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NEUROIMAGING: MANIA, REVOLUTION, OR TECHNOLOGICAL EVOLUTION? - A CRITICAL REVIEW

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NEUROIMAGING: MANIA, REVOLUTION, OR TECHNOLOGICAL EVOLUTION? - A CRITICAL REVIEW

1. Introduction

Imaging has become an increasingly important tool in both research and clinical care.

A range of neuroimaging technologies provide unprecedented sensitivity to visualisation of brain structure (i.e. anatomy) and function (i.e. physiology) from the level of individual molecules to the whole brain.

Many imaging methods are non-invasive and allow dynamic processes to be monitored over time. Imaging is enabling researchers to identify neural networks involved in cognitive processes; understand disease pathways; recognise and diagnose diseases early, when they are most effectively treated; and determine how therapies work.

The emergence and explosion of functional imaging continue to grow in sophistication and utility; but they have also incurred sceptical attitude and criticism.

2. Neuroimaging as a mania

In the short book “Neuromania”¹, neuro-psychologists Legrenzi and Umiltà provide an insightful and comprehensible overview of methods and techniques from the origins of brain science to today’s MRI (magnetic resonance imaging) scanners. However, rather than emphasizing state-of-the-art procedures and technologies, they focus on the limitations of the field, covering methodological aspects and controversial assumptions by putting brain science in a broader perspective, and discuss its socio-political-economic implications. Neuroimaging techniques (especially fMRI – functional magnetic resonance imaging) have been applied to a wide range of issues – from people’s artistic or religious experiences to their preferences for specific products or political parties. As a consequence, many established concepts in the social sciences gained the prefix “neuro-” and a profusion of new disciplines emerged (neuro-economy, neuro-aesthetics, neuro-ethic, neuro-politics, neuro-marketing, and even neuro-theology). Thus, the brain becomes the system of reference in explanations of human mind and behaviour, relegating to the background an alternative approach that emphasized the social and cultural aspects of the human mind, and forgetting that to think about such issues from a strictly biological point of view may be completely misleading.

In the authors’ words: *«Viene così legittimata la speranza che se, in futuro, si riuscisse ad analizzare in dettaglio il funzionamento di tutte le parti del corpo umano, avremo una corrispondenza biunivoca tra quanto scoperto dagli psicologi sperimentali e quanto emerge dall'esame dei meccanismi biologici elementari. Si potrebbe così frantumare la complessità della vita quotidiana dietro le sue molteplici apparenze. Essa sarebbe così riconducibile ad una realtà sottostante, di natura biologica»* [pag. 55].

Legrenzi and Umiltà are completely right in thinking that explanations of psychological phenomena seem to generate more public interest when they contain neuro-scientific

¹ Legrenzi, P., Umiltà, C. (2009), *Neuromania. Il cervello non spiega chi siamo*. Bologna, il Mulino.

information. Even irrelevant neuroscience information in an explanation of a psychological phenomenon may interfere with people's abilities to critically consider the underlying logic of this explanation.

Doubtless, neuroimaging cannot reveal directly how the mental processes work, and our brain cannot reveal who we are (as the authors quote under the title of their book *<<Il cervello non spiega chi siamo>>*), even though it must be seriously kept into consideration that alone and in combination, imaging techniques are transforming our understanding of how immune cells function, and how brain immune cells (microglia) interact with the brain in health and disease, and, on a more general level, how the brain functions. Moreover, they are offering a new opportunity to investigate a wide range of language topics, from speech comprehension, speech production, and word retrieval in healthy adult brain, to early diagnosis for dyslexia in children, from language acquisition in monolinguals, to language processing in bilinguals. Functional magnetic resonance imaging is also used to identify mirror neurons in the inferior frontal gyrus of humans, with a repetition suppression paradigm while measuring neural activity. Since mirror neurons were first discovered in the premotor area (F5) of macaque monkey, a number of neuroimaging studies have claimed that a mirror neuron system exists in humans and that homologous areas in the human brain are activated when observing and executing movements with the same purpose (Rizzolatti et al., 1996).

3. Neuroimaging applications in language studies

The cognitive neuroscience of higher order auditory processing has advanced enormously in a brief time, in large part benefiting from neuroimaging approaches. A significant amount of progress has been made, and much of it can be attributed to the possibilities for crossing boundaries afforded by neuroimaging tools.

Meltzoff and colleagues (2009) survey the variety of learning contexts that people experience, and discuss how recent advances in neuroscience and robotics are driving a new synthesis of acquisition. Neural signatures of children's early language acquisition can be documented using event-related potentials (ERPs). Children become both native-language listeners and speakers, and brain systems that link perception and action may help children achieve parity between the two systems. In adults, fMRI studies show that watching lip movements appropriate for speech activates the speech motor areas of the brain. Early formation of linked perception-production brain systems for speech has been investigated using brain imaging technology, in particular magneto-encephalography (MEG). MEG reveals nascent neural links between speech perception and production.

The adult human brain exhibits anatomical and functional specialisation for speech processing, and to understand this adult organisation, it must be clarified how it emerges in the course of development through a combination of brain maturation constraints and environmental influences. Behavioural studies in infants indicate that considerable language acquisition is already taking place in the first year of life in the domains of phonology, prosody, and word segmentation. Recordings from ERPs indicate that the temporal lobes contain neural circuits for phoneme discrimination, which become attuned to the mother language in the first year of life.

As ERPs do not provide spatially accurate information on the active brain areas, functional magnetic resonance imaging (fMRI) can be used to study the functional organisation of the infant

brain. In a study by Dehaene-Lambertz and colleagues (2002), results for infants showed that, as in adults, listening to speech activates a large subset of the temporal lobe, with a significant left-hemispheric dominance. Listening to the native language (versus a foreign language or backward speech) induces greater activation all along the left superior temporal sulcus, extending posterior into the left angular gyrus. When adults retrieve verbal information from memory, the pre-cuneus and dorsolateral prefrontal cortex are activated, while there is no evident difference in activation in the infant temporal lobe, suggesting that this area undergoes changing during infancy. Moreover, activation of both regions in 3-months infants may indicate the early engagement of active memory retrieval mechanisms.

In the debate on language and innatism, the prefrontal activation, in coordination with left lateralised temporo-parietal activation partially similar to that found in adults, goes in favour of a description of language acquisition as a progressive differentiation of a pre-constrained network of left-hemispheric regions under the influence of active mechanism of attention and effort.

A large body of neuroimaging findings supports a role for a ventral pathway in speech processing and in non-speech auditory object processing (Zatorre et al. 2004; Warren et al. 2005). A spatial processing role for the dorsal pathway has also been supported by many neuroimaging studies (Baumgart et al. 1999; Pavani et al. 2002; among others).

In a review of hundred fMRI studies on speech comprehension and production published in 2009, Cathy Price (2010) provides an integrated picture on experiments with pre-lexical, single words and sentences stimuli. A pre-lexical processing occurs prior to the semantic recognition of the auditory stimulus. It includes acoustic analysis of the frequency spectrum and the integration of auditory features over different time frames. The result is phonemic categorisation of the speech signal and the morphological parsing of word stems and inflectional affixes.

To summarise results of different studies, pre-lexical processing of auditory speech increased activation in bilateral superior temporal gyrus but left lateralised responses were observed when the noise merged into speech (versus music) or when there was a mismatch between the stimulus presented and the stimulus expected. In both these contexts, left lateralisation may be driven by top-down predictions from prior experience rather than bottom-up processing. For example, the emergence of speech over time allows the participant to predict the morphing of the stimulus; and mismatch responses have been associated with the failure of top-down processing to predict the stimulus.

In synthesis, semantic processing of familiar auditory stimuli activates a distributed set of regions that surround the ventral, anterior, and posterior borders of the perisylvian regions supporting pre-lexical auditory speech processing. The extended distribution of semantic activations suggests that there are numerous pathways supporting speech perception and comprehension.

Studies on speech comprehension report activation in four key regions: anterior and posterior parts of the left middle temporal gyrus, bilateral anterior temporal poles, left angular gyrus, and the posterior cingulate/precuneus. And when sentence comprehension becomes more difficult, activation is consistently observed in the left pars opercularis. This contrasts to the temporal and parietal regions that are more activated for sentences with plausible meanings. The most likely explanation is that activation in the pars orbitalis reflects semantic competition at the single-word level and activation in the pars opercularis reflects top-down predictions on the plausible sequence of events. Syntactic processing has been investigated by comparing sentences with and without grammatical errors; and for sentences with more versus less syntactically complex structures. In both cases, the demands on syntactic processing are confounded by the differing demands on semantics because both grammatical errors and complex sentences make it more

difficult to extract the meaning of the sentence. It is not surprising that the left pars opercularis areas that were more activated for sentences with implausible versus plausible meanings are also more activated for sentences with grammatical errors or complex structures. More generally, the overlap in the location of activation for speech production and difficult speech perception may reflect the use of the speech production system to make predictions during speech perception.

To sum up, the observation that pre-lexical and semantic processing of spoken words extends in anterior, ventral, and posterior directions suggests that the same speech inputs can follow multiple different pathways. The location of pre-lexical activation would then be determined by the task demands. For example, when an articulatory response is required, top-down expectations from motor programs may stabilise and enhance pre-lexical processing in the dorsal processing direction; but when a lexical decision is required, top-down expectations from semantic knowledge may stabilise and enhance pre-lexical activation in the ventral direction. In this way, the cortical networks supporting language comprehension are dynamically determined by the task and context.

Differences in the role of the left and right temporal lobes have been of particular interest because lesion studies indicate that it is the left rather than right temporal lobe that is needed for speech recognition and production. In this context it is surprising that the comparison of speech and closely matched non-speech stimuli result in bilateral temporal lobe activation. The specialisation and lateralisation for temporal lobe speech function may therefore be driven by non-acoustic differences between speech and non-speech stimuli. These non-acoustic differences include our significantly greater experience with speech than non-speech stimuli, the resulting categorical qualities of the perceptual representation of speech, the ability to produce as well as to perceive speech, and the influence of spatial orienting. Frontal lobe activations during speech comprehension are more consistently left lateralised than temporal lobe activations. The proposal developed by Price (2010) is that lateralisation in the temporal lobes may be driven top-down from higher level processing in frontal areas. Moreover, different parts of the frontal cortex may determine lateralisation in different temporal regions. If this hypothesis is correct, then the more damaging effect of left temporal lobe lesions compared to right temporal lobe lesions on language function might be a consequence of loss of top-down connections from anterior speech areas.

In a large scale review of functional neuroimaging studies of the neural systems that store and retrieve semantic memories, Binder and colleagues (2009) identified seven left-lateralised regions associated with amodal semantic processing: (i) inferior frontal gyrus, (ii) ventral and dorsal medial prefrontal cortex, (iii) posterior inferior parietal lobe, (iv) middle temporal gyrus, (v) fusiform, (vi) parahippocampal gyrus, and (vii) the posterior cingulate gyrus. Their contribution to speech production depends on the task and the type of semantic information that needs to be retrieved. In addition to the widely distributed set of regions associated with semantic/conceptual processing during speech production and comprehension, many other sensory-motor areas may play a role in accessing words with specific meanings: the retrieval of words belonging to visual categories activated extra-striate cortex (a secondary visual processing area), retrieval of words belonging to motor categories activated the intra-parietal sulcus and posterior middle temporal cortex; and retrieval of words belonging to somato-sensory categories activated post-central and inferior parietal regions. It has been demonstrated that lexico-semantic processing during speech production is distributed across brain regions participating in sensorimotor processing. This is argued to be a consequence of the sensorimotor experiences that occurred during word acquisition.

3.1. Neuroimaging and the brain basis of dyslexia

Functional neuroimaging studies have revealed differences in brain function and connectivity that are characteristic of dyslexia.

Difficulties in learning to read, despite reasonable effort and instruction, form the basis of dyslexia. Gabrieli (2009) presented reviews on the latest research into the causes of dyslexia.

A combination of evidence-based teaching practices and cognitive neuroscience measures may identify infants and young children at risk for dyslexia, give early notice of impending dyslexia, and early interventions may prevent dyslexia from occurring in the majority of children who would otherwise develop it. Neuroimaging has revealed, in children with dyslexia, reduced engagement of the left temporo-parietal cortex for phonological processing of print, altered white-matter connectivity, and functional plasticity associated with effective intervention. Specific patterns of atypical brain activation in dyslexia relate to the specific reading or language processes examined in a neuroimaging study. When performing tasks that demand phonological awareness for print, such as deciding whether or not letters, words, or pseudo-word letter strings rhyme, typically developing child and adult readers recruit several brain regions, including the left temporo-parietal cortex. In contrast, children and adults with dyslexia exhibit reduced or absent activation in this region. Hypo-activation of the left temporo-parietal cortex is evident when dyslexic children are compared with typically developing readers who are three years younger and reading at the same level as the dyslexic children. Therefore, left temporo-parietal hypo-activation appears to be related to the etiology of dyslexia, rather than delayed maturation of reading level. It is hypothesized that this left temporo-parietal region supports the cross-modal relation of auditory and visual processes during reading. Atypical activations in dyslexia are also found in the left prefrontal regions associated with verbal working memory, left middle and superior temporal gyrus associated with receptive language, and left occipito-temporal regions associated with visual analysis of letters and words.

Once children are diagnosed with dyslexia because of reading failure, treatments are instructional. Moreover, functional neuroimaging studies have revealed brain plasticity associated with effective intervention for dyslexia. In general, effective remediation is associated with increased activation, or normalisation, in the left temporo-parietal and frontal regions that typically show reduced or absent activation in dyslexia for phonological processing of visually presented letters, words, or sentences. Immediately after intervention, increased right-hemisphere activations are also observed, although – as Gabrieli points out - neuroimaging studies have not yet revealed what is different in the brains of children who do or do not respond to an intervention or sustain the benefits of intervention.

3.2. Neuroimaging applications in Second Language Acquisition studies

In the last decades, the use of neuroimaging techniques has opened a new window onto the neuro-functional perspective of language processing in bilinguals.

Neuroimaging studies on bilingualism have investigated both comprehension and production. The passive reading of a text will demand the recruitment of brain regions which may not be the same as those recruited when the participant is told to read the text for answering questions about it afterwards. The variability in tasks demands imposes a difficulty for grouping studies by reference to the specific linguistic aspect investigated, and consequently for drawing conclusions about this processing. Although these issues apply to studies with monolingual populations as well, the impact of these factors on the understanding of language processing by bilinguals is further challenged by the variety of language combinations and the degree of overlap between the

structural properties of these languages

Functional magnetic resonance imaging is applied in investigations on representation of multiple languages in the human brain. In a study conducted at the Department of Neurology and neuroscience at the Cornell University (Kim et al., 1997), fMRI has been applied to determine the spatial relationship between L1 (English, Korean, Spanish, German) and L2 (English, French, Japanese) in the human cortex, and showed that within the frontal lobe language-sensitive regions (Broca's area) L2s acquired in adulthood (late bilingual subjects) are spatially separated from native languages. However, when acquired during the early language acquisition stage of development (early bilingual subjects), native and second languages tend to be represented in common frontal cortical areas. In both late and early bilingual subjects, the temporal lobe language sensitive regions (Wernicke's area) also showed effectively little or no separation of activity based on the age of language acquisition.

This discovery of language-specific regions in Broca's area advanced the understanding of the cortical representation that underlies multiple language functions.

The observation that the anatomical separation of two languages in Broca's area varies with the time at which the second language was acquired, suggested to the authors that age of language acquisition may be a significant factor in determining the functional organisation of this area in human brain. Human infants, initially capable of discriminating all phonetically relevant differences, may eventually modify the perceptual acoustic space, based on early and repeated exposure to their L1.

Although these neuroimaging studies have reported different patterns of cerebral organisation for two languages in bilingual adults, a vast body of research has also suggested a convergent representation for native and second languages. The difference between the results of the reported investigation by using fMRI and PET studies in which multiple languages were found to generate overlapping regions of activation within the inferior frontal gyrus, may be reconciled in part by the higher effective resolution of fMRI technique. Findings of the above mentioned study at Cornell University, are consistent with distinct roles for the anterior and posterior language areas in the processing of human language, and raise questions regarding the role of Broca's area in processing the phonetic structures of different languages.

A study led by Dehaene (Dehaene et al. 1997) investigates the inter-subject variability in the cortical representation of language comprehension processes. Sentence comprehension in both L1 French and L2 English (acquired at school after the age of seven) by moderately fluent bilinguals was measured using fMRI techniques. They found that in all subjects a similar set of areas in the left temporal lobe was activated during listening to L1 while activations displayed inter-subject variability with decreased left-lateralisation or even complete right lateralisation during listening to L2. The results led the researchers to conclude that L1 acquisition relies on a left-hemispheric network while late L2 acquisition is not necessarily associated with a reproducible biological substrate. They suggested that the inter-subject variability in the cortical representation of L2 may be ascribed to the exact age of second language acquisition (SLA), the proficiency of subjects in L2, the typological differences between two languages, the context of SLA and the methods of teaching L2.

4. Imaging techniques in detail

Many structural and functional imaging techniques are relatively recent.

Positron Emission Tomography (PET) was the first major technology to measure physiological

functioning in the brain. It is based on the principle that changes in regional cerebral flow and metabolism in brain regions are coupled to changes in neural activity in those regions. When introduced clinically in the 1970s, PET provided a fundamentally new opportunity to explore the parts of the brain that were activated in undertaking specific tasks. More recently the main functions for PET are focused on the study of neurotransmitters (electro-chemical signals passed from one brain cell to another one to communicate), the actions of pharmaceutical drugs, and the expression of specific genes in the brain. Due to the need for the expensive cyclotron at the clinical site and the subsequent development of alternative physiological imaging techniques, PET is not used extensively to study brain areas that are activated when undertaking a specific cognitive or motor task ("task activation" studies). Anyway, PET identifies brain cell networks using a specific neurotransmitter to communicate, and also helps to see whether abnormally high or low transmitter levels are associated with specific brain conditions.

4.1. Non-invasive Structural and Physiological Imaging: the MRI Technologies

Magnetic Resonance Imaging (MRI) is based on the principle of nuclear magnetic resonance and uses radiofrequency waves to probe tissue structure and function without requiring exposure to ionizing radiation. Clinically, MRI has become the most important diagnostic imaging modality in neuroscience. One of the many benefits of MRI in the central nervous system is that the radiofrequency signals readily penetrate the skull and spinal column, allowing the tissue within it to be imaged with no interference. It provides the best visualisation of parenchymal (neurons and glial cells) abnormalities in the brain and spinal cord including tumours, demyelinating lesions, infections, vascular lesions such as stroke, developmental abnormalities, and traumatic injuries.

In addition to MRI's uses in clinical care, functional MRI (fMRI) is used to identify specific brain areas involved in activation of motor and cognitive tasks, and to detect reorganisation in the brain following injury to a localised area. The sensory, motor, and language centres have been mapped with fMRI.

Most MRI techniques use signals from water, which constitutes about two-thirds of human body weight, to develop information on brain structures and functions. It can be said that fMRI shows the brain in action, as it identifies those areas of the brain that are activated when a person undertakes a specific cognitive or motor task. It is a highly sensitive measure, as it can detect small changes, and is relatively inexpensive compared to PET. It is an indirect measure, however, because the time it takes for dynamic changes to occur in blood flow is much longer than that for neurons to fire off their electrochemical messages. Like functional imaging with PET, it is based on the general principle that changes in regional cerebral blood flow and metabolism are coupled to changes in regional neural activity involved in brain functioning, such as memorising a phrase or remembering a name. Almost all fMRI techniques use the contrast BOLD (blood oxygenation level dependent) mechanism. Functional contrast is produced only when the oxygen is released from iron and taken up by brain cells. Loss of the oxygen enables iron to become highly magnetised when exposed to the MRI magnetic field.

As an example of application, researches started in the early '90s conducted utilizing MRI scans found differences specific to dyslexia in the neuroanatomical regions involved with language processing. Additional findings in these studies indicated no differences in the cerebral hemispheric area or posterior areas in dyslexic subjects. These findings strongly implicate areas thought to be important in language processing. No differences were found in brain size, and in addition left and right volumes of the corpus callosum were symmetrical and not related to the diagnosis of a reading disability. As technology has improved, it's becoming possible to view how

the brain processes phonemes, words, and strings of words and sounds. Some studies suggested three left-hemispheric neural systems utilised for reading based on neuroimaging research. The anterior system involves the inferior frontal gyrus and is involved in articulation and word analysis. The second system involves the area of the brain in the parietal and temporal juncture and is involved in word analysis. Finally the third system is involved in the occipito-temporal region and is involved in rapid and fluent identification of words (Pugh et al., 2001; Shaywitz, 2003). The area of the brain that is involved in rapid and automatic processing of written material (occipito-temporal region) has been found to be disrupted in impaired readers (McCrary, Mechelli, Frith, & Price, 2005). This region may also be involved in the word-finding problems that children and adults with dyslexia frequently experience. Shaywitz et al. (2003) studied participants from the Connecticut Longitudinal Study from five years of age until 22.5 years of age. These participants completed annual assessments of their reading skills throughout this time period. Findings identified three groups of readers: (1) non-impaired; (2) accurate but not fluent readers, and (3) persistently poor readers. fMRI found that when asked to determine if two non-words rhymed, the accurate but not fluent readers showed disruption of the left hemispheric posterior reading systems, but not the anterior. The non-impaired readers and the poor readers showed similar activation of the posterior reading system. For the non-impaired readers activation of the posterior systems was correlated with the anterior system. However, for the poor readers activation was present in the frontal regions bilaterally indicating that the memory system was also engaged as the person attempted to read words that were not automatic and thus required additional cognitive resources. The accurate but not fluent readers were more similar to the non-impaired readers and showed similar types of connectivity of frontal and posterior reading systems in the left hemisphere.

There are several other major MRI techniques. Each technique has a highly specialised function. Diffusion-tensor MRI (DTMRI) measures microscopic water motion in any tissue, and in the brain this motion is facilitated along white matter tracts (the brain's communication cables that connect brain regions). Computerized mathematical models then construct the images of the white matter tracts. It is, therefore, used to visualise white matter tracts connecting different parts of neural networks in the brain.

Resonance Spectroscopy (MRS) focuses on magnetic resonance signals from molecules other than water; it has much poorer spatial resolution than MRI, but it has greater specificity. It can be used to identify the size and stage of specific kinds of brain tumours that are known to contain high levels of certain chemicals. This ability to track progenitor cells also may provide information on whether neuro-genesis slows in adulthood.

4.2. Electrical Recording and Ultrasound Imaging Techniques

Whereas fMRI and PET are based on the coupling of neural and blood flow activities, electrophysiological methods directly reflect brain cells' electrical activity. These non-invasive methods include electro-encephalography (EEG) and magneto-encephalography (MEG).

EEG measures the electrical activity that is produced by neurons as recorded from electrodes placed along the scalp. MEG maps brain activity by measuring magnetic fields that are generated by neural activity in the brain. It is used to investigate the basis of sensory processing and motor planning in the brain. Both EEG and MEG provide information about global as well as regional neural activity. Often combined with fMRI or PET, they both provide complementary information about normal and disturbed brain function. EEG and fMRI are used together, for instance, to localise where in the brain a seizure starts and where it spreads thereafter. MEG is used with MRI

in brain tumour patients prior to their surgery to identify the hemisphere controlling language and to precisely locate the areas involved in expressive and receptive language so that surgeons can spare these areas during surgery. Sometimes, patients who will be undergoing this pre-surgical planning will agree to participate during the MEG/MRI procedure in research designed to explore brain processes that may be involved in stuttering, or in memory.

Transcranial magnetic stimulation (TMS) is a non-invasive technique that is used to map cortical functions in the brain, such as identifying motor or speech areas. With TMS, a large electromagnetic coil is placed on the scalp, near the forehead. An electromagnet is then used to create a rapidly changing magnetic field, inducing weak electric currents. It increases plasticity and excitability of neural circuits.

4.3. Combined Imaging Technologies

New combination techniques are already advancing the threshold of applying imaging innovations to further understanding brain functions and the effects of experiences, diseases and therapies in altering these. Combining molecular imaging with anatomical and physiological imaging technologies is fundamentally advancing scientific understanding of how the brain functions and the translation of that understanding to improve human health.

5. Concluding remarks

Neuroimaging technologies give us information about the structures and functions of the brain. We can now visualise where the brain has been damaged to better understand how the anatomy of the brain correlates with deficits in thoughts, feelings, and movements.

The combination of microstructural maps with functional imaging data has not only improved the precision of localisation of the functional activations, but led to new discoveries (e. g. the subdivisions of the primary motor cortex, the Brodmann'area 4, into an anterior and posterior part, both serving different functions).

More sophisticated experiments combined with fMRI and EEG are helping to know what the brain is doing as people perform cognitive, emotional, and behavioural actions.

MEG technology will allow linguists to explore how social interaction and sensorimotor experience affects the cortical processing of language in children; and the combination of behavioural and brain measures may enhance the certainty with which dyslexia can be predicted for a child and promote the possibility of preventive intervention.

Standardised protocol fMRI allows neurosurgeons to address functional brain organisation in individual patients and neuroscientists to better understand the underlying brain mechanism in brain pathologies (Deblaere et al. 2002; Rutten et al. 2002). Studies of brain tumours using fMRI and PET have focussed on sensorimotor and language functions to reveal functional imaging as a tool to localise eloquent brain areas and indicate functional alteration in brain activation pattern.

Many studies started to investigate the functional connectivity of the language system either by exploring the anatomical connections between regions, conducting functional connectivity analyses, or by combining fMRI data with neurophysiological techniques that have high temporal resolution including MEG, ERP, and TMS. There is also increasing evidence that individual differences in activation are related to the underlying brain structure and that brain structure predicts language performance. Therefore, future investigations can be fostered by the combination of structural, functional, and behavioural data (Price, 2010). However, as the

cognitive function of any region depends on the areas that it interacts with, it may only be possible to dissociate the functions of speech regions by examining how they interact with other brain regions, and how these regional interactions are modulated by task demands.

Functional imaging has confirmed the concept that the neural system underlying semantic knowledge is distributed in the brain. Dynamic maps of conceptual and lexical-semantic representations appear to be modulated by modality of stimulus presentation (typically, words vs. pictures), category membership (e.g. objects, actions, abstract concepts) and task requirements (naming, categorising, monitoring, etc.) (Cappa 2012). Especially task requirements play a crucial role in eliciting brain activity; and this aspect may have induced a sceptical attitude towards so many experimental results. But it must be acknowledged that neuroimaging techniques have offered important evidence of brain anatomical and functional details. Therefore, we cannot consider neuroimaging as either a mania or a revolution, but as a significant technological advancement providing a new approach to understanding the neural basis of human sequential processing.

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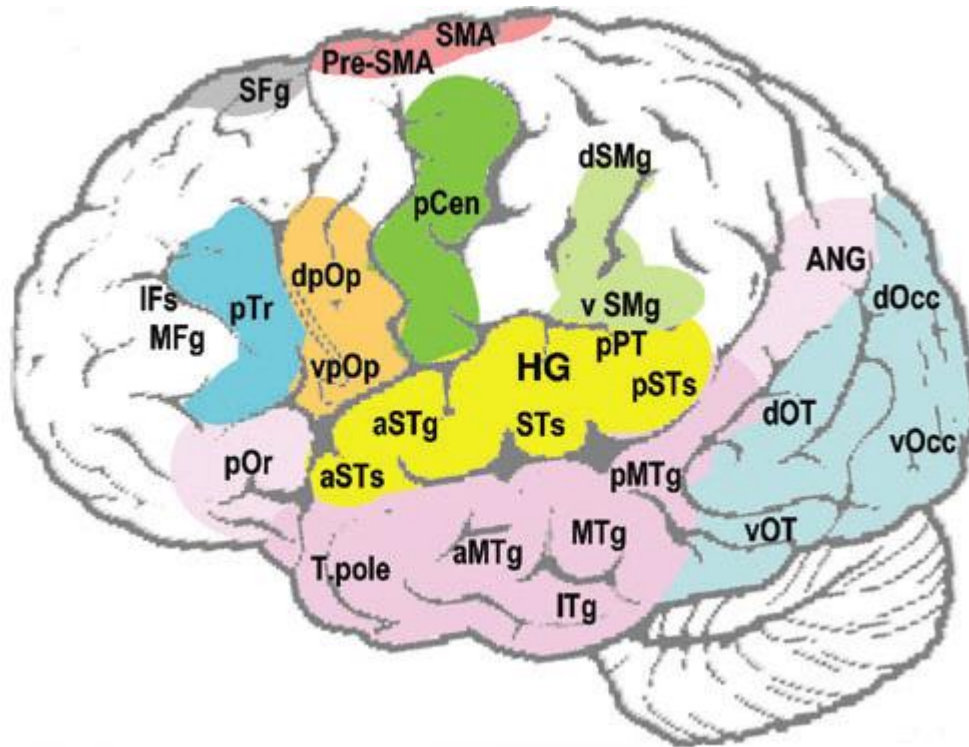
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Appendix I



vOCC/dOCC: ventral and dorsal occipital
 vOT/dOT: : ventral and dorsal occipito-temporal
 aMTg/pMTg: anterior and posterior middle temporal gyrus
 ITg: inferior temporal gyrus
 T. pole: temporal pole
 HG: Heschl's gyrus
 STg: superior temporal gyrus
 aSTs/pSTs: anterior and posterior superior temporal sulcus
 pPT: planum temporale, posterior to HG
 vSMg/dSMg: ventral and dorsal supramarginal gyrus
 ANG: angular gyrus
 pCen: precentral gyrus
 SMA: supplementary motor cortex
 SFg: superior frontal gyrus
 IFs: inferior frontal sulcus
 MFg: middle frontal gyrus
 pOr: pars orbitalis
 pTr: pars triangularis
 vpOp/dpOp: ventral and dorsal pars opercularis

Figure 1. Sketch representation of the left hemisphere (from Price, 2010).