

Integrative Neuroscience

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A fundamental impediment to an 'Integrative Neuroscience' is the sense that scientists building models at one particular scale often see that scale as the epicentre of all brain function. This fragmentation has begun to change in a very distinctive way. Multidisciplinary efforts have provided the impetus to break down the boundaries and encourage a freer exchange of information across disciplines and scales. Despite huge deficits of knowledge, sufficient facts about the brain already exist, for an *Integrative Neuroscience* to begin to lift us clear of the jungle of detail, and shed light upon the workings of the brain as a system. Integrations of brain theory can be tested using judicious paradigm designs and measurement of temporospatial activity reflected in brain imaging technologies. However, to test realistically these new hypotheses requires consistent findings of the normative variability in very large numbers of control subjects, coupled with high sensitivity and specificity of findings in psychiatric disorders. Most importantly, these findings need to be analyzed and modeled with respect to the fundamental mechanisms underlying these measures. Without this convergence of theory, databases, and methodology (including across scale physiologically realistic numerical models), the clinical utility of brain imaging technologies in psychiatry will be significantly impeded. The examples provided in this paper of integration of theory, temporospatial integration of neuroimaging technologies, and a numerical simulation of brain function, bear testimony to the ongoing conversion of an *Integrative Neuroscience* from an exemplar status into reality.

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INTRODUCTION

There is such an abundance of microscopic scale neuroscience that for many people it has come to mean neuroscience in its entirety. It is that relatively neglected part of neuroscience, the whole brain as a system, that I would like to address in this paper.

In microscopic scale neuroscience there is a close correspondence between models and data. At the whole brain scale (including its application to psychiatry), the relation between theory and data is more casual than causal, with small and disparate data sets mainly interpreted empirically and most theories drawn from the domain of psychology. Nevertheless, it is possible to begin to place the exploration of data on a firmer footing, and bring together models of the brain within and across scale.

A combinatorial explosion of mechanisms with time courses of activity that span milliseconds to years reside in every neuron. Most brain models thus far focus on this microscopic scale and specialized networks, with an emphasis on the reductionism of their myriad elements: including details of their anatomical structure, linear and nonlinear

physiological mechanisms, neurochemical receptor subtypes, and molecular processes. The complexity of this microscopic scale is daunting and has appropriately constituted the essential building blocks underpinning most of brain science. However, there are real limits on the extent to which mechanisms operating in a single neuron or specialized network can be scaled up into useful models of the whole brain, which is characterized by highly interconnected networks and by phenomena that result from the collective behavior of many interacting networks operating in parallel.

A fundamental impediment to an *Integrative Neuroscience* is the sense that scientists building models at one particular scale, often see that scale as the epicentre of all brain function (a dynamic I call 'Neural Epicentrism'). Reconciling these different scales remains the most difficult problem. This problem is exacerbated by the different degrees of abstraction: ranging from explicit biochemical and biophysical processes to concepts such as information processing, symbol manipulation and self-organization. As a result, we might appear to have in brain science a modern-day 'Tower of Babel' (Figure 1), built with a single purpose, but nevertheless doomed by jargon, misunderstandings between the various builders, as well as superficial parodies and denigrations about each other's context and content. This is indeed a pity, since not only is the common goal not reached, but researchers are often discouraged from venturing beyond their own specialty.

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"Tower of Babel" across scales and disciplines

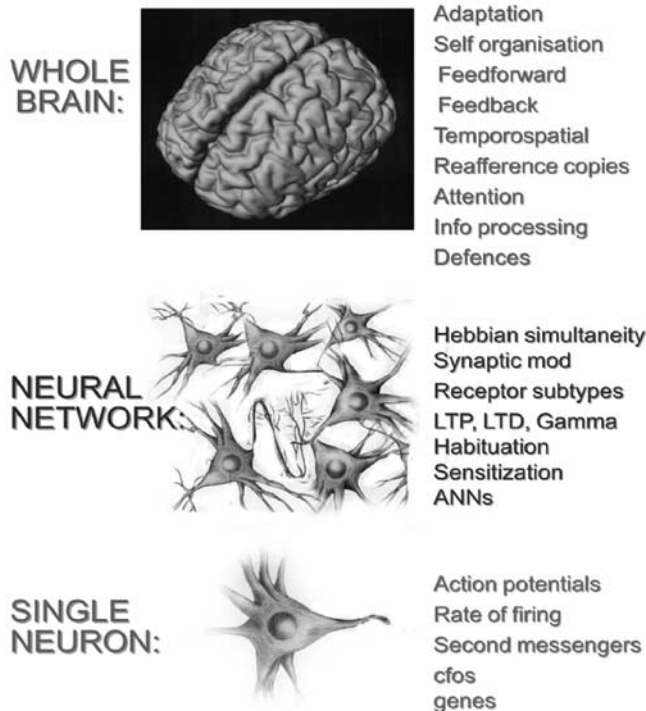


Figure 1 Different mechanisms at different scales of brain function.

This fragmentation has begun to change in a very distinctive way. Multidisciplinary efforts have provided the impetus to break down the boundaries and encourage a freer exchange of information across disciplines. *Integrative Neuroscience* (Gordon, 2000) reflects the manner in which many of the brain's processes are inter-related within and across scale, as well as across disciplines. It also explores the virtues of integrating data into quality-controlled databases.

The description of the brain is of course utterly incomplete. However, my contention underlying this optimistic integrative perspective is that sufficient facts about the brain already exist, for an *Integrative Neuroscience* to begin to lift us clear of the jungle of detail, and shed light upon the workings of the brain as a system: through integration of existing theory within disciplines and across scale, and through brain imaging data analyzed with more appropriate new analyses and models (including quantitative models) in quality-controlled databases (Figure 2).

INTEGRATION OF THEORY

A preliminary sketch of an integration of brain theory should include selected overarching organizing principles and a summary of selected mechanisms across scale. This acts as a frame of reference for elucidating the basic information flow in the whole brain, constructed from a juxtaposition of the most commonly cited whole brain biological models across disciplines.

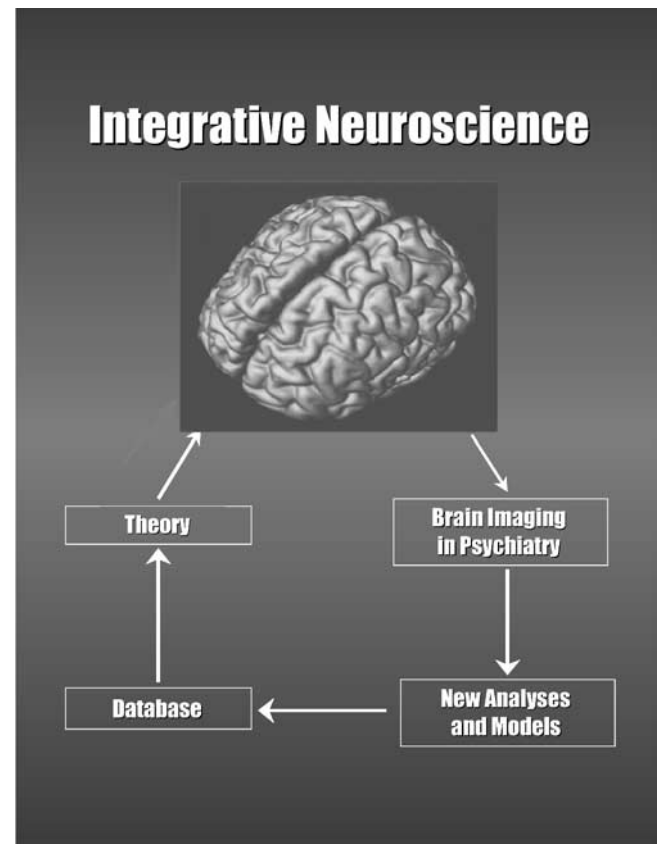


Figure 2 Core components of integration.

Such integrations provide the basis for speculations about the overall workings of the brain and specific hypotheses of dysfunction in a number of psychiatric disorders, which can be tested using judicious paradigm designs and measurement of temporo-spatial activity reflected in brain imaging technologies.

Overall Organizing Principles

An integrative perspective hints at the possibility that underlying all of the brain's functions is a relatively small number of organizing principles, including: adaptation; feedforward-feedback dynamics; localizationist-distributed continuum processing according to specific situation and task demands; different rules of function may occur at different scales.

Overall Neural Activity and Information Flow

The details of specialized sensory-motor and language (as well as lateralized network) activities have thus far formed the bulk of models at the whole brain scale. Most of these endeavors have conceived of the functions of the brain primarily in terms of many discrete structural areas that are specialized for specific purposes or modular functions. Examples of these modular functions include: hard-wired reflexes for breathing, heart rate, and digestion; detail, depth, motion, and color networks associated with vision; frequency and location networks in hearing; the basal

ganglia and cerebellum underpinning movement and the acquisition of skills; Broca, Wernicke's, and arcuate networks associated with speech; occipito-temporal networks with face recognition; hippocampus with memory; amygdala with emotion; the prefrontal cortex with motor execution and planning, and the orbitofrontal cortex with impulse control.

Over the past two decades, we have seen a paradigm shift from this narrow fixed modular conception of the brain, to one which consists of multiple modules widely distributed and interacting in parallel. Nevertheless, this paradigm shift still retains an essentially phrenological view of the brain.

A growing contention is that we are in the midst of a second paradigm shift, of conceiving the human brain as an adaptive system—where most networks are far from fixed, but are engaged according to situation and task demands. This adaptive system approach focuses on the timing of the brain's processes, which occur over a fraction of a second. It also explores the implications of the brain being such a highly interconnected system, as well as its overarching mechanisms for control—such as feedforward processing, homeostasis, and stability (rather than its specialized modules).

When we juxtapose some of the most commonly cited whole brain scale biological models across different disciplines (eg the models of Luria, 1973; Goldberg, 1990; Posner and Petersen, 1990; LeDoux, 1997, 1998; Sokolov, 1960, 1963, 1975, 1990, [1960–1990]; Gray, 1982, 1995, 1998 [1980–2000]; Damasio, 1994; Schore, 1994; Halgren and Marinkovic, 1994), a more complete picture emerges of the overall flow of information processing (carried out by the mechanisms and principles previously outlined). A discernable outline of the dynamical flow of information processing emerges from this integration of mainstream whole brain models across disciplines: Sensory-motor information is processed posteriorly to anteriorly, with core decision-making about stimulus significance occurring as matching or mismatching (of external vs internal signals) in the limbic system, with modulations by brain stem and cortical networks (Figure 3). Relatively 'automatic' subcortical survival vigilance processing is crude and rapid, whereas detailed relatively 'controlled' processing is undertaken more slowly and engages widespread subcortical and cortical networks.

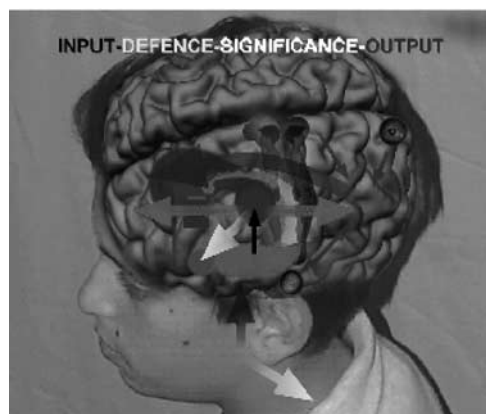


Figure 3 Overall information flow in the brain.

Currently, the field of brain imaging is testing many elements of this overall spatio-temporal pattern of information processing in health and disease. Among physiologists and cognitive scientists, there is a growing interest in testing mechanisms such as Gamma (40 Hz) phase synchrony (and the synchrony of other frequencies) as the neural coordination principles underlying information processing in the brain (as exemplified in the Bressler paper in this series). Various methods of 'connectivity analysis' are also being employed in fMRI and PET, but these reflect functional processes on a much slower time scale than gamma. Physicists are beginning to develop preliminary numerical models to explicate fundamental physiological mechanisms across scale (see the example below under Brain models). However, few approaches to analyze brain function yet incorporate the linear/nonlinear anticipatory feedforward/feedback adaptive dynamics that underpin real-time brain function in a rapidly changing environment (see Freedman's paper in this series for a key model that does address this dynamical complexity).

In an overall sense, the brain seems to operate predominantly in two modes: At the single neuron level, there are burst and tonic modes of firing, while at the neural network scale there is either synchronizing or desynchronizing activity. The balance between these modes of function determines the brain's stability. At marginal stability an optimal balance may occur between linear synchronized and nonlinear desynchronized behavior, which is known as the 'edge of chaos'. Synchronous activity may reflect aspects of consolidation. Desynchronized activity may allow increased variability and adaptability by increasing entropy. This edge of chaos may provide an effective way to process a lot of information, and retain an optimal balance between flexibility and stability. Langton (1990) suggests that the enhanced flexibility of function found at the 'edge of chaos' has been a naturally selected dimension in the evolution of the brain. Such dynamics need to be examined using new methods of analysis and current brain imaging methodology.

BRAIN IMAGING

Figure 4 provides a summary of the spatial ('where') and temporal ('when') dimensions that these technologies are

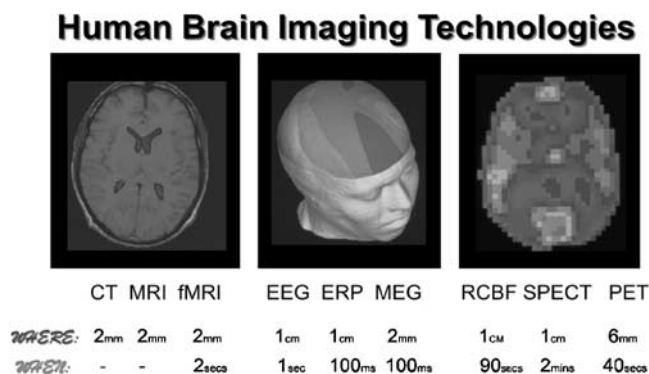


Figure 4 Spatial (where) and temporal (when) resolutions of brain imaging technologies.

able to explore in the brain. The brain imaging technologies are subdivided to make explicit their complementarity.

In spite of some significant advances, the sophistication of models and methods employed in the field of brain imaging lag behind the innovation of the technologies themselves. This field is generating large amounts of seductive color images without commensurate investigation of the functional dynamics and the mechanisms of what the measures actually mean. There is still a preponderance of 'spatial localizationist' studies rather than explication of the functional dynamics offered by EEGs and ERPs. In addition, exotic cognitive paradigms are being focused upon, rather than more robust simpler paradigms that tap the brain's core functional sensory, motor, startle, habituation, and memory processes.

Until we have consistent findings of the normative variability in large numbers of control subjects, coupled with high sensitivity and specificity indices of dysfunctions in psychiatric disorders, and these findings are analyzed and modeled with respect to the mechanisms underlying these measures, the useful application of brain imaging technologies in psychiatry will be significantly impeded.

Complementarity of Brain Imaging Technologies

While each imaging technology has sophistication and a particular strength, the measures obtained are still limited compared to the actual complexities of overall brain function. Considered together however, they provide complementary temporal and spatial indices of brain structure and function.

Multimodal brain imaging undertaken in conjunction with appropriately designed activation tasks are able to activate brain networks underlying aspects of cognition. However, standardized neuropsychological tests cannot simply be grafted into the brain imaging arena—they need to be carefully modified to be consistent with the physiological time scales of measurement provided by each brain imaging technology (also see Gur and Gur, 1991).

What is still being resolved, is the cost-benefit of which combination of technologies are appropriate for application to which neuropsychiatric disorders and under what circumstances.

NEW ANALYSES

Our limited understanding of imaged brain function may not have as much to do with what we have measured, as with the level of sophistication with which we have analyzed these complex signals. For example, traditional averaging of electrical brain function (EEG and Event-Related Potentials or ERP) has resulted in a number of associations between EEG/ERPs and aspects of information processing.

However, new mathematical, signal processing, and statistical approaches extract more fundamental information from these measures of overall brain function. I will use our group's (Brain Dynamics Centre, www.brain.dynamics.net) specific examples to demonstrate this point. We have focused on Gamma synchrony, integrating brain and body measures, and single-trial ERP analysis.

There has been increasing evidence that synchronous high-frequency oscillations are an important coding method

in the brain. The earliest evidence of this arose at the microscopic scale from studies in the cat visual cortex by Wolf Singer and other researchers in the early 1990s (Singer and Gray, 1995). However, gamma synchrony related to cognitive processing has since been observed across scales, even up to the whole brain level, and with widely separated EEG electrodes (eg between hemispheres). It seems therefore that synchrony may be an important coding mechanism across multiple scales of brain organization. The gamma 40 Hz phase candidate mechanism has been developed by Albert Haig from our group to explore this mechanism at the whole brain scale (Haig *et al*, 2000). We are now exploring phase synchrony among other brain frequencies.

My primary interest was to facilitate an integration of models and measures from the field of psychophysiology into brain imaging. As an evolutionary biologist, I was persuaded by the effect that processes such as arousal and orienting reflect core brain function survival processes, such as mismatch detection (which is crucial to keep us alive in a rapidly changing environment). To quantify these effects, we measure electrodermal arousal and orienting simultaneously during EEG, ERP and fMRI studies. Most imaging studies examine *averaged activity* across the trial, which is an appropriate first step. However, arousal and orienting vary in a systematic manner across the trial and can be separately subaveraged and assessed (providing complimentary information to the average measures). The same data that are traditionally averaged are used to derive subaverages of both ERP and fMRI, based on simultaneously measured electrodermal orienting (or not orienting) to the stimuli (Bahramali *et al*, 1997; Lee *et al*, 2001; Williams *et al*, 2000, 2001).

Single-trial ERP analysis has been undertaken by our group as follows. Albert Haig has implemented a method of globally optimal cluster analysis, classifying single trials into groups based on similarity in morphology (Haig *et al*, 1995). He then experimented with modeling ERP waveforms, in order to examine the effects of component overlap (Haig *et al*, 1997) and used conventional single-trial methods for analyzing the P3 component (Haig and Gordon, 1998). Since then, Dmitriy Melkonian (2001) has done further development of single-trial analysis techniques. His method involves modeling single-trial ERPs in the frequency domain, rather than in the time domain.

BRAIN IMAGING IN PSYCHIATRY

Across levels, there is a balanced reciprocal relation between excitation and inhibition that underlies homeostasis. Disruption of ANY of the myriad possibilities in this ongoing homeostasis (any organizing principle, mechanism at any scale or disturbance in information flow) may create a functional disconnection or asynchrony in the brain's feedforward-feedback dynamics. If the disconnection or asynchrony is severe, it may result in loss of BALANCE between overall excitatory:inhibitory activity. This could trigger a compensatory processing enhancement to attempt to re-establish balance. If the instability continued, a compensatory shutdown of function may follow (or any variant of compensatory over or under processing). The

details of the across scale distribution of the temporospatial network imbalance will determine the specific profile of symptoms seen behaviorally.

Given the combinatorial explosion of possible interactions at the microscopic scale, the current obsession with finding reductionistic microscopic scale 'magic bullets' of disturbance that are distinctive in each disorder, might benefit from concomitant explorations of possible patterns of overall disconnection or asynchrony at the whole brain scale (including longitudinal developmental and adaptive studies in the same subjects).

Since changes in brain function *antedate* symptomatology, imaging technologies will increasingly be used to identify pathology prospectively, clinically to identify subtypes and practically to assess the effects of medication on the brain as a system.

However, fundamental progress in these applications awaits a clearer understanding of what these seductive color imaging deficits in neuropsychiatry disorders actually mean with respect to mechanism.

BRAIN MODELS

Converging evidence from animal models and numerical models offer windows of explication into possible fundamental mechanisms. Numerical models capture the essence of the mass of neuroscience details, determine their possible interactions in an explicit manner, elucidate mechanisms, and compare theory with real data. In a brain with 100 billion highly interconnected neurons, only models can realistically be expected to winnow out the more significant network interactions, and infer correctly the consequences of all those interconnections.

It is best left to the excellent review by Churchland and Sejnowski (1994) in 'The Computational Brain', Walter Freeman (1995), and others to summarize microscopic scale brain models.

Whole Brain Dynamics

Our group's focus has been on whole brain models and our association with a whole brain simulation began owing to our collaboration with Jim Wright from Auckland and significant reformulation and extensions to his model by Peter Robinson *et al* (1997, 2000) and Rennie *et al* (1999) from the school of Physics at The University of Sydney. In this model, there is no attempt to reproduce the firing patterns of individual neurons. Instead it aims to model the collective behavior of large ensembles of neurons, matching the whole brain scale of EEGs. The parameters in the model are biologically realistic including: details about how neurons are interconnected over short and longer range; the rate of firing of network activity; the speed of conduction of electrical activity in the brain; the effect of various excitatory or inhibitory neurotransmitters; and modulation of overall brain stability (see Wright and Robinson papers in this series for further details of this model).

There is the potential for this numerical simulation to move beyond simply modeling the physical mechanisms of EEGs and ERPs, by adding any anatomical or neurochemical parameters. And because it is a numerical simulation

rather than a box and arrow model, any addition of neurochemical or other parameters can be assessed as to how well the numerical simulation (with their added parameters) matches real data in the database.

This particular model may ultimately turn out to be insufficient. However, it has been demonstrated that integrating key aspects of brain anatomy, physiology, and chemistry into a realistic whole brain model, is now achievable to elucidate possible fundamental mechanisms of overall brain dynamics, and dysfunction of these dynamics in psychiatric disorders.

DATABASES

Neuroimaging databases provide a frame of reference for the comparison of diverse findings in neuropsychiatry. In a recent *Nature* editorial (Chicurel, 2000) entitled 'Databasing the Brain', it was highlighted that 'progress in neuroscience might be faster if researchers shared their results in a network of databases'. With more than 50,000 neuroscientists and 300 specialist journals they outline the scale and scope of the unwieldy data sets that are being generated in neuroscience. 'Several prominent neuroscientists are now arguing that the time has come to tame this monster. They believe that progress could be boosted by creating interoperable databases, allowing researchers to share the results and make links between data from labs around the world'. However, they also highlight three significant obstacles: reaching a consensus on what is worth including in databases; the technical differences across disparate information; and the reluctance of researchers to share their data ('it's a data-hugging community' observes Michael Arbib, Director of the Brain Project at the University of Southern California).

Neuroimaging databases are rapidly being developed, but significant issues such as quality control and consistency of activation paradigms across laboratories are still to be resolved.

There will ultimately be a family of brain imaging databases worldwide. Databases such as that being undertaken under the auspices of NIMH as 'The Human Brain Project' coupled with the emerging field of 'Neuroinformatics' (Koslow and Huerta, 1997) show the potential to bring together diverse information about the brain (including across species) and comprehensively explore the variability of brain structure and function (eg see Arthur Toga's UCLA facility, which is a seminal part of The Human Brain Project at <http://news.bbc.co.uk/hi/english/sci/tech/newsid>). For an example from our 'integrative' psychophysiological database, see Figure 5.

There are hundreds of studies showing possible distinctive patterns of brain function in health and disease, but they have been undertaken in small databases (sample sizes of less than 30). It may however be myopic to continue to generate large numbers of such outcomes, without some evaluation of the relative amount of variance (r^2 or η^2) explained by the factors listed above, and the sensitivity and specificity of findings across different psychiatric disorders (all too many studies have between-group results but fail to report the amount of variance explained by the findings or details about the individual variability of findings).

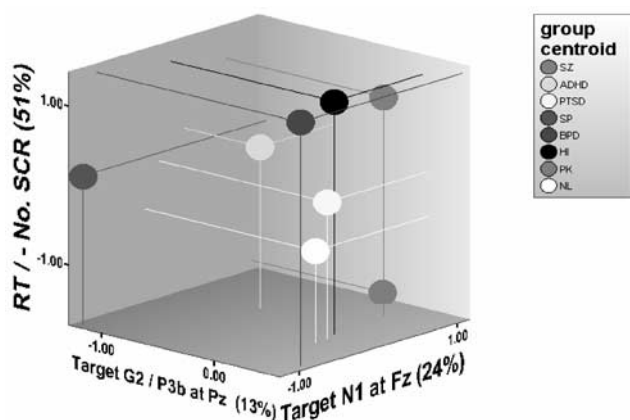


Figure 5 This figure serves to show one example of the potential for exploring multidimensional inter-relation in a standardized database across different clinical groups. This discriminant function plot shows the first three discriminant functions which best separate the groups (in a 500 subject database from the Brain Dynamics Centre (www.BrainDynamics.med.usyd.edu.au)). The groups are spaced along the discriminant functions based on their centroids. These groups (SZ, schizophrenia; ADHD, attention deficit hyperactivity disorder; PTSD, post-traumatic stress disorder; SP, social phobia; BPD, borderline personality disorder; HI, head injury; PK, Parkinson's disease; NL, normal subjects) are best separated by Performance (RT), Electrodermal orienting (SCR), Target N1 ERP at Fz and Gamma phase synchrony (G2)/P3b ERP at Pz.

Our international consortium is in the process of setting up the first total quality-controlled international neuroimaging, database (EEG, ERP, MRI, fMRI, psychometric battery genetics), on the human brain (Figure 6).

Data is acquired using identical demographics, clinical workup, brain imaging paradigms, psychological tests, and genetics. The database currently has over 1000 normal controls and will have thousands of patients with numerous psychiatric disorders. Such quality-controlled databases can then have the same analyses undertaken across different disorders and compared to age and gender-matched controls—which would allow directly testing the relative merits of competing hypotheses, the sensitivity and specificity of findings across disorders, and the relative amount of variance explained by each significant result (including the using new analyses and models described).

CONCLUSION

Now that the boundaries across disciplines have come down, there are increasing numbers of scientists across disciplines transcending their need for personal 'Neural Epicentrism' and spending the quality time that it takes to speak genuinely 'to' each other rather than 'past' each other. Such activity has begun to erode the Tower of Babel and achieve some integration of context and content about the brain as a system, and possible imbalances in psychiatric disorders.

The confluence of multidisciplinary theory, judicious use of multimodal imaging, converging evidence from animal research, realistic numerical simulations, encyclopedic and quality-controlled databases have been demonstrated to some extent by numerous groups (including our own) to be plausible.

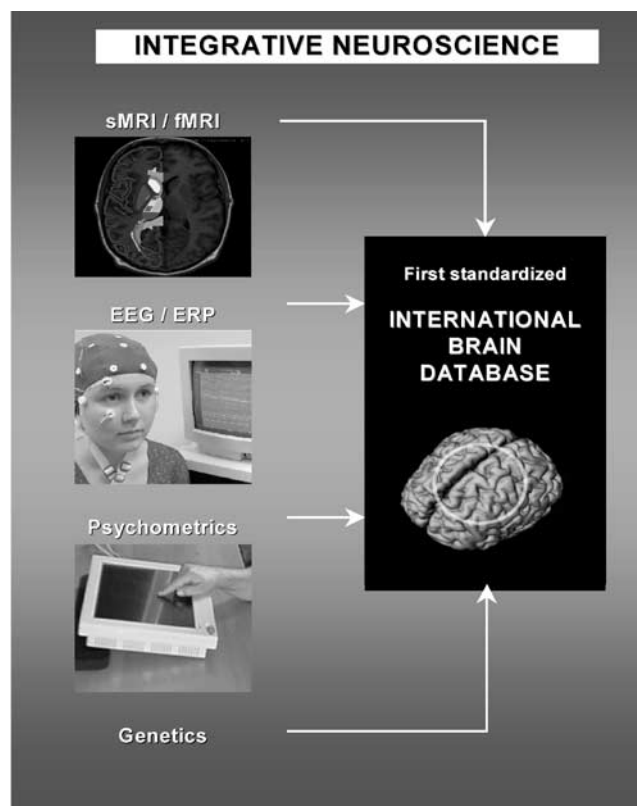


Figure 6 The first standardized international brain database (www.brainresource.com).

The genome project has been an extraordinary exemplar of integration at the microscopic scale. Growing funding targeting 'Megascience projects', the recently launched Journal of Integrative Neuroscience, and many examples around the world of university and state-based facilities for multidisciplinary neuroscience, are testimony to the ongoing conversion of an 'Integrative Neuroscience' from an exemplar status into reality.

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