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Review

# In vivo assessment of use-dependent brain plasticity—Beyond the "one trick pony" imaging strategy

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ABSTRACT

This article has been written as a comment to Dr Thomas and Dr Baker's article "Teaching an adult brain new tricks: A critical review of evidence for training-dependent structural plasticity in humans". We deliberately expand on the key question about the biological substrates underlying use-dependent brain plasticity rather than reiterating the authors' main points of criticism already addressed in more general way by previous publications in the field. The focus here is on the following main issues: i) controversial brain plasticity findings in voxel-based morphometry studies are partially due to the strong dependency of the widely used T1-weighted imaging protocol on varying magnetic resonance contrast contributions; ii) novel concepts in statistical analysis allow one to directly infer topological specificity of structural brain changes associated with plasticity. We conclude that iii) voxel-based quantification of relaxometry derived parameter maps could provide a new perspective on use-dependent plasticity by characterisation of brain tissue property changes beyond the estimation of volume and cortical thickness changes. In the relevant sections we respond to the concerns raised by Dr Thomas and Dr Baker from the perspective of the proposed data acquisition and analysis strategy.



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In their article "Teaching an adult brain new tricks: A critical review of evidence for training-dependent structural plasticity in humans" Dr Thomas and Dr Baker emphasise the importance of two key issues in brain plasticity studies using magnetic resonance (MR) imaging: first—the question about reliability of evidence for use-dependent changes and second—the biological substrates of MR measures. Aiming at constructive scientific dialogue we expand on the second key point concerning the main biological contributors to MR

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contrast, which was only sketchily covered by the critical review. We also consider the fact that the major points of Dr Thomas and Dr Baker's criticism come as no surprise to researchers in the field of neuroimaging accustomed to factorial design and were already brought to the readership's attention in previous studies (Kriegeskorte et al., 2009; Nieuwenhuis et al., 2011). Further, we propose a complementary approach for data acquisition and analysis based on quantitative assessment of brain tissue properties, which is particularly advantageous for longitudinal study design with multiple scan time points. This strategy has also the potential to provide more straightforward interpretation of plasticity associated structural findings by decomposing the MR contrast to its main contributors—myelin, iron and water protons bound to macromolecules.

## Brain plasticity and neurobiological mechanisms

Brain plasticity is defined as the intrinsic lifelong capacity of the mature mammalian brain for reactive change in behavioural flexibility and is driven mainly by a mismatch between functional supply and environmental demand (Lovden et al., 2010). Intensive research on animal models in the last decades helped to understand basic neurobiological mechanisms, which underlie the reorganisation of the brain. According to rodent studies, the morphological substrate of use-dependent brain plasticity is characterised by dendritic growth and synaptic rewiring modulated by the presence of structural and functional "brakes" limiting morphological changes (Holtmaat and Svoboda, 2009; Pizzorusso et al., 2002). At a coarser scale, changes in de-/remyelination rate (Ullen, 2009), in regional co-localisation of iron and myelin (Fukunaga et al., 2010) or alterations affecting the myelin containing perineuronal nets (Pizzorusso et al., 2006) are among the factors with major impact on brain tissue properties. The direct link between plasticity associated (sub)cellular changes and the main contributors of MR contrast—myelin, iron and water protons, motivates the use of tissue property sensitive MR imaging techniques to study use-dependent brain plasticity.

## Brain plasticity and grey matter changes

A steadily growing number of voxel-based morphometry (VBM) studies based on anatomical MR imaging and longitudinal study design demonstrate training-induced brain structure changes in humans (for a recent review on the topic please see Zatorre et al., 2012). However, VBM studies published to date failed to provide further insight into the underlying neurobiological processes. Main reason for this is the fact that the current state-of-the-art imaging assessment of brain anatomy relies mostly on relative changes in grey matter volume, density and cortical thickness derived from T1-weighted (T1w) data. T1w imaging is a non-quantitative MR technique, influenced by various contributions to MR contrast—myelin, iron, and water protons bound to macromolecules (Tofts, 2003). Systematic differences due to training and learning could influence each one of these components in a different way, which will be mirrored in differential success of VBM detecting the correlates of one or another behavioural intervention. Additionally, radio-frequency transmit field inhomogeneities (i.e. B1 field) will inevitably lead to inter-scanner variability (Weiskopf et al., 2011), thus explaining difficulties reproducing previous results across study sites. Differential temporal trajectories of training-induced changes depending on the paradigm used and the time span between data acquisition time points can further contribute to these controversies.

With the aim to differentiate the impact of use-dependent tissue property changes on MR contrast from "true" volume/density or cortical thickness changes researchers can make use of an established quantitative brain imaging approach (Helms et al., 2008). It includes whole-brain multi-parameter mapping at high resolution (Fig. 1), correction for radio frequency transmit inhomogeneities using B1 mapping, and automated voxel-based quantification—VBQ. Using VBQ we demonstrated parameter-specific distribution patterns in healthy ageing and suggested a biophysical interpretation, which corroborates with histological studies showing age-dependent iron accumulation and rate of de-/remyelination (Draganski et al., 2011). The majority of quantitative mapping studies, particularly the few recent explorative studies in neurodegenerative disorders, were restricted to one or two parameters within predefined 'regions-of-interest' (ROI) (Cherubini et al., 2009a, 2009b; Peran et al., 2009). However, ROI analysis is insensitive to changes in all parts of the brain and provides inadequate adjustment for the confounding effects of macro-anatomical volume changes on parameter statistics.

Considering the fact that the removal of myelinated perineuronal nets is a permissive step for structural brain plasticity (Pizzorusso et al., 2006) and that training could potentially increase the rate of remyelination resulting in augmentation of intracortical myelin content, the directionality of myelin changes cannot be predicted. However, assessment of the myelin co-localised iron changes, measured with the effective transverse relaxation rate $R2^*$ could offer a potential solution. This is due to the fact that iron and myelin both increase $R2^*$, whereas they have opposing effects on the resonance frequency—paramagnetic vs. diamagnetic shift (Fukunaga et al., 2010).

## Brain plasticity and white matter changes

According to the predominant opinion in the field of computational anatomy, VBM results derived from T1w images are not informative for white matter volume changes due to low regional specificity. Diffusion-weighted imaging offers a direct way for investigation of use-dependent white matter microstructure changes by inferring directionality and magnitude of water diffusion (i.e. fractional

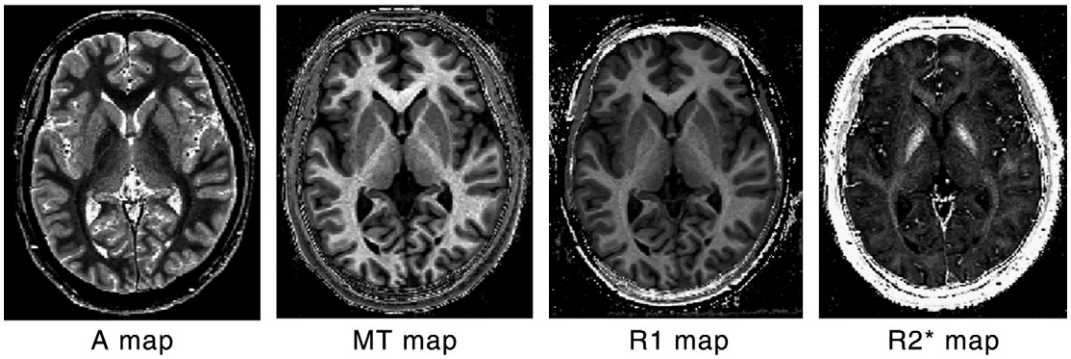


**Fig. 1.** Example of parameter maps—signal amplitude (A) proton-density map, magnetization transfer saturation (MT), longitudinal relaxation rate ($R1 = 1/T1$) and effective transverse relaxation rate ($R2^* = 1/T2^*$) reflecting water content, myelination and iron concentration.

anisotropy and mean diffusivity) (Pierpaoli and Basser, 1996). Identically to VBM, cross-sectional voxel-based studies of fractional anisotropy differences between groups of experts and non-experts in a particular domain (Bengtsson et al., 2005) were followed by longitudinal investigation of use-dependent brain plasticity (Sagi et al., 2012; Scholz et al., 2009; Taubert et al., 2010). Methodological limitations of the voxel-based analysis methods on diffusion parameter data are the neglected impact of linear and non-linear interpolation on the parameter values during spatial transformation, followed by the lack of reference to the underlying anatomical properties in the case of crossing or "kissing" fibres. Importantly, there are recent attempts to correlate in vivo obtained diffusion-tensor derived indices with histology results (Concha et al., 2010) and resolve interpretational issues (Douaud et al., 2011).

## Proof of principle—histology correlation

We fully agree with Dr Thomas and Dr Baker's impetus to carry out proof of principle studies aiming at correlation between imaging findings and histology. The proposed concept of looking for brain plasticity correlates at the microscopic level in animals has its limitations—results from animal models cannot easily be extrapolated to humans due to the fact that many cognitive processes cannot be studied in animals. Even more, the applied histology techniques in animal research bring practical hurdles due to the fact that one can investigate only a limited volume of the brain, which is further hampered by limitations of existing strategies for adjusting the effects of linear and non-linear spatial registration on parameter data of histological specimen. Thanks to ultra-high field MR scanners we may achieve spatial resolution scales required for a direct comparison between histology and MR imaging data, however, we still lack an integrative theoretical framework allowing for unbiased feature selection and statistical analysis of multi-modal data. In our opinion, MR imaging based on defined biophysical models provides a feasible in vivo alternative in humans where indirect comparison between brain tissue properties can easily overcome the major scaling problems.

## Statistical considerations

Dr Thomas and Dr Baker critically address the analytical methods used in previous studies for assessment of use-dependent brain structure changes. The authors' concerns about statistical issues (e.g. group-treatment interaction effects, independent data orthogonal contrasts) are pertinent to the neuroimaging field in general, but not always relevant to the topic of brain plasticity and often stemming from misinterpretation of the currently applied methods. We provide here some comments to the problematic issues raised by the authors.

### *Limitations in spatial pre-processing*

Dr Thomas and Dr Baker's concerns about limitations in spatial pre-processing are valid to neuroimaging studies in general and they are certainly not limited to VBM studies of brain plasticity. It is clear that one should be aware of these limitations but it is also evident that spatial registration procedures are getting more sophisticated and accurate (Klein et al., 2009).

### *Limitations of spatial resolution*

Dr Thomas and Dr Baker's wrote "Finally, we note that the effect size reported in some human studies is very small relative to the size of the voxels" and further "Given that such effect sizes are many times smaller than the sampling frequency of the method, these results need to be carefully evaluated and interpreted with caution." These statements suggest that the authors are conflating the notion of "spatial resolution" and "spatial precision". Spatial resolution is the intrinsic image resolution unit combined with the additional smoothing applied to the data. Importantly, the "spatial precision" can be much higher and will represent the accuracy of locating the peaks of statistical maps (Price and Friston, 2005). A typical and extreme example is given by Mintun et al. who demonstrate that even for PET data with 18 mm in-plane resolution, the "spatial precision" is below 2 $mm^3$ (Mintun et al., 1989).

### *Interaction effects and the usage of set of independent data*

Dr Thomas and Dr Baker advocate the usage of an independent data set for testing the interaction effects. They wrote: "… any test of anatomical specificity needs to avoid the statistical bias introduced by pre-selecting voxels for a specific effect and then testing the anatomical specificity using the same data" followed by the statement that "this could be achieved by performing a split-half analysis, splitting the data over subjects". In our opinion, the suggested analysis is redundant due to the fact that in an ANOVA design the main effects and interaction effects are completely orthogonal. It is therefore sufficient and legitimate to select a region based on the main effect for further testing the interaction model. Splitting the data in half will only result in a loss of power for detecting the effects of interest.

### *Interpretation of interaction with behaviour*

Dr Thomas and Dr Baker express concerns regarding the interpretation of main effects and the effect of a covariate when they write "Finally, it is unclear how to interpret differences in regions that show a significant effect of training on structural measures and those that show a correlation between behavior and structural changes." In statistical terms, it seems to us that the authors are referring to an ANCOVA design where an additional covariate is added to the design. The interpretation is usually straightforward and the different regressors are interpreted in terms of intercept and slope with the only caveat when the effect of the covariate is significantly different between groups. In this case the interpretation of the intercept is also modified because the between-group difference is conditional on the value of the covariate.

In general, the main problems of interpretation brought by Dr Thomas and Dr Baker are simplified if one thinks in terms of model building, which is also a fruitful framework to address the causality underlying structural brain plasticity. The statistical inferences on use-dependent brain structure changes require beyond data characterisation and specification of statistical model most importantly the definition of the (neurobiological) question of interest. There are two types of questions that the researcher wants to address—the first is about *estimation* of the temporal dynamics of training/learning associated plasticity and the second addresses the strategy for optimum *detection* of changes. The within-subject assessment of longitudinally acquired multiple data points provides a powerful method to address the first question relative to the estimation of temporal trajectory whereas between-group comparisons are optimal for the detection of changes. Critically, for both design types and for better handling of the noise and model fit, we need an established biophysical model of how the MR data is generated.

$$Y_t = g(X_t) + e \quad (1)$$

### *Generative models*

In *within-subject* designs the time dependent observation at hand ($Y_1$—e.g. T1w MR contrast) is a transformed version of a realisation (X) due to an unknown latent process. The link function (forward model) between the observation and the underlying process is very likely to be complex and non-linear. Because of this complexity it

cannot be understood using simple correlation measures between MRI contrast measures and characteristics derived from histology studies. On the contrary, the use of multi-parameter data allows for developing a generative model of the observed signal and accurate approximation of the link function. For example in Eq. (1), $g(X_t)$ can be approximated, in first instance, by a linear combination of multi-parameter data (A, MT, R1 and R2* maps). An even more fruitful approach is the computation of an inverse model that combines data with prior information from MR physics and neurobiology—i.e. biophysical model underlying the multi-parameter approach.

*Predictive model of individual differences*

In *between-group* designs, which use a pre-test/post-test design that compares baseline ($Y_0$) and follow-up measures ($Y_1$) are well appropriate for making inferences about training/learning effects. This type of analysis is simple and easy to perform and does not require knowledge of the link function assuming that it is the same for both groups. However, there are multiple ways to analyse data, which sometimes can lead to contradictory results (Huck and McLean, 1975). The statistical analysis can take the form of a simple analysis of variance (ANOVA) on the differences between pre-test and post-test ($Y_1 - Y_0$) or a similarly repeated measures ANOVA testing group-by-time interaction. Nevertheless, this analysis is often inappropriate if there are individual differences at baseline (i.e. post-test value depends on pre-test measure), one alternative approach then is an ANCOVA model that includes pre-test measures as covariates in the analysis. More generally, predictive models of individual differences in performance provide more sensitive design by removing/explaining between subjects source of variance.

*Causal pathways*

Mass-univariate statistical analyses are not suited to address Dr Thomas and Dr Baker's plea for a necessity to assess the regional specificity of training-induced anatomical findings. This idea is better understood if models are recast in two analytical approaches based on fundamentally different basic principles—*segregation* and *integration*.

In the first, longitudinal neuroimaging data is explored in a classical mass-univariate and multivariate way looking across the whole-brain for regional changes or even distributed effects correlating with the measures of behaviour over time. From a *segregation* perspective the findings within a region showing significant effects will be more informative when using multi-parameter data. However, the analysis of multi-parameter images in a comprehensive manner is challenging because of the high-dimensional, multivariate and multi-modal nature of the data. Each component of the multi-parameter data (A, MT, R1 and R2* maps) can be analysed separately using univariate methods, allowing tests of specific hypotheses regarding the contribution of each parameter. Univariate models, based on the general-linear-model framework can be extended to a combined mass-multivariate approach where each voxel is considered as a multi-dimensional vector and tested with multivariate tests. Practically, this implies fitting a multivariate model at each position in the brain, using tools such as multivariate regression or MAN(C)OVA (Kherif et al., 2002). When using multivariate models several modalities are considered simultaneously, decreasing considerably the number of tests that need to be performed. In addition, local multivariate statistical tests are generally more powerful than their univariate counterpart (e.g. reduction of type 2 error).

With the *integration* approach the aim is to assess the interregional dependencies and causal pathways in defined circuits making use of generative models (similar to dynamic causal modelling for fMRI/EEG). The integration strategy will allow deciphering how behavioural changes result from the temporal dynamic of interaction between brain regions induced by intensive training/learning. In addition to the crucial causality inferences on spatial and temporal characteristics of imaging data and behaviour, this model will be also naturally suited for an unbiased identification of inter-individual differences in brain tissue properties. The underlying hypothesis is that regional changes are not only driven by exogenous stimuli but also influenced by past or concomitant endogenous changes in remote regions.

## Conclusions

The main aim of our article is to challenge, from the neuroimaging perspective, the agnostic view on use-dependent brain plasticity as simple dynamics of grey matter volume, density or cortical thickness changes derived from non-quantitative T1-weighted data - a “one-trick pony” strategy. Imposing a neurobiological perspective on imaging data interpretation, together with a generative model inferring causality has the potential to provide the grounds for multi-scale inferences linking histology studies at the (sub)cellular level with non-invasive human imaging research at the systems level.

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