effect that would produce in effect a new state of matter akin to a Bose-Einstein condensate, and no physical processes is known that could, in principle, deliver the requirements of Orch OR.

The Penrose-Hameroff Orch OR model has attracted much attention and much debate since it was initially proposed in part because it holds the fascinating possibility of quantum mechanical effects playing a central role in cognitive function, and in part because, at least superficially, the model appears physically reasonable. Here we have shown that when tested objectively the basic physical assumptions upon which the Orch OR model depends simply do not hold either from a structural, dynamic or energetic perspective and we hope that with this work we can finally put to rest this intriguing but fundamentally flawed model of cognitive function.

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