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INTRODUCING TRANSCRANIAL MAGNETIC STIMULATION (TMS) AND ITS PROPERTY OF CAUSAL INFERENCE IN INVESTIGATING BRAIN-FUNCTION RELATIONSHIPS

ABSTRACT. Transcranial magnetic stimulation (TMS) is a method capable of transiently modulating neural excitability. Depending on the stimulation parameters information processing in the brain can be either enhanced or disrupted. This way the contribution of different brain areas involved in mental processes can be studied, allowing a functional decomposition of cognitive behavior both in the temporal and spatial domain, hence providing a functional resolution of brain/mind processes. The aim of the present paper is to argue that TMS with its ability to draw causal inferences on function and its neural representations is a valuable neurophysiological tool for investigating the causal basis of neuronal functions and can provide substantive insight into the modern interdisciplinary and (anti)reductionist neurophilosophical debates concerning the relationships between brain functions and mental abilities. Thus, TMS can serve as a heuristic method for resolving causal issues in an arena where only correlative tools have traditionally been available.

1. FUNCTIONAL DECOMPOSITION AND LOCALIZATION

The discovery and development of ways to decompose the functional organization of brain–mind processes has proved to be very beneficial for the cognitive sciences (Bechtel 2002). By building models of cognitive behavior using the functional component principle, that is dividing cognition into discrete information processing units, it becomes feasible to develop sophisticated ways of disentangling the workings of cognitive functions. Bechtel (2002) distinguishes a phenomenological and mechanistic decomposition. The former, Bechtel argues (2002) reflects the attempt of psychology to identify and categorize different cognitive faculties, while the latter seeks to identify how the processes that give rise to cognitive constructs really operate and interact. The differentiation can be best understood in terms of ‘what’ kind of cognitive construct and components can be identified and ‘how’ they are generated.

A large difference of opinion between the functionalists and structuralists lies in the mechanistic decomposition approach, that is

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in the implementation of function within the brain. Whereas the traditional functionalists hold to the idea of 'multiple realizability,' whereby localization of function may be impossible in principle, the structuralists argue that function is predictably related to the operations of specifiable brain systems (Fodor 1975; Putnam 1975). 'Multiple realizability' also encompasses the idea that function, and cognition in particular, can be implemented in various physical entities, such as silicon chips and brain matter. The crucial notion, however, entails the fact that specific types of hardware implementation are independent of functional issues. The hard functionalists state that if cognition can be decomposed and hardwired, in for instance silicon chips, then one has all the information and knowledge regarding the underlying process at hand. In order to understand a given cognitive function one does not need neuroscientific research or to even consider the brain *per se*. This, of course, is an enormous assumption, and the most telling criticism is that many different processes can lead to the same end result. This concept can be visualized easily through the metaphor of any mathematical equation, where the results to the right of the equal sign could be achieved by a vast number of factor structures to the left. From a naturalistic point of view, the critical question is how brains actually achieve the functions that they do, in fact, exhibit. Thus, it follows that an accurate functional analysis of mind functions simply has to be restrained and guided by neuroscientific facts. Human cognition, no matter how shaped by environmental inputs, is fully dependent on the workings and properties of the brain.

Seemingly paradoxically, the functionalistic approach was initially a reaction to the explanatory shortcomings of behaviorism. However, functionalism is actually a modern version of the latter (at least the black-box variants) in which constructs such as cognition are refined and decomposed on the descriptive level, but which remain independent of physical realization, ultimately resembling a new form of dualism (Chalmers 1996). From the functionalist perspective, the physical implementation can again be treated as a black box. For example, cognitivists interested in artificial intelligence build machines which can actually mimic human cognitive outputs to an extent, but these remain mere simulations of how one thinks a given brain function might work.

The functionalistic approach is fruitful in its own right, however, for a complete explanation of human mentation one has to start thinking how function and its architecture are realized in the brain.

The only way to understand function completely is by starting to disentangle the system properties of the brain on which function supervenes. With the advent of various neuroimaging techniques a decade ago, some of the structural correlates of underlying complex human behavior became accessible through *in vivo* investigations of the brain, providing bridging principles between function and structure (Churchland 1992; Toga and Mazziotta 2000). The structuralist way of studying behavior has more or less dominated scientific research ever since. While many cognitive scientists still believe that the realization of complex behavior can be studied secondary to structural issues, neuroscientists realize that the intrinsic properties of the structure itself and the resulting neurodynamics are of the essence in fathoming the way functions work (Schutter 2001). The whole idea is based on the principles of functional decomposition, localization of the relevant component functions, and a specification of their interactions.

This type of work is guided by the pragmatic premise that there may exist, at least in a first-pass analysis, a tight relation between the functions and their neural realizations (Bechtel 2002). In neurophilosophy this assumption is better known as the 'identity' theory, which states that by decomposing cognition one is able to localize the different units as separate neural structures and systems in the brain. Figure 1 illustrates, based on the 'identity' or 'token' theory, the direct relationship between the processing units of a function and its local neural representations. Although this viewpoint accepts that mind functions may be partly 'modular' in the intact adult brain, it

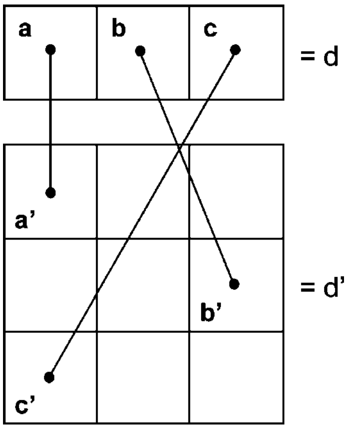

Figure 1. Function d can be decomposed into a, b, and c and its structural representation d′ is localized in a′, b′ and c′ respectively.

does not simply accept that these are evolutionarily derived modules. Many specializations, especially the cortical ones, could as readily be epigenetically derived because higher brain systems resemble random access type memory fields programmed by more genetically dictated patterns of subcortical sensory and emotional circuitries (Panksepp and Panksepp 2000).

In any event, with the advent of modern neuroimaging these different neural representations, whether genetically dictated or epigenetically emergent, can be partly localized in the brain and potentially linked up to the decomposable processing units. The method has been remarkably successful in identifying brain areas that mediate emotions and various emotional disorders (Damasio et al. 2000; Mayberg and McGinnis, 2000; Drevets 2001; Phan et al. 2002), language functions (Grabowski and Damasio 2000), as well as a host of other brain functions (Toga and Mazziotta 2000). This method of localizing is inherent to the relative high spatial resolution of the various neuroimaging techniques and very valuable with respect to studying the different structures of the brain in relation to the expression of cognitive functions *in vivo*. However, important reservations regarding this research method have been recently raised by Uttal (2002) and others (e.g., Logothetis 2002), and it is ever more widely recognized that such approaches need to be supplemented by many others.

Although Uttal acknowledges the great potential importance and contributions of such approaches to the understanding of the relation between structure and cognitive function, he and others argue that there are major conceptual difficulties when using imaging techniques. By coining the term the *new phrenology*, Uttal highlights these fundamental problems. The workings of complex cognitive behaviors may not be capable of being unraveled on the basis of decomposition approaches, for the assumption of a one-to-one relation between the function and the localization of its underlying neural representations may be false. Even if it would be possible to provide for a structural solution of cognitive function, it would be impossible to include, for instance, the temporal course of activity and the precise interactions across the different structures involved.

On the other hand, a recent study by Logothetis et al. (2001) demonstrated that the neurophysiological basis of the blood-oxygen-level-dependent (BOLD) fMRI signals probably rely on a different neural property than electrophysiological activity. More specifically, the BOLD signal is argued to reflect activity at the pre-synaptic level, whereas EEG results are based largely on post-synaptic neural activities. At the same time, there is some cross-species data indicating that visually evoked single-unit activities correlate well with fMRI signals from comparable human studies (Rees et al. 2000). In any event, hemodynamic responses emerge at relatively longer time scales and are likely to be equally sensitive to synchronous and asynchronous sources of electric activity.

The combined applications of EEG and fMRI can provide for a high temporal and spatial resolution and might constitute part of the solution. However, taking into account that one has to make far fetched mathematical assumptions on how to align fMRI and EEG in time, this endeavor suddenly becomes more complex and difficult than one might have originally anticipated (Horwitz and Poeppel 2002). Regarding this notion, Uttal (2002) is pessimistic and states that it will not be possible to create a full comprehension of cognition based on such current technologies.

We certainly acknowledge such problems, especially since it is obvious that correlative techniques can only give hints concerning causality. However, this does not *a priori* imply that no useful causal knowledge and insight can be obtained from investigating the biological underpinnings of cognition using high-tech neuroimaging, including new approaches such as *coherence* measures and other cross brain area correlational analyzes. In concordance with this notion, Bechtel (2002) argues that neuroimaging can indeed be very useful in our aspiration to find out more about the working mechanisms underlying cognition and function in general. Each technique has limitations, and it is only through the convergence of various methodologies and findings that substantive knowledge can be achieved in this area. Even though brain imaging might not be able to solve all brain-cognition problems, the technique can be used as a heuristic method of scientific exploration for relevant neural correlates that can guide future causal studies.

Although the 3D visualization methods and the functional activation maps have high face validity with respect to the partial representations of certain functions within the brain, it should not be overestimated what this functional activity actually stands for. For instance, active processing of a function and active inhibition of a function could lead to increased blood flow in areas mediating those functions. Thus, even if a correlation between function and local brain activity can be established, a causal link remains to be investigated by other methods. For instance, animal brain studies have already provided for an enormous number of causal manipulations.

Only a few of them can be applied in humans (Panksepp, 1998). In general, the three major types of causal manipulations are (i) contextual and psychological challenges, (ii) neurochemical ones (e.g., psychopharmacological manipulations), and (iii) direct electrophysiological ones (e.g., brain stimulation). In general, the first two are rather global causal variables that typically affect much of the brain. For the second set of variables, localized brain manipulations cannot be achieved as is routinely done in animal studies where chemical agents are commonly placed directly into specific brain areas. Likewise, electrical brain stimulation in humans has, with few exceptions been achieved secondarily to medically indicated neurosurgical procedures (Heath 1996). There is presently no way to stimulate deep brain structures of humans non-invasively (although, as will be discussed later, that is a theoretically feasible possibility). Recently, however, an approach has emerged for stimulating the human cortical surfaces extracranially, which provides, for the first time, powerful causal ways to manipulate cerebral functions in normal individuals and thereby evaluate the causal roles of many potential structure-functions correlates that have been provided by brain imaging.

2. TRANSCRANIAL MAGNETIC STIMULATION (TMS)

The most robust brain stimulation method presently available which can be utilized to analyze causal relationships between brain structure and function in normal humans is a technique called transcranial magnetic stimulation (TMS). TMS is based on Faraday’s law of electromagnetic induction, which states that, when situated near conductors, a magnetic pulse oriented in the right direction is transformed into an electric current. When the magnitude of this magnetic pulse varies in the order of a few hundred microseconds a secondary current is generated (Pascual-Leone et al. 2000). Applied over the scalp the electromagnetic induction will result in the depolarization of underlying cortical nerve cells that are tangentially oriented to the magnetic field (Bohning 2000). The axons excited are oriented in the plane of the induced electric field parallel to the curvature of the heads at the stimulated area. From a neuro-anatomical perspective this technique can influence all cortical areas that face the cranium, even though in practice one has difficulty stimulating many areas such as orbitofrontal and low temporal areas because of the concurrent, and often painful, contraction of major head muscles.

TMS was introduced by Anthony T. Barker in 1985, who demonstrated that *in vivo* stimulation over the motor cortex induced involuntary hand movements in healthy human subjects (Barker et al. 1985, 1987). TMS is a non-invasive method which can, depending on stimulation parameters, transiently inhibit or facilitate on-line information processing. Although, the size of the effective stimulating field and the amount of current spread in the tissue of the head are dependent on intensity and current cortical thresholds, with the use of specially designed stimulation coils, TMS may be capable of mapping cortical functional regions on the scalp with a spatial resolution of about a square centimeter. The cone-shaped field strength directly under the coil can be as large as 2.5 Tesla (T) (Stewart et al. 2001). The standardized stimulation parameters consist of frequency, intensity and duration. It seems evident that stimulation frequencies of ~1 Hz suppress, whereas frequencies of $\geq$ 5 Hz typically increase neural excitability (Pascual-Leone et al. 1999, 2000). Since on the cellular level TMS is similar to direct electrical stimulation (George and Belmaker 2000) the underlying working mechanisms of TMS and its effect are presumably due to transient changes in the intra- and extra-cellular concentrations of sodium (Na^+), potassium (K^+) and chloride (Cl^-) ions.

Based on the neuro-modulatory properties of TMS, one line of research has focused on studying the role of the frontal cortex in relation to psychopathological conditions, such as major depression, in which a relative left hypometabolism has been implicated (for overview, see Nahas et al. 2004, but see Schutter et al. 2003a for an alternative view). Several clinical studies have been able to show antidepressant efficacy by applying fast frequency over the left frontal cortex to increase neural excitability (Pascual-Leone et al. 1996; George et al. 1997; Fitzgerald et al. 2003), although negative results have been shown also (for reviews see George et al. 1999; Wassermann and Lisanby 2001). Furthermore, Klein et al. (1999) and Fitzgerald et al. (2003) reported antidepressant effects by dampening neural excitability after slow frequency TMS over the right FC as well, encouraging them to suggest that in particular the homeostasis in brain activity and interplay between the left and right frontal cortex are disturbed in major depression. There are already a sufficient number of studies, that several meta-analyses have been published demonstrating efficacy across studies and laboratories (McNamara et al. 2001; Burt et al. 2002; Kozel and George, 2002) and the procedure is now medically approved in Canada and Israel.

Although TMS can induce changes in cortical excitability, basically, the neural firing that TMS promotes is random and can best be perceived as noise induction (Stewart et al. 2001). In other words, changes in neural activity have no intrinsic meaning to the system itself and can therefore be utilized as a 'virtual lesion' technique, in which the information processing in a targeted part of the brain can be investigated by means of transient disruption (Pascual-Leone et al. 1999, 2000). Using this method, it becomes possible to investigate the specific contribution of an underlying brain area in complex information processing. In this context, it can be noted that for simple responses, such as motor movements, the TMS-induced neural activation can activate the function of a brain area (e.g., a thumb twitch from the motor cortical representation area of the thumb, which can be further facilitated by motor imagery (Fadiga et al. 1999), but in situations where an area has to process complex information, the stimulation effect might invariably be a more functional disruptive one. Thus, wherever one gets a facilitation of a function with high frequency TMS, one can surmise that a generalized arousal state has been promoted, whereas if both low and high frequency parameters have similar effects, one can surmise that detailed information processing was disrupted. For instance, the ability of left temporoparietal TMS to reduce auditory hallucinations in schizophrenics may arise from disruption of the internal generation of faulty perceptual signals (Hoffman et al. 2003). In any event TMS can provide a definitive causal manipulation to evaluate the role of cortical areas in specific types of psychological functions.

Whereas fMRI and EEG for instance have high spatial and temporal resolution respectively, TMS has so-called functional resolution, in which spatial and temporal aspects of activation in brain structures can be combined and causally related to its function. For instance, Amassian et al. (1989) demonstrated the inability for healthy subjects to detect a visually presented stimulus when TMS was applied over the occipital cortex 80–100 ms after stimulus presentation. This work has not only provided causal evidence for the involvement of the occipital cortex in vision, but also provides some information about the conduction velocity from the retina to the occipital cortex.

Wassermann et al. (1992) were among the first to use TMS in non-invasively mapping the muscle representations of the human motor cortex, and now TMS has been used extensively to study the motor neurophysiology of psychiatric disorders (Maeda and Pascual-Leone 2003). Abundant work has shown that stimulation over the left inferior frontal cortex (Broca's area) blocks speech output, so-called speech arrest (Epstein 1998). By topographically mapping the language representations one can readily locate important brain areas which should be spared in patients suffering from epilepsy who are about to receive resection of brain regions in the vicinity of Broca's area. Although it is theoretically feasible and correct to infer that the language area can be mapped, TMS is for instance not capable of inducing speech arrest in every single subject, arguably due to inter-individual variance in brain morphology, which also makes its clinical utility somewhat limited. TMS can easily deal with issues concerning intra-individual variance with respect to functions represented in the superficial layers of the cortex. However, when the critical brain region for speech production in a given individual are buried deep in sulci they are more difficult to reach, since current TMS techniques are not capable of targeting more medial regions of the cortex without focality loss.

Grafman and Wassermann (1999) reviewed the specific contribution of cortical areas in different aspects of learning and attention with the use of TMS and the concept of functional decomposition. More recently, TMS studies by D'Alfonso et al. (2000), Schutter et al. (2001), Van Honk et al. (2002a, b) found evidence for the involvement of the left and right prefrontal cortex (PFC) in the processing of the emotions of anger and fear, respectively. Furthermore, Aleman et al. (2002) demonstrated that the parietal and not the occipital cortex participates in top-down visuospatial mental imagery by showing that TMS over the parietal cortex resulted in the deterioration of imagery task performance, which was not evident after occipital and sham stimulation.

With respect to predictions that can be made on the basis of existing brain imaging data, a double dissociation between cognitively and affectively driven inhibition control in monkeys was recently demonstrated (Dias et al. 1997). Damage to the lateral prefrontal cortex was accompanied by a loss of inhibitory control in attention selection, while a dysfunctional orbitofrontal cortex resulted in the loss of inhibitory control in affective processing. Interestingly, a TMS mapping procedure could be utilized to investigate whether this double dissociation applies to the human cortex as well, even though the use of TMS over orbitofrontal areas is difficult because of discomfort induced by direct stimulation.

On the basis of its ability to decompose complex cognitive functions into separate units and localization, TMS can determine which brain areas are on what moment actively involved in specific functions. Since the strength of the induced magnetic field as a function of distance fits a decaying exponential function (Bohning, 2000), the actual depth of penetration is only a few centimeters, thus initially only neocortical tissue is affected directly. However, recent studies have demonstrated that apart from the local effects, more remote effects can be obtained (Fox et al. 1997; Nahas et al. 2001; Schutter et al. 2003b; Daskalakis et al. 2004). The magnitude of temporary lesions effects can be enhanced by preceding activation of brain tissue with rTMS (Iyer et al. 2003).

The brain consists of functionally interconnected networks, hence stimulating a specific part induces changes in other areas of the network as well. For example, Paus et al. (1997) and Strafella et al. (2001) demonstrated such transsynaptic effects by obtaining distal cerebral blood flow responses in the posterior cerebral regions after stimulating an anterior region of the cortex. It remains possible that these remote effects, which are filtered through normally operating brain functions, reflect promotion rather than disruption of brain functions. This would, of course, complicate the interpretation of findings achieved with TMS.

The above-mentioned studies nicely demonstrate the uniqueness of TMS to directly link function and underlying structural representations (isomorphy). Such cortical mappings of function resemble what Uttal (2002) called the *new phrenology*. However, TMS adds a whole new dimension to the discussion that Uttal did not consider. Not only is TMS unique in its ability to establish causal connections between functions and the underlying neural representations in spatial as well as the temporal domains of information processing, but by combining TMS with brain imaging, it can also help map participating brain systems to a fuller extent (e.g., Bestmann et al. 2004; Nahas et al. 2004). This can lead to highly resolved hypotheses about what various brain regions contribute to the whole. Still, a main caveat regarding TMS research is the basic assumption that cognition and structure are directly related in an isomorphic fashion; a linear relationship between function and implementation. For simple cognitive behaviors, such as face recognition which use anatomically restricted functional architectures, this is not problematic. However, complex (meta)cognitive behaviors seem not to be wired up in simple structural clusters in which local computations are performed. Indeed, most higher-order cognitive functions, such as reasoning and problem solving, may emerge from very dynamic, distributed and complex non-linear brain processes. Those types of issues will have to wait further resolution of technological methodologies.

3. TMS, REDUCTIONISM AND EXPLANATORY PLURALISM

According to the antireductionists, neurobiological models are not suitable in modeling complex cognitive function. McCauley and Bechtel nicely elucidate this notion by writing '…since these antireductionists insist that any of various considerations (such as multiple realizability or intractable complexity or the impregnable uniqueness of intentional contents or the elusiveness of subjective consciousness) suffice to block the necessary mapping the classical models of reduction require' (2001; p. 739). On the other hand, Sober (1999) argues that the essence of reductionism (i.e., relating the higher (functional) and lower (structural) orders of modeling) is the claim that the effect on the appearance of the higher functional attributes are caused by the lower structural properties of the system. Whereas modern neuroimaging can only reveal correlations between the higher and lower orders, TMS provides access to causal manipulations that may yield bridging principles between the former and the latter. Although most mind-scientists agree that the basis of cognitive function is neural by nature, they vary widely with respect to how the brain actually accomplishes the instantiation of function, and more importantly, whether it actually tells us something about the intrinsic properties of the function itself.

McCauley and Bechtel advocate the idea of explanatory pluralism and the heuristic identity theory (HIT) by stating that 'Explanatory pluralism holds that a proper interpretation of the consequences of successful inter-theoretic mapping depends (at least) upon the theories' respective levels of explanation in science and their temporal relations' (2001; p. 737). According to the HIT both the cognitivistic and reductionistic levels of explanations can refer to an independent ontological status. Unique and distinct properties of function can be revealed on both levels and can be used as heuristics to promote cross-disciplinary research to link levels in either non-radical reductionist or supervenient relationships. Furthermore, the HIT states that the neural identities are not the end-points of scientific research, but rather constitute the necessary premises in ultimately explaining function. In this respect, the HIT approach provides for an important philosophical ground for the emergence of a 'gentle' reductionism in interdisciplinary research and TMS is one of the main approaches that can currently contribute to the understanding of the physiological underpinnings of functions within the intact human brain.

Most TMS research targets a single cortical site at a given time, but the use of multiple coils over different locations and specified latency times of stimulation might be able to reveal more dynamic and distributed patterns of neural processes underlying a function both temporally and spatially. For instance, Anand et al. (1998) and Pascual-Leone and Walsh (2001) stimulated two distinct sites in the visual system at different time points in close proximity in order to investigate signal propagation. The above TMS studies were able to reveal feed-forward and feed-backward projections between the striate and extra-striate cortex, demonstrating a functionally dynamical yet structurally localized approach to investigating the brain-function relationships A recent study by Harris et al. (2002) actually demonstrated that the primary sensory cortex served not only as a local conduit for on-line sensory processing, but also forms a temporary representation for information storage (memory trace) that contributes to working memory.

The maximum magnetic field strengths that current TMS machine can generate lie between 1.5 and 2.5 T. Although presently only cortical areas can be stimulated directly, machines with larger output would be able to penetrate more deeply into the brain, albeit this could make analysis more complex, since more brain areas would be concurrently influenced. Alternatively, in combination with the use of several TMS coils one might eventually employ the so-called non-invasive gamma-knife approach, originally introduced by Lars Leksell in 1967. In this procedure, multiple weak sources are used to produce a single strong focus. The gamma knife operates by a process called stereotactic radiosurgery, wherein multiple beams of radiation converge in three dimensions to focus precisely on a small volume or structure with a spatial resolution up to 0.3 mm^3. This way the focality of stimulation can be maximized to target subcortical regions of interest, especially those that have been shown to anatomically converge on specific brain areas. In such endeavors, neuro-navigation using structural MRIs (Neggers et al. 2004), and potentially fMRIs (e.g., Nahas et al. 2004), can be utilized to further enhance the anatomical precision of stimulation.

It is clear that the existing tools are not yet able to unveil *all* the mysteries surrounding the spatial and temporal representations of specific psychological functions in the brain. Nevertheless following Bechtel (2002), we would like to argue that this type of work is setting the stage for substantive progress. Neuroimaging techniques, despite their many false negatives and some false positives, have been very valuable in providing new insights regarding brain–mind inter-relations, and now these ideas have to be cashed out with causal manipulations such as those that TMS and psychopharmacological interventions provide. Fully in line with the arguments of McCauley and Bechtel (2001), we agree that the identity claims made in a research program presently serve as a heuristic method for guiding progressive thinking and future research in the field. It is premature to assert that either the brain is too complex or that we humans are not sufficiently cognitively sophisticated, to make progress on such issues. At the same time, we agree that assertions that we can solve *all* brain–mind problems with the current available set of techniques are delusional, but no more so than claims that we are incapable of making remarkable progress with the tools already at hand.

Considering for how short a time we have had such sophisticated approaches to link mind and brain issues, concluding that the brain–mind relationship remains forever inscrutable is premature, and potentially counterproductive. There are already striking examples where a problem that was once deemed inscrutable, namely the nature of affective experiences, is now in the realm of the solvable because of advances in neuroscience and evolutionary biology (Panksepp 1998; Damasio 1999). The analysis of those systems has been greatly enhanced by the fact that we share various psychobiological functions with other animals, which is now permitting the analysis of human mysteries to be undertaken at a molecular level in carefully chosen animal models (Panksepp et al. 2002). The current rise of this ‘bottom-up’ philosophy of science is also known as *new wave metascience* (Bickle 2003).

4. CONCLUSION

TMS is a valuable tool for a causal evaluation of brain–mind identity theories. It can promote explanatory pluralism with respect to our endeavors to fathom complex cognitive processes and to bridge the gap in our understanding of how localized cortical areas participate in constructing those processes. Although TMS cannot account for the explanatory gap between neurophysiological dynamics and how subjective experiences arise from such functions of the brain (Chalmers 1996), these new and innovative techniques can identify and locate certain psycho-neural entities (or at least key nodes within the greater whole) by means of true causal analyses. In this complicated realm, it might be useful to make a distinction between how causation is conceptualized by brain-scientists on the one hand and mind-scientists on the other. Since neuroscientists are primarily interested in the biological representation of function they consider direct neurophysiological manipulations, such as TMS, to be close to the proximal sources of causation. Mind-scientists on the other hand envisage more distal environmental/psychological manipulations to be ‘causal’ as well. Whereas the former allow access to biological mechanisms on which brain–mind functions supervene, the latter only permit access to distal functional issues, important as they are, with no possibility of deriving information about the neurophysiological causes, imposing a large constraint on studying brain-function mechanisms.

Regarding the neuroscientific approach, with the availability of new neurophysiological and neurochemical manipulations, we no longer have to rely simply on mere causal suppositions that can arise in abundance from correlations between structure and function derived from modern brain imaging. When supplemented with additional causal tools, the mind–brain conundrum should yield substantially to the onslaught of the modern affective, behavioral and cognitive neurosciences. Extreme skepticism about the utility of such approaches is premature. We encourage the skeptics to be patient, and to endeavor to evaluate the available technologies directly as opposed to highlighting the all too abundant difficulties merely from the sidelines. It is only by fully entertaining the combined possibilities of all the new technologies and methodologies that substantive understanding of these very difficult mind–brain issues can emerge.

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