Plasticity of the human brain - “We never use the same brain twice”

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Summary

With the advent of non-invasive neuroimaging the human brain has become accessible for in-vivo investigation of brain states offering the unique possibility to identify changing brain function and structure induced by new experiences, i.e. brain plasticity. Pioneering human studies have confirmed prior animal work highlighting plasticity as not being confined to the developmental phase but as an ongoing process throughout life. While large amounts of data have been collected on many different learning styles, peripheral deafferentiation, central lesions, and recovery after lesions, the poor specificity of imaging signals leaves crucial questions un-answered. Challenges ahead, as discussed in this review, lie in the elucidation of specific electrophysiological, molecular, cellular, and systemic mechanisms underlying brain plasticity and its modulation by genetic identities. Most fundamentally, an integrative theory / understanding of underlying principles is still lacking. Another line of (translational) research will attempt to “optimize learning” in healthy subjects as well as to improve functional recovery in patients with focal brain lesions.
I Introduction: Plasticity, a general feature of the brain

Traditionally, the concept of brain plasticity (structural and functional changes/adaptations of the brain) referred entirely to the phase of brain development, i.e. as an episode during ontogeny. With the onset of adulthood at the latest, the brain was thought to be “completed” and during adulthood, the brain was viewed as relatively stable, until “aging” initiates “degenerative” decline.

Experimental findings, however, which were obtained during the last decades, have completely revised this picture. Several long-held “dogmas” were challenged and finally discarded. First, it was shown in experimental studies in animals, that even the adult brain can undergo massive reorganization of brain structure and function. In first studies, changes in brain activation pattern were noted after abolishing peripheral inputs, e.g. due to amputation or peripheral nerve damage (for an early review see Kaas et al. 1982). Since then, it has become clear that the living brain is constantly changing its functional and structural properties depending on changing inputs and experiences (“we never use the same brain twice”). These insights founded theories and rules of plasticity (Hebbian, non Hebbian, spike time dependent plasticity etc.) that may determine plasticity-inducing neuronal / synaptic events such as long-term potentiation (LTP) or long term depression (LTD). While LTP and LTD are generally seen as “functional” events at “preexisting structures”, morphological changes encompass synaptic and axonal sprouting accompanied by the growth of new glial and vascular structures. Finally, the dogma that neurons do not reproduce themselves has been shattered by pioneering studies on neurogenesis in female canaries (Goldman and Nottebohm 1983). Subsequently, further evidences for neurogenesis were found in the adult brain of mammals and indirectly in the postmortem human brain (Eriksson et al. 1998), albeit it seems mostly restricted to hippocampal areas.

While from the above mentioned studies it can be clearly concluded that plasticity is an essential aspect of the brain in all stages of life, the necessity of invasive technologies initially prevented any studies in living human subjects. Fortunately, this situation has changed with the advent of non-invasive neuroimaging methods offering the possibility for longitudinal and interventional studies on brain plasticity.
II Neuroimaging Approaches to identify brain plasticity in human subjects

In the last decades a variety of new neuroimaging methods has been developed and several of those methods can identify "plasticity" in the human brain. Studies can be grouped into (i) structural, (ii) functional, and – still largely a perspective - (iii) molecular imaging approaches.

(i) **Structural Imaging.** Magnetic resonance imaging with T1-weighted imaging sequences has a good signal to noise ration which allows for high-resolution brain imaging (e.g. isotropic voxel at a size of 1mm$^3$) offering a remarkably good tissue contrast of grey and white matter. These prerequisites have allowed for volumetric studies and the development of "voxel based morphometry", a statistical evaluation of grey matter density across all brain voxels (Ashburner and Friston 2000).

In a landmark study, Maguire and colleagues (Maguire et al. 2000) showed that the posterior hippocampus of London taxi driver was larger than in a control group. The positive correlation between the time spent as taxi driver and the size of the posterior hippocampus suggested behavior induced brain plasticity rather than an inborn/antecedent trait. Direct evidences that such changes in grey matter volume could be induced by behavior / training came from a study by Draganski and colleagues who found increased grey matter volume in areas which are known to be related to processing and storage of complex visual motion three months after subjects had learned juggling (Draganski et al. 2004). Scholz and colleagues extended these findings showing juggling-induced reshaping” of brain architecture with additional structural alterations even in white matter suggesting a re-wiring of brain regions involved in the acquisition of the new skill (Scholz et al. 2009). Structural changes could already be observed after few months which suggest that functional and structural plasticity are not strictly separated and sequentially organized processes, but may go hand in hand in many instances such as learning complex sensorimotor skills which are required for juggling.

Furthermore, structural imaging can be used to visualize morphological alterations occurring in reaction to focal brain lesions, e.g., stroke and many other diseases with an impact on the brain, but also during recovery with and without associated rehabilitation strategies.

(ii) **Functional imaging.** Analogously to invasive animal studies in which changes in cortical maps had been demonstrated after peripheral deafferentation, changes of cortical maps in humans have been non-invasively observed with different methods that can be utilized to assess brain function. Mapping of altered maps within the motor cortex were achieved with transcranial magnetic stimulation (e.g.,
Ziemann et al. 1998). This non-invasive brain stimulation is used to modulate brain states or to induce virtual lesions in cortical targets (not only motor cortex) with subsequent impact on behavior and cortical outputs.

After limb amputation, reorganization of cortical maps was identified with magnetoencephalography which allows the non-invasive assessment of (mostly) superficial cortical activity (Flor et al. 1995). The degree of reorganization covaried with pain severity which suggests that ongoing pain initiates and maintains brain plasticity which in turn may represent one of many crucial sources that support the development of chronic pain syndromes such as phantom limb pain. Whether pain-induced brain plasticity is source or cause of chronic pain syndromes is still under ongoing debate (i.e., the chicken or egg problem).

In further studies using fMRI (i.e., a method that allows the investigation of hemodynamic or neural responses) and EEG (i.e., superficial neuronal recordings), it was confirmed that changes in cortical patterns did not only occur after peripheral lesions, but also accompanied procedural learning (Pleger et al. 2001, 2003). The modulation of such learning procedures using pharmacological agents allows inference on the underpinning receptors and mediators (Dinse et al. 2003).

Brain plasticity as indicated by altered patterns of functional activation was also found after central (focal) lesions, especially after stroke. Pioneering studies utilized radioactive receptor tracers which are applied intravenously and which invade brain regions containing high density of the traced receptor. The accumulation and emission of radioactivity in specific brain regions can then be visualized with positron emission tomography (Chollet et al. 1983, Weiller et al. 1983). In follow-up studies, a more systematic assessment of the time course of lesion-induced brain plasticity indicated that the acute phase of stroke is accompanied by a general reduction of brain activation in the affected territories, followed by a period of enhanced network activity which – in case of good recovery – is followed by a relative normalization (Saur et al. 2006).

An innovative variant of fMRI is functional connectivity resting state fMRI (fc-fMRI). No task / stimulation is required, but rather the cross correlation of voxels across the brain in a low frequency domain (<0.1 Hz) is used as a measure of functional connectivity (fc-fMRI) (Biswal et al. 1995, Fox and Raichle 2007). Recently, fc-fMRI has proofed its sensitivity to assess changes in functional architecture of the brain after limb amputation (Pawela et al. 2009) which suggests its general suitability for the investigation of brain plasticity.
(iii) Molecular Imaging

While so far, the potential of molecular imaging has by far not being exploited in the setting of brain plasticity, it is mentioned here as an important pillar for the future. Positron Emission Tomography (PET) is quite flexible since it uses exogenous tracers (see also (ii)). Studies on dopamine receptor density, serotonin transporters, nicotinergic neurotransmission hold great promise to bridge findings obtained with the less specific approaches of functional and structural magnetic resonance imaging to the molecular level. Studies on brain plasticity using the PET tracer tryptophane showed that increased serotonin synthesis occurs in the striatum after cortical resection of an epileptogenic focus in children. In subjects with various forms of addiction, a decrease in striatal D2-receptor density was shown suggesting an impaired feedback to reward. Given the feasibility of human studies, the potential of direct integration with MRI, and the continuous development of new and more-specific tracers, the role of PET-based molecular imaging will tend to increase significantly in the future providing a link between the “unspecific” MRI signal and underlying molecular events.

Preliminary conclusion. Where do we stand?

The overall assessment of the current state of plasticity research comes to an ambivalent conclusion: On the one hand, a plenitude of methods has been applied to assess “human plasticity” in many different settings including learning in healthy subjects, rehabilitation in patients with brain disorders, and during interventions in healthy subjects and patients. However, conceptualization and theory building (“understanding”) has not kept pace with the accumulation of this large amount of data (similarly to the whole field of neuroscience). Subsequently, the main shortcomings / challenges are listed and approaches to overcome them are suggested:

III Challenges:

(i) From unspecific “brain signals” to “physiology empowered brain imaging”. Non invasive brain imaging typically relies on imaging signals, e.g. in MRI which are very poorly defined in terms of underlying anatomy / physiology. For example, fMRI is based on vascular signals such as cerebral blood flow (CBF), cerebral blood volume (CBV) or (in by far most studies) the Blood Oxygenation Level Dependent (BOLD) contrast. While it is known that BOLD contrast roughly corresponds to changes in
local content of deoxygenated hemoglobin (which is paramagnetic in contrast to oxygenated hemoglobin), it is far less clear what such changes mean in terms of underlying neurophysiological events. Extensive studies conclude that changes in BOLD signal (or cerebral blood flow) “best correlate” with local field potentials (Logothetis et al. 2001, Mathiesen et al. 1998) as opposed to spiking activity itself. However, we are far away from solving this “inverse problem of fMRI” also because the temporal resolution of fMRI (in the order of seconds) is about three orders of magnitudes away from the time scale of neuronal events (milliseconds). In animal studies, the problem can be partially overcome by incorporating invasive electrophysiology into the measurement apparatus (Logothetis et al. 2001), which, of course is not a viable solution for human studies.

How then to measure brain activity on a time scale of neuronal activity and assess specific neurophysiological events as spiking activity, synchronized activity, etc. in human subjects? One way to tackle this problem in humans is to combine non-invasive electrophysiological methods (i.e., EEG) with non-invasive fMRI for simultaneous measures of neuronal and neural brain responses. EEG has a good temporal resolution which can match the one of neuronal activity (ms). Joint EEG / fMRI studies (Lemieux et al. 1997, Bonmassar et al. 1999, Thees et al. 2002) can thus take advantage of both, the good spatial resolution of fMRI and the good temporal resolution of EEG e.g. comparing evoked activity on single trial level (Debener et al. 2005). Furthermore, EEG allows for assessment of synchronized neuronal activity (EEG rhythms) including background rhythms (Alpha, Beta) and Gamma rhythms. While not measuring at a single neuron level, it assesses networks which are reflecting synchronization at a neuronal level. As predicted from animal work (Niessing et al. 2005), different rhythms are differently reflected in BOLD signal changes and thus, simultaneous EEG/fMRI can be used to localize the distributed brain areas involved in these synchronized neuronal events: Simultaneous EEG / fMRI recordings have allowed to localize areas involved in occipital alpha background rhythms (Goldman et al. 2002, Laufs et al. 2003, Moosmann et al. 2003), sensorimotor alpha and beta background rhythm (Ritter et al. 2009), and Gamma rhythm (Mantini et al. 2007). Interestingly, there are also ultra high frequency EEG rhythms (600 Hz) occurring during somatosensory stimulation (Curio et al. 1994, Hashimoto et al. 1996) which reflect bursts of neuronal spiking activity (Baker et al. 2003). In a joint EEG/fMRI study, it has recently been shown that this measure of actions potentials can be incorporated into fMRI and the observed spiking activity can be related to changes in BOLD signal close to the presumable generator structures in thalamus and primary somatosensory cortex (Ritter et al. 2008).

(ii) From single brain sites towards small-world brain networks. The old dichotomy of localized versus holistic organization of brain function seems to resolve in an approach that attributes cognitive
functions to distributed networks of mutually interconnected brain areas. Within these networks, certain brain areas fulfill specialized subtasks. Thus brain mapping, i.e. allocating certain functions to single brain areas, still is meaningful but older nomenclatures for parcellating the brain into single functional areas should be revised in order to (i) take into account the role of an area within the entire “connectome” of brain areas, and (ii) to identify areas in the individual subject not relying on gyral landmarks or cytoarchitectonict maps of reference brains. Both points become particularly relevant in macroscopic studies on related structural and functional plasticity.

At least two approaches exist (measures of functional connectivity or resting state fMRI and measures of structural connectivity, i.e. diffusion tensor imaging), which seem to meet the above mentioned requirements. Both approaches have recently identified a small world network structure as a major organizational principle of the brain (Buckner et al. 2009, Hagman et al. 2008). Another line of research has developed new methods for both approaches allowing for parcellating brain areas based on connectivity assessment in functional-anatomic units (Cohen et al. 2008, Draganski et al. 2008). While in the future several different network measures may be used in parallel, we believe that connectivity based brain parcellation represents the most promising approach with crucial relevance for studies on brain plasticity.

(iii) Linking human plasticity to molecular events. In invasive animal studies, plasticity can be traced to cellular and molecular processes. In order to relate human findings to such “molecular” insights from animal studies, it will be important to relate human neuroimaging findings to the underlying molecular level. However, the poor specificity of macroscopic imaging signals largely precludes molecular information. An increasing number of approaches, however, exists that could fill this gap. Such approaches are based either on radioactive tracer (PET), fluorescent tracers (optical imaging), and MRI contrast agents. Of these methods, PET is already successfully employed in humans, however, there is still a conspicuous lack of prospective studies on brain plasticity. The integration of PET into MRI measurements (PET/MRI) with simultaneous recordings of radioactive and hemodynamic brain responses opens new and promising prospects for the future (Judienhofer et al. 2008).

Fluorescence is a widely used tracing technology, for brain imaging. Its limitation lies in the poor depth penetration of light into the brain. Using near-infrared imaging, it has been shown that fluorescence can be detected in human subjects non-invasively through the intact skull (Liebert et al. 2006), thus,
applications which look into events on the brain cortex seem feasible in the future (Steinbrink et al. 2008).

For MRI, several molecular contrast agents are being developed, however, their sensitivity has been too low so far to be applied in human subjects.

(iv) Linking human plasticity and genetics. The nature / nurture debate obviously has one of its most virulent applications in the field of human behavior and brain function. With the possibility of whole genome analysis at hand, combined with behavioral / cognitive testing and neuroimaging, it now becomes possible for the first time to differentiate inborn versus environmental factors and to identify interactions between the two. Open questions remain about the optimal setting to perform such genotype/phenotype studies. On the one hand large scale cohort studies are under way at specific locations (e.g. the Leipzig LIFE study comprising about 15,000 subjects) or in multicentre settings (e.g., the planned German cohort study on 200,000 subjects), on the other hand some researchers focus on smaller scale, hypothesis driven studies with more in depth genetic analysis (sequencing, epigenetics). Probably, these approaches will be complementary, the respective value yet to be determined. In any event, the enormous additional data which arises from simultaneous genetics and neuroimaging will require entirely new kinds of statistical approaches.

(v) Human Settings: ‘Internal’ (Aging and diseases) and ‘External’ (Social Setting etc.). There are various crucial determinators of plasticity which by themselves constitute huge research fields. The general notion “plasticity being always present in the living brain” does not preclude aging as a crucial factor determining plasticity (see review by Ulman Lindenberger) since certain genetic factors seem to express themselves preferentially at certain age ranges. The same accounts for brain disorders of various kinds, such as degenerative disorders (Alzheimer disease, Parkinson’s disease etc.), vascular events (stroke), or inflammatory processes (Multiple Sclerosis). The issues of ‘aging’ and ‘disorders’ are most likely highly interrelated since hallmarks of “diseases” are present in “normal” brains also (e.g. Alzheimer plaques).

In addition to these personal / individual aspects, the social setting of the respective individual is also of extremely high relevance for brain plasticity. The area of social neuroscience which links social sciences
with brain science is a rapidly evolving field and analogously to other cognitive functions of the brain, the plasticity aspect of the “social brain” is becoming an important aspect of it.

(vi) **Translation to learning and clinical rehabilitation.** Previous attempts to optimize learning in healthy subjects and recovery after brain lesions relied on the traditional approach of optimizing cognitive / behavioral strategies by their outcome which of course is “perfectly fine”. However, new approaches rely on a better understanding of brain processes in healthy humans, e.g., by using drugs known to enhance reward feedback or neuronal sprouting, by stratifying subjects / patients according to their genotype or using brain computer interfaces coupled with biofeedback. These approaches allow optimization of “surrogate” parameters of learning or rehabilitation. Another exciting approach consists of external or internal electrical / magnetic stimulation devices which have been shown to change excitability of specified brain areas and thus to improve learning / recovery strategies.

Most likely, optimal strategies in future will combine several of the above mentioned approaches and most importantly will have to be tailored to individual condition (genetics, age, competencies etc.).

(vii) **Conceptualizing / Brain Theory.** As mentioned earlier, in the field of brain research and its subarea brain plasticity, research is still mostly about accumulation of data / facts, and very little about conceptualization. Computational models of brain activity and plasticity may fill this gap. Of course, such modeling has to be performed in close interaction with empirical research in order to allow the ping-pong of testing theories, modifying, re-testing and so forth.

**Brain Plasticity at Max Planck Society**

Work on brain plasticity is being performed at several Max Planck Institutes, in the GSHS (Berlin: Human Development, Leipzig: Human Brain and Cognitive Sciences, Nijmegen: Psycholinguistics) and BMS (Tübingen: Biological Cybernetics, Munich: Psychiatry, Neurobiology, Cologne: Neurology, and Frankfurt, Brain Research).
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