Cogn Process (2014) 15:297–306
DOI 10.1007/s10339-014-0609-1

REVIEW

Neuroenergetics at the brain–mind interface: a conceptual approach

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Received: 18 November 2013 / Accepted: 10 March 2014 / Published online: 17 March 2014

Abstract Modern neuroimaging techniques, such as PET and fMRI, attracted specialists in cognitive processing to the problems of brain energy and its transformations in relation to information processing. Neuroenergetics has experienced explosive progress during the last decade, complex biochemical and biophysical models of energy turnover in the brain necessitate the search of the general principles behind them, which could be linked to the cognitive view of the brain. In our conceptual descriptive generalization, we consider how the basic thermodynamical reasoning can be used to better understand brain energy. We suggest how thermodynamical principles can be applied to the existing data and theories to obtain the holistic framework of energetic processes in the brain coupled with information processing. This novel and purely descriptive framework permits the integration of approaches of different disciplines to cognitive processing: psychology, physics, physiology, mathematics, molecular biology, biochemistry, etc. Thus, the proposed general principled approach would be helpful for specialists from different fields of cognition.

Keywords Energy turnover · Neuroenergetics · Free energy · Energy field

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Introduction to energetic concepts

As this article aims to provide a conceptual understanding of brain energy for cognitive scientists, we will begin with a discussion on the concepts of energy and its different types avoiding the formulas but emphasizing their physical content. Energy is an abstract quantity that is used to describe interactions between different objects and processes. The advantage of the notion of energy is that it permits comparison of totally different processes (e.g. one can compare climbing a hill and boiling a can of water in terms of their energy requirements). Another important advantage of energy notion is that it permits linking totally different processes using the idea of energy transformation between them (e.g. to link energy in a piece of bread with energy needed for the muscles to lift an object). Thus, energy permits obtaining a general idea of something in common between totally different processes or drawing a link between them without going into details of exact interactions and transformations, which are always quite complicated (Stowe 2007).

For example, one can generally say that energy of glucose is partly transformed to the energy of electric fields in neural cells. This statement is true even if we do not provide any details about the mechanisms of this transformation. Even if we know the principal steps of the transformation, we do not describe it precisely in terms of how atoms and electrons interact with each molecule and between the molecules. Thus, the notion of energy permits following the general mechanism without getting lost in complicated molecular and quantum details at each step.

Interactions between objects are usually due to the fact that they are in motion or they have a special position in space. When an object is in motion, it has kinetic energy. When it is in a certain position, which may potentially lead

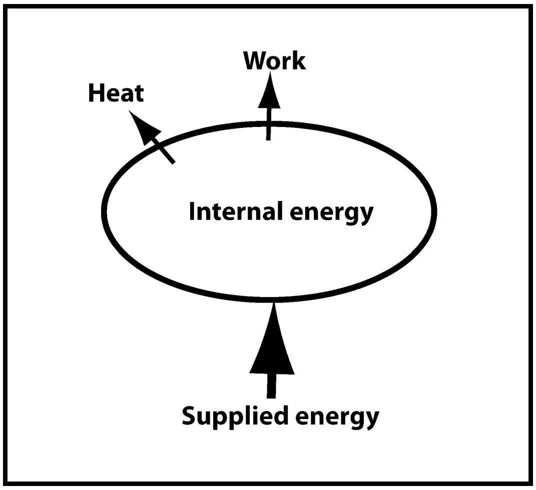

Fig. 1 Basic transformations of energy in a system. If energy is supplied to a non-isolated system (represented by the oval), part of it does work, part heats up the system, and part is dissipated to the surroundings as heat. These transformations are reflected in the basic physical principle of energy conservation and in the first law of thermodynamics. When the system is isolated and no energy is supplied, its internal energy is conserved (energy conservation). When the system is isolated but energy is supplied, the system heats up and transforms part of the acquired energy into work (the first law of thermodynamics). The depicted non-isolated system, which can also dissipate part of the acquired energy as heat in the environment, is a more general case realized in biological systems. However, this case can be easily reduced to the energy conservation principle if we imagine an isolated container encompassing the whole set of processes in Fig. 1 so that energy supply also happens from the inside of this container. For example, one can put an animal into the isolated chamber with food in it. In such a chamber, the sum of all types of energy is constant, whatever happens with food and animal—internal energy within the chamber is conserved

to motion, it has potential energy. For example, different parts of a complex molecule have a certain position with respect to each other that defines the potential energy of the molecule—the potential of its parts to move with respect to each other.

If we hold something in our hand without moving, this object has a potential to fall; thus, it has potential energy due to its position. If we release the object, it falls and acquires kinetic energy due to its movement. In this way, potential energy is transformed into kinetic energy. Importantly, as the two types of energy mutually transform, their sum remains unchanged. The same concerns, for example, gas molecules in a certain closed and isolated container—the total sum of potential and kinetic energies of molecules remains the same. That is why the term internal energy was proposed, which is the sum of kinetic and potential energies of all molecules in the container under the given conditions. The way to change the internal energy of the container would be to change conditions, e.g. to heat it. Heating would increase internal energy of the container.

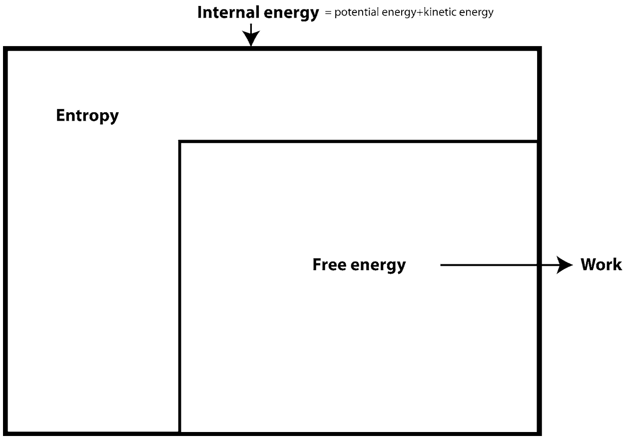

Fig. 2 Internal energy and free energy. Internal energy (the *large rectangle*) is composed of the free energy (*smaller rectangle*) and the entropy at the given temperature. The free energy can be used as work. The entropy reflects unusable energy related to the disordered motion of parts of the system. Thus, the free energy reflects the maximal part of internal energy the system can convert into work

Without changing the surroundings, i.e. without putting energy into the system or taking energy from it, the internal energy of the isolated object does not change with time, but rather is conserved. This is known as energy conservation principle.

Energy can be used to do work; in this case, one can say that energy is converted into work. For example, if there is a piston in the container, heating the container will move the piston to the molecules of the gas producing work on it. Part of the internal energy will be converted into work. In general, part of the amount of heat supplied to a closed system changes its internal energy, and another part is converted to work done by the system on its surroundings. This is the first law of thermodynamics, which is closely linked to the energy conservation principle: if no heat is supplied, the internal energy in a closed system is conserved. However, most of the systems, including the brain, are not insulated; they dissipate heat in the environment. In this case, if we supply energy, part of it does work, part heats up the system, and part is just dissipated to the surroundings as heat (Fig. 1).

It turns out that the more disordered the system is, the less its internal energy can be converted into work. Intuitively, this is because disordered motion is less effective to do work compared with ordered motion. To take this into account, the free energy concept was introduced. Free energy is the internal energy minus the unusable energy related to the disordered motion of parts of the system (Fig. 2). The entropy (measure of disorder) of a system multiplied by temperature mathematically defines this unusable energy. Thus, the free energy reflects the maximal part of internal energy the system can convert into work.

With these general ideas on energy in mind, it is possible to consider more specifically brain energy.

Metabolic aspects of brain energy

In this section, we aim to clarify the link between energy concepts and metabolic processes in the brain at the most general level not entering into the details of metabolic pathways (which can be found in the cited reviews of brain metabolism). The brain like other organs can be considered a certain molecular complex where organic molecules form various cellular and extracellular structures. All the molecules in the brain either move or have a potential to move so that the brain has a certain internal energy at each moment of time. If we put our body into an insulated chamber, internal energy within this chamber should be conserved according to the energy conservation principle (Fig. 1). It follows that no new energy can be generated in the body from nothing; the amount of energy received by each organ is converted into work and heat. How does the brain receive energy? Energy for the brain comes in the form of organic substances (glucose) carried by the blood and in the form of the heat of the blood. Heat energy provided by the blood to the brain is important because it participates in maintaining the optimal temperature for the work of numerous enzyme molecules. Metabolic energy stored in glucose is used to transform various complex molecules in the brain (Nehlig and Coles 2007; Gjedde 2007). Transforming a molecule means moving it or its certain parts, thus increasing kinetic energy, also changing the position of the molecule and its parts, and thus increasing potential energy. The increase in kinetic and potential energies of molecules leads to the increase in the internal energy of these molecules. Thus, the incoming energy is used to increase the internal energy of the brain. Further, this increase in internal energy is partly used for brain work and another part is dissipated as heat in the surroundings (Fig. 1).

Though it is theoretically clear that the incoming energy should increase the internal energy of the brain, there is no practical way to measure internal energy by some tests on the surface of the brain or in its surroundings. It should be measured in every point inside the brain. If we knew internal energy in each point inside the brain, the sum of these values would provide internal energy for the whole brain. This is of course a very complicated issue from the technical standpoint. Existing methods permit only indirect estimations of internal energy in small volumes of the brain (voxels) on the basis of the average blood flow, blood oxygenation, and metabolism within these small volumes (Aubert et al. 2007; Raichle and Mintun 2006; Logothetis and Pfeuffer 2004).

Glucose is a molecule consisting of six carbon atoms. Each bond between carbon atoms stores a certain amount of potential energy, which can be used to do work in the brain. Thus, the complex biochemical processes of glucose metabolism have one goal—to cleave the bonds between carbon atoms and to obtain energy from this cleavage in a usable form. This cleavage can be divided into two main stages (see McKenna et al. 2012 for details). In the first stage, the six carbon glucose molecule is cleaved into two identical three carbon fragments. Each of them is called pyruvate. This stage does not require oxygen (i.e. it is anaerobic), it occurs in the cytoplasm, and is only moderately efficient for energy production. In the next stage, each of the two pyruvate molecules is totally cleaved resulting in six carbon atoms bound with oxygen. Evidently, this stage requires oxygen (i.e. it is aerobic); it happens in mitochondria and leads to the greatest release of energy. In both of these stages, energy from the carbon bonds cleavage is not totally dissipated as heat but is transferred to the energy in the bonds of the other molecule called ATP. Within this molecule, the energy is stored in the energy-rich phosphodiester bonds. The ATP molecule is transported to the different parts of the cell where cleavage of its phosphodiester bonds happens and the released energy modifies various reactions and molecular processes in the cell. The resulting changes happen both in the movements of molecules and their parts and in their positions, thus both kinetic and potential energies of brain molecules increase, i.e. there is an increase in the brain's internal energy by the energy originating from glucose. Oxygen is vitally important because without it anaerobic metabolism provides only four molecules of ATP per glucose molecule. In the presence of oxygen, energy efficiency dramatically increases to up to 38 molecules of ATP per glucose molecule.

Importantly, the energy of ATP (originating from glucose) is mainly used to establish the electrochemical gradients across cell membranes in the brain (Gjedde 2007). Thus, most of glucose energy is transformed into the potential energy of electromagnetic fields. This potential energy stored across the cellular membrane is further transformed into the kinetic energy of ions, which move across the membrane and create the flows of energy propagations in different directions within the brain. Energy flows are the transformations of energy that propagate in certain directions along the cellular structures (axons, dendrites, synapses, etc.) (Strelnikov 2010). As local changes in metabolic energy turnover cannot propagate quickly to the other sites of the neural system, the speed of metabolic changes being measured in seconds, these changes are transmitted in the form of electromagnetic field energy changes, which happen in milliseconds. On the other hand, a permanent level of metabolic energy turnover in cells is needed to maintain the mechanisms of electromagnetic fields generation (transmembrane potential, etc.). Thus, metabolic energy is linked to the energy of electromagnetic processes; the spatial and temporal reorganization of the whole system is required for the processing of the incoming stimuli. Electrical signalling processes are the major consumer of energy in the brain, and the largest component of the signalling energy use is on synaptic transmission (Harris Julia et al. 2012).

According to the earlier speculation of Shulman et al. (2001), after passing through the blood–brain barrier, glucose enters only astrocytes, where it is converted into lactate, which is then taken up by neurons for oxidation. This model emphasizes the energetic coupling between neurons and glia at the level of energy metabolism. However, the real-world situation is probably more complex: oxidative glucose metabolism in glia is discussed in the literature (Gruetter and Leif 2003; Aubert et al. 2007; Hyder et al. 2006; Simpson et al. 2007). See Gjedde (2007) and Belanger et al. (2011) for a detailed discussion of the rates of glycolysis and oxidative phosphorylation in neurons and glial cells. Therefore, it is still not evident which factors influence the distribution of oxidative and non-oxidative metabolism among neurons and astrocytes, including the fractions of the total glucose oxidation in neurons that originate in astrocytes and in direct glucose uptake (see Riera et al. 2008 for a detailed review).

Brain energy and information processing

Even if the molecular mechanisms of energy turnover in the brain were completely understood, there would be quite a separate problem of how to link these energetic properties of the brain to information processing, which is the main function of the brain. It is evident that energy transformations in the brain are related to brain work. Work in physical terms can be defined as energy transfer between objects, which are molecules and cells in the case of the brain. The coupling between work (energy) and information is a crucial process, which happens in the brain, and brain work realized to transform information is different in its meaning from the simple mechanical understanding of work (Gjedde 2007).

To understand the basic physical link between energy and information, let us imagine a container divided by a partition so that only one-half of the container is filled with gas and another half is completely empty. When we take away the partition, the gas will expand to the whole volume of the container. The gas will release energy as heat into the environment, and its own internal energy and temperature will drop. In the new, larger volume, there are more possible positions in the space for each gas molecule. We are more uncertain about the positions of molecules in the larger volume. Thus, one can see that gas expansion leads to the loss of information about the spatial positions of the molecules accompanied by heat release to the environment. Landauer's principle states that heat will be released even if there is only one particle, which is initially either in the right or in the left part of the container with a partition. When the partition is removed and the particle freely moves in the whole volume of the container, one bit of information is lost and a corresponding amount of heat is released (see Bennett 2003 for discussion). This is an important relation between the changes in information and energy, which can also be applied to biological systems (Smith 2008). Evidently, similar approaches are needed to complement the molecular studies of energy turnover in the brain and to clarify their link with information processing.

As we have seen in the above example, changes in information content are related to the internal energy of the gas in the container and to the changes in the "disorder" of gas particles known as entropy. We discussed in the "Introduction" that free energy is a certain difference between internal energy and entropy. During gas expansion, its internal energy decreases, its entropy ("disorder") increases, thus its free energy diminishes. Thus, one can see that changes in free energy are related to information transformations. We also discussed in the "Introduction" that free energy can be interpreted as part of internal energy, which can be transferred into work (Fig. 2). It follows that free energy of the brain may be related to brain work to process information. Friston (2005, 2010), Friston et al. (2006) mathematically elaborated such an approach, attempting to link energetic states of the brain with information processing on the basis of the free energy minimization principle.

The notion of free energy minimization has several interesting applications with respect to brain function. One direction to think about it would be in terms of stability. In the above example about gas in the container, one can intuitively say that the situation of the gas being distributed throughout the volume of the container is more "stable", less likely to be violated, than the situation where the gas is accumulated in a part of the container when partition is removed.

The other aspect of free energy minimization in the brain concerns energy saving. To maintain high kinetic and potential energies of its molecules, the brain needs glucose. If these energies are minimized, glucose consumption is at the optimal level.

These are biophysical and metabolic aspects of free energy minimization but Friston (2005), Friston et al. (2006) emphasizes another aspect derived from mathematical modelling. In mathematical modelling, free energy minimization is equivalent to the minimization of surprise. In fact, this corresponds to the biophysical interpretation in terms of stability. To have a certain stable state given the perceived environment (i.e. to minimize surprise), the brain should maintain an appropriate representation of the environment. In this case, whatever is perceived in the environment produces no surprise. In metabolic terms, novel information, which produces surprise, demands more energy to analyse it. Thus, minimization of surprise also means saving energy for the brain. Another recently described application of this principle is the consideration of accuracy and complexity in brain coding under the conditions of the optimized computational and metabolic efficiencies: given the same level of accuracy, complex representations of the environment in the brain are penalized (Sengupta et al. 2013c).

Concerning the computational link of metabolic energy and information processing in the brain, Sengupta et al. (2013a) assessed the performance (bits/s), energy consumption (ATP/s), and energy efficiency (bits/ATP) of compartmental models and demonstrated that the largest compartments have the highest information rates but the lowest energy efficiency for a given voltage-gated ion channel density. Their computational model suggested that it is more energy efficient for information to be encoded at lower rates in many small neurons rather than a few large, high-information-rate neurons. Balanced inhibitory and excitatory synaptic currents with stronger inhibitory than excitatory conductances were shown to increase both coding efficiency (bits/spike) and energy efficiency (ATP molecules/bit) in comparison with excitatory inputs only and equal excitatory and inhibitory conductances (Sengupta et al. 2013b).

A typical electrophysiological demonstration of the free energy minimization mechanism is mismatch negativity (MMN). It is a negativity in event-related potentials (ERPs), which is elicited by infrequent variations (called *deviants*) in frequently presented stimuli (called *standards*) (Naatanen et al. 2007). This negativity reflects a deviance from the expectations, which is a surprise in terms of the free energy minimization theory. We proposed a mechanism to explain deviance detection or surprise at the neural level (Strelnikov 2007) where, for the sake of simplicity, we presented the schematic case of no prior knowledge when no internal representation of the stimulation exists in the brain, so that stimulation is perceived without top–down selective regulation:

1. Receptors register the physicochemical parameters of the environment.
2. The receptor information is delivered to the brain, where it changes the pattern of spontaneously generated activity.
3. Spontaneously generated brain activity serves to predict the subsequent possible state of the environment; predictive coding of the environmental conditions is created.
4. Perception of the expected environmental changes by the appropriate neural subsystem is enhanced at the synaptic level by such mechanisms as long-term potentiation (LTP).
5. If the next incoming information coincides with predictive coding, its neural processing follows the preformed neural path. In this case, the brain response is typical; no new neural profile of adaptation to the environment is created. Energy is saved by not adapting neural circuits anew to the incoming information; an inherent stability of the system precludes non-dissipative population dynamics (David et al. 2005). In this way, according to the fundamental principle of neurodynamics (Friston 2005), the free energy is minimized.
6. If the incoming information does not coincide with predictive coding, its neural processing does not follow the neural path facilitated by LTP. The free energy then increases: silent synapses are switched on (Luscher et al. 2000), additional neural circuits are formed, and additional loci of excitation occur.

The additional sources of neural excitation at the last stage may result in the observed negativity to the deviant stimuli. The preformed neural paths, which reflect the internal representations of the expected phenomena, constitute a complex organization of energy flows in the brain at rest (Strelnikov et al. 2010). Energy flows can be defined as coherent spatial and temporal changes in the energy turnover of neuroglial units accompanying information treatment (Strelnikov 2010). As these energy flows are used to code the usual environment, they constitute the neural basis of adaptation, which exists in the brain even without stimulation. Energy flows in the brain also participate in spontaneous activity underlying dreams, creativity, imagination, etc. The role of these states in cognitive processing may be in the maintenance and transformation of internal representation, which are further used to perceive the external world.

Based on the above considerations, one can define brain activation in response to stimulation as information-driven reorganization of energy flows in and among populations of neuroglial units, leading to a total increase in energy utilization in these populations (Strelnikov 2010). The general concept of energy flows used in this definition includes the turnover of both metabolic and electromagnetic energy, e.g. the energy of electromagnetic fields (Ioannides 2006). As metabolic energy is linked to the energy of electromagnetic processes, the spatial and temporal reorganization of the whole energetic system is required for the processing of the incoming stimuli. At rest, the organization of this system reflects the adaptive predictive coding, and the degree of its reorganization caused by stimulation depends on the degree of the deviance of this stimulation from predictive coding.

Since the brain permanently receives energy from the environment via food and sensory channels and dissipates it to the environment, predictive coding may reflect an attempt of the brain to establish a sort of energy equilibrium with its environment. Indeed, according to energy conservation principle and the laws of thermodynamics, all the energy input to the brain should be transformed to work and heat. If a certain amount of the incoming energy is not transformed into work, it is transformed into heat. However, there is no reason to overheat the brain or heat the environment by dissipating the excessive heat from the brain. Thus, the excessive incoming energy should be minimized. At the behavioural level, an attempt of the brain to establish such equilibrium with its environment may manifest itself as an attempt to adapt to the environment (Strelnikov et al. 2010). In the case of the lack of sensory input as in profound deafness, one can expect the diminished predictive activity in the auditory cortex. If afterwards the auditory input is restored by cochlear implants, one can expect the reactivation of predictive coding in the auditory areas. On the other hand, as behaviourally such patients use visual cues to compensate for the disturbed sound through the implant, one can also expect the formation of the compensatory visuo-auditory predictive coding in the brain. We showed with PET the reactivation of the auditory and visuo-auditory areas at rest in experienced cochlear implant users at rest (Strelnikov et al. 2010). Furthermore, in these areas, there was an increase in activity between inexperienced and experienced implanted patients, which corresponds to the increase in their auditory performance and thus reflects the decrease in prediction error. We believe that our study of the restored sensory loss demonstrates a direct link between the free energy understood as predictive error reduction and metabolic activity.

There are also studies that suggest the diminishing of the BOLD response with learning, i.e. with the behavioural decrease in prediction error (e.g. Klingner et al. 2014; Toni et al. 1998). This diminishing may be due to the increase at baseline predictive activity as discussed above for our PET study.

We have discussed so far the free energy minimization as internal energy minimization. However, as we noted in the “Introduction”, the free energy is not just internal energy but a difference between internal energy and entropy at the given temperature (Fig. 2). It follows that even at the same level of internal energy, the free energy can be, however, minimized by increasing the entropy in the given brain volume.

We mentioned in the “Introduction” that entropy is a measure of disorder. However, stated like this, there is no evident advantage for the brain to increase its disorder. If we define “disorder” in more physical terms, it is the number of ways in which a system may be arranged given that we do not know in which particular state the system in the present moment is. To explain this complex definition, a simple example from everyday life may be helpful. If we do not know whether a coat is in the wardrobe or under the sofa, the disorder (and entropy) is evidently higher than when we know that the coat has a single state ranged in the wardrobe. In the first case of the higher entropy, we know a certain macroscopic state “the coat is in the room” but we do not know exactly what the position of the coat is. Considering by analogy the molecular systems, entropy is defined by the number of possible microscopic configurations of the individual atoms and molecules, which could give rise to the macroscopic state of the system.

This more detailed consideration of entropy suggests its useful implementation in the functional architecture of the brain. It permits maintaining different representations of the same object or a class of objects. For example, though we know before entering an unfamiliar office that there should be a table inside, we do not know exactly the form of the table, how many legs it has, etc. There is a certain “disorder” or uncertainty in the constructions of the table, which the brain needs to account for in its internal representation of a table. By increasing entropy, the brain can minimize its surprise with respect to the variability of the same object, i.e. minimize free energy.

In the above considerations of the free energy, we used a descriptive physical approach; however, Friston’s theory of free energy minimization is not based on the physical conception of the free energy but on mathematical modelling (hierarchical dynamical models and variational Bayes); physical parallels are introduced only as illustration. Those interested in mathematical formulations of this principle may address Friston’s reviews of this issue (Friston 2005; Friston et al. 2006). It should be noted that variational free energy derived mathematically by Friston’s theory is not exactly the same as physical (Helmholtz) free energy. Variational free energy can be represented as the difference between complexity and accuracy of neural coding. In this case, as clarified in (Sengupta et al. 2013c), one can understand metabolic efficiency in terms of minimizing complexity (which minimizes Helmholtz free energy), under the computational constraint that sensory inputs are represented accurately.

Minimizing the free energy is equivalent to reducing prediction error, thus one can predict that cognitive conditions, which lead to the diminishing of prediction errors (e.g. learning, adaptation), should lead to the decrease in stimulation-induced metabolic activity in specialized neuroglial populations. At the same time, predictive coding at rest should increase the resting-state metabolic activity of these areas. Though the discussed above studies confirm such predictions, they should be further verified for a large range of cognitive loads using neuroimaging techniques. Another prediction, as described above, is that to minimize the variational free energy and Helmholtz free energy, the brain will need to decrease the complexity given the same accuracy. This prediction can be tested using different neural modelling approaches.

Though the free energy minimization principle provides some interesting generalizations, it should not be considered as the only principle governing brain work. For example, animals tend to escape from usual environment to less predictable surroundings, many people like to travel and obtain surprising experiences, and the brain itself produces unpredicted information manifested as creativity (see Friston et al. (2012) for the discussion of some of these aspects). Thus, the free energy minimization principle can be complemented by some other unknown principles, which present a perspective for further studies of brain work. For example, another interesting perspective, though mostly on economic grounds, was proposed suggesting that the brain network organization optimizes a trade-off between the cost and the behavioural value of network function (Bullmore and Sporns 2012).

Functional neuroimaging and energy fields

In recent decades, neuroimaging techniques, such as PET and fMRI, have been developed to obtain three-dimensional pictures of brain activity (Raichle and Mintun 2006). Measuring the fourth dimension, which is temporal, remains problematic due to the low temporal resolution of these techniques. As a result of the average brain activity that occurs during any given stimulation, neuroimaging techniques indicate a certain level of brain activity in small volumes of the brain called voxels. When each small volume, or voxel, has a certain scalar value attributed to it, the whole spatial structure can be mathematically characterized as a scalar field of three dimensions. Thus, modern neuroimaging techniques represent time-averaged brain activity as a scalar field. Cognitive neuroimaging aims to decode how environmental information is spatially encoded in the three-dimensional energy/activity field of the brain. The measures of energy or activity in the brain are indirect, e.g. they do not provide the values of internal energy or free energy. These estimations at present are mostly based on the measures of the local blood flow and blood oxygenation, which reflect the brain demands in energy.

As in the physical models of energy transformations (e.g. in the room's air), the exact properties of each individual particle are not described, the conception of energy field in the brain does not consider individual molecules and cells in the brain. Instead, it considers the brain as an agglomeration of small volumes with a certain value of energy in each volume (Strelnikov 2010). We do not know the size of the smallest information-encoding volume in the brain; it may be infinitesimal. For practical purposes, the size of these brain volumes (voxels) can be arbitrarily chosen on the basis of the technically available spatial resolution and the need for precision.

Thus, functional neuroimaging techniques represent the brain as a three-dimensional field of energy with a specific structure: three-dimensional peaks, valleys, etc. The classical analysis of brain activity reflects a peak of energy turnover in a specific region but neglects the local changes of brain activity in the vicinity of the peak that should be explored by spatial differentiation. The energy field view of brain activity reconciles localizationism and connectionism (Miller 1986): each field is a holistic entity, but has local peculiarities, such as peaks. The physical relation between energy and information transformations described in the previous section permits to think of brain energy fields as the sources of virtual spaces, in which information transformations during cognitive processing are operated.

One can investigate peculiarities of brain energy fields with existing mathematical techniques that are widely used in physics. By analogy with electric potential, which determines electric forces and flows of particles (currents) in the electric field, free energy is called thermodynamic potential because it also determines generalized thermodynamic forces and flows of particles in the energy field. Our biophysical consideration (Strelnikov and Barone 2012) based on the free energy minimization principle (Friston 2010) suggested that high spatial differences (gradients) of energy between adjacent voxels should spontaneously disappear with time. However, we discovered stable task-related gradients of activity at the group level (Strelnikov and Barone 2012), suggesting the existence of stimulation-related processes that act to maintain the described gradients.

A persistent high difference between the adjacent voxels in one direction would correspond to two situations. In the first case, electric activity propagates in this direction and causes an increase in spikes fuelled and amplified by metabolic energy as indirectly reflected in the BOLD signal (backward propagation in the same direction being blocked, see Strelnikov and Barone 2014 for discussion). In the second case, there is a high inhibitory input in this direction, which abruptly stops activity propagation. Both cases correspond to the propagation of electric currents, which result from stimulation-driven transformations of energy along axons and dendrites in neuroglial networks. Excitatory interpretations are more probable because glutamate-related processes account for approximately 70 % of total energy turnover (Shulman et al. 2004), while GABAergic processes account for only about 15 % of total energy turnover by neurons and glia (Patel et al. 2005).

Besides, minimizing variational free energy as proposed by Friston (2005) is not exactly the same as destroying thermodynamic free energy gradients. According to the arguments in the last section of Sengupta et al. (2013c), these would only occur when the brain was deprived of sensory input for a very long time. This is an interesting perspective on sleep, deep anaesthesia, or coma where one might expect the activity gradients noted above to be attenuated.

Mathematically, the gradient vector indicates the direction of the highest increase in the vicinity of a point (Matthews 1998). Positive divergences or sources in the field indicate the loci of the net increase of activity in the neighbourhood of the given voxel. We detected significant positive divergences in the visual areas during face perception and in the temporal auditory and speech areas during word perception. Thus, our approach revealed that the information coded in the fields of brain activity is far more detailed than just one scalar value per voxel (Strelnikov and Barone 2012).

If a certain point of the brain has a gradient vector whose length and direction are specific to the given stimulation, another type of stimulation will change the length and direction of this vector. Physicists and mathematicians transform vectors by defining the changes in their projections on the axes. For example, if we want simply to double the length of the vector, we double its projections on the x, y, and z axes. In contrast, if we multiply the projections on the x, y, and z axes by different numbers, then we can change both the length and the direction of the initial vector. The multiplying numbers for each projection are usually indicated along the diagonal of the 3×3 matrix (wherein the non-diagonal elements are zeros for the orthogonal coordinate system). The resulting transformation matrix for the given vector is called a tensor of rank 2, or a dyad. We need a tensor to transform a vector in each point of the 3D space. When we obtain a tensor associated with each point of the 3D space via an analogy with a vector field, this new quantity is called a tensor field.

Thus, for the vector in each voxel, we can construct a tensor that transforms this vector between stimulation conditions. It follows that the tensor field of brain activity reflects the incoming sensory input that is changing the state of the brain. Using the conception of tensor fields, we have shown that one can analyse the incoming cognitive input that is transforming the brain activity separately from the resulting brain activity (Strelnikov 2013). Tensor fields can be conceptualized as virtual spaces of sensory activity, which act on brain energy fields to transform virtual spaces of internal representations coded in brain energy fields.

Brain activity is neuropsychologically considered to integrate the perceived information (e.g. Gerlach et al.

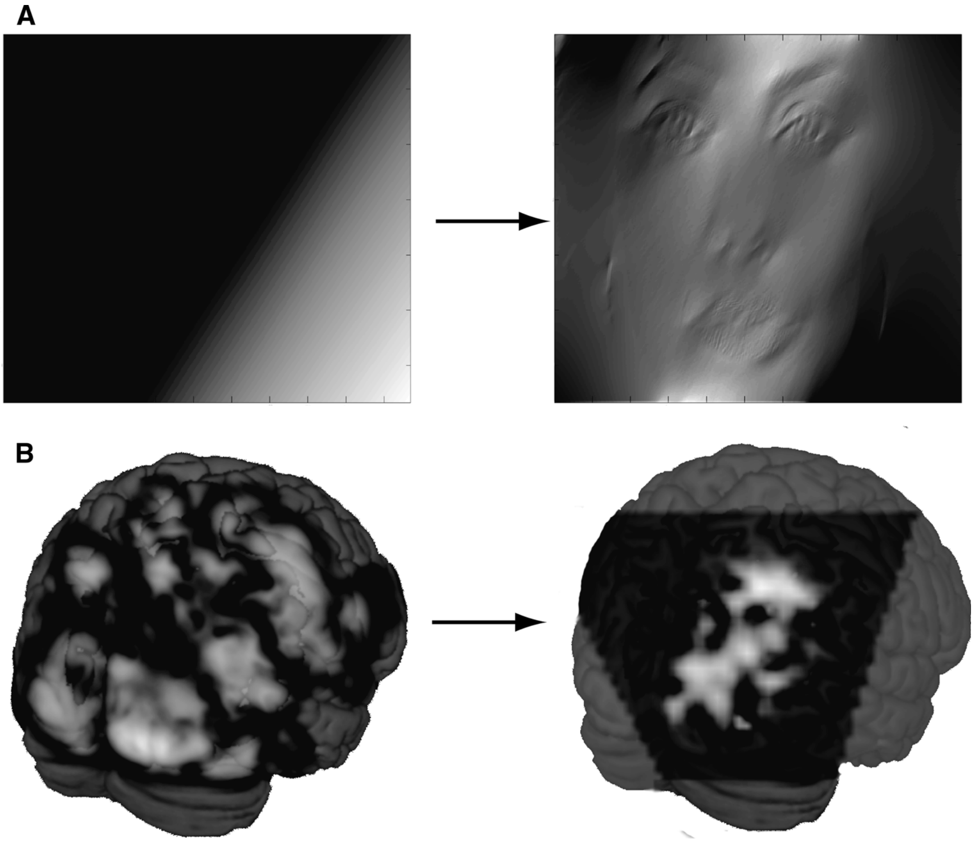

Fig. 3 Example of spatial differentiation applied to the scalar field of activity. **a** On the *left*, a simulated two-dimensional "activity", which is obtained by spatial integration of a female face. On the *right*, the virtual space obtained by the mixed second-order differentiation of the simulated "activity". **b** On the *left*, the group fMRI activity obtained during face perception. On the *right*, the virtual space obtained by the mixed third-order differentiation of the fMRI activity. A general face pattern can be observed at the occipito-temporo-parietal junction

2002; Basar 2012). As differentiation is the opposite operation to integration, an interesting perspective would be to apply a rather general differential approach to study the peculiarities of brain activity. In this approach, the differences between the neighbouring voxels are first considered along one axis, then the differences between the differences are calculated along the other axes. This approach mathematically corresponds to the third-order mixed spatial differentiation, and the result does not depend on the axis chosen first. In a 3D space, this provides a unique value per voxel, which summarizes the differences between the neighbouring voxels in relation to the changes along all three coordinate axes together. Such a differentiation estimates the variations of activity between the neighbouring voxels, and one can test the hypothesis that they participate in information coding in the brain.

Figure 3 illustrates how the simulated two-dimensional "activity", which originates from the integration of a human face, may be restored with mixed differentiation. To generate the left picture in Fig. 3a, an image of a female face was double-integrated using the inverse (integrated) gradient function (http://www.mathworks.com/matlabcentral/fileexchange/9734-inverse-integrated-gradient). In spite of a certain loss due to the approximations in integration algorithms, the female face pattern could be reconstituted by differentiation with respect to the x and y coordinates as shown in Fig. 3a. Thus, a face is a pattern in the virtual space, which is decoded by spatial differentiation from the simulated integrative two-dimensional "activity". Figure 3b illustrates the virtual space originating from the three-dimensional differentiation of the real brain activity, which is a group average during face perception available at the SPM site (http://www.fil.ion.ucl.ac.uk/spm/data/face_rfx/). The resulting face pattern in the virtual space at the occipito-temporo-parietal junction may be anecdotic; it is presented here just to illustrate the perspectives of differential approaches to investigate virtual spaces coded by brain energy fields. Besides, it would be too risky to assume that integration of information happens only between the neighbouring voxels in brain activity; long-range connections can also participate in virtual field creation. The roles of short- and long-range connections in coding virtual spaces are also perspectives for future research.

Conclusions

As can be seen from the above exposure, the fundamental conception of energy can be applied to the brain function and can be rather intuitively developed on the basis of the known physical principles such as energy conservation and thermodynamic laws. Even in its most general and descriptive form, the energetic approach to brain function provides a unique framework to consider molecular and cellular processes, population-level organization of brain activity as well as information treatment, which turns out to be directly related to brain energy. No other approach to brain function comprises the whole set of its levels in intimate coupling with information treatment, and no other approach permits integrating the approaches of different disciplines to brain function: cognitive psychology, physics, mathematics, molecular biology, biochemistry, cell physiology, etc. Hypotheses in different domains could be derived from the same basic principles of brain work. This concerns not only mathematical hypotheses but psychological and cognitive hypotheses as well.

Neuroenergetic considerations provide the novel perspectives of information coding by brain energy fields including the studies of virtual spaces for cognitive processing coded by these fields. Thus, we consider the recent direction of neuroenergetics, the most prospective direction of cognitive neuroscience.

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