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Connectivity-based fixel enhancement: Whole-brain statistical analysis of diffusion MRI measures in the presence of crossing fibres

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ABSTRACT

In brain regions containing crossing fibre bundles, voxel-average diffusion MRI measures such as fractional anisotropy (FA) are difficult to interpret, and lack within-voxel single fibre population specificity. Recent work has focused on the development of more interpretable quantitative measures that can be associated with a specific fibre population within a voxel containing crossing fibres (herein we use *fixel* to refer to a specific *fibre population* within a single *voxel*). Unfortunately, traditional 3D methods for smoothing and cluster-based statistical inference cannot be used for voxel-based analysis of these measures, since the local neighbourhood for smoothing and cluster formation can be ambiguous when adjacent voxels may have different numbers of fixels, or ill-defined when they belong to different tracts. Here we introduce a novel statistical method to perform whole-brain fixel-based analysis called connectivity-based fixel enhancement (CFE). CFE uses probabilistic tractography to identify structurally connected fixels that are likely to share underlying anatomy and pathology. Probabilistic connectivity information is then used for tract-specific smoothing (prior to the statistical analysis) and enhancement of the statistical map (using a threshold-free cluster enhancement-like approach). To investigate the characteristics of the CFE method, we assessed sensitivity and specificity using a large number of combinations of CFE enhancement parameters and smoothing extents, using simulated pathology generated with a range of test-statistic signal-to-noise ratios in five different white matter regions (chosen to cover a broad range of fibre bundle features). The results suggest that CFE input parameters are relatively insensitive to the characteristics of the simulated pathology. We therefore recommend a single set of CFE parameters that should give near optimal results in future studies where the group effect is unknown. We then demonstrate the proposed method by comparing apparent fibre density between motor neurone disease (MND) patients with control subjects. The MND results illustrate the benefit of fixel-specific statistical inference in white matter regions that contain crossing fibres.

Abbreviations: AFD, apparent fibre density; AFROC, alternative free-response receiver operator curve; AUC, area under the curve; CFE, connectivity-based fixel enhancement; CHARMED, composite hindered and restricted model of diffusion; CUSP-MFM, cube and sphere multi-fascicle model; DWI, diffusion-weighted imaging; FA, fractional anisotropy; Fixel, a specific fibre population within a voxel; FBA, fixel-based analysis; FOD, fibre orientation distribution; FWE, family-wise error; FWHM, full width at half maximum; HMOA, hindrance modulated orientational anisotropy; MD, mean diffusivity; MND, motor neurone disease; MRI, magnetic resonance imaging; ROC, receiver operator curve; ROI, region of interest; SIFT, spherical deconvolution informed filtering of tractograms; SNR, signal to noise; SPM, statistical parametric mapping; TBSS, tract-based spatial statistics; TFCE, threshold-free cluster enhancement; VBA, voxel-based analysis.

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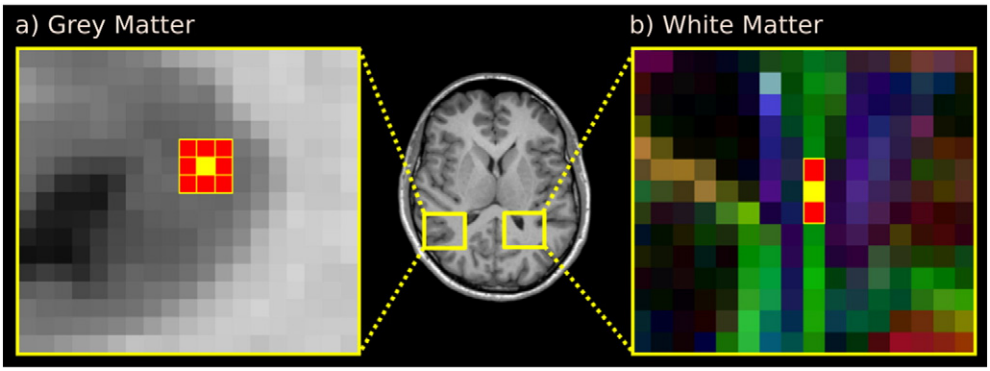

Fig. 1. a) In grey matter, it is reasonable to assume image intensities are spatially correlated with neighbours isotropically for the purposes of smoothing and cluster formation. Illustrated in yellow is a voxel of interest with neighbouring voxels coloured red. b) White matter anatomy is oriented and extended in nature, therefore an isotopic neighbourhood is not appropriate. Shown is a fractional anisotropy map coloured by the direction of the primary tensor eigenvector (red: left–right, green: anterior–posterior, blue: inferior–superior). Not all voxels adjacent to the voxel of interest (yellow voxel within the optic radiation) are relevant for smoothing and cluster formation since neighbouring voxels contain different fibre tracts (e.g. tapetum of corpus callosum and arcuate fasciculus). In this example only the voxels anterior and posterior (shown in red) should be considered as neighbours for clustering and smoothing.

Introduction

Voxel-based analysis (VBA) is an image analysis technique for performing whole-brain voxel-wise statistical tests across and within groups of subjects, originally introduced in the form of statistical parametric mapping (SPM; Friston et al., 1991). A particular strength of the VBA approach is that, in addition to enabling specific hypotheses to be tested, it has the ability to localise group differences or correlations without any prior spatial hypothesis. Over the last two decades, VBA has been applied in many fields of neuroimaging to investigate quantitative information derived from image intensity (e.g. positron emission tomography (Worsley et al., 1992) and functional MRI (Friston et al., 1995)) and image morphology (e.g. voxel-based morphometry (Ashburner and Friston, 2000) and tensor-based morphometry (Ashburner, 2000; Gee, 1999)).

VBA commonly involves four key steps:

1. Obtain anatomical correspondence by transforming all subject images to a common template using an image registration algorithm.
2. Smooth images to boost the signal-to-noise ratio, alleviate registration misalignments, and improve the normality of residuals when performing parametric statistical analysis.
3. Perform a statistical test at each voxel resulting in a test-statistic image (also known as a statistical parametric map).
4. Statistical inference (assign p-values to voxels, peaks or clusters of voxels).

One caveat in VBA is the need to account for the large number of multiple tests during statistical inference. Random field theory (RFT) (Worsley et al., 1992) and non-parametric permutation testing (Nichols and Holmes, 2002) are two commonly used methods to compute family-wise error (FWE) corrected p-values. While these methods can be used to make voxel-level inferences, they can also be applied to derive FWE-corrected p-values for clusters of contiguous voxels above a predefined threshold (Friston et al., 1994; Poline and Mazoyer, 1993). Cluster-level inference can be more sensitive than voxel-level inference by exploiting spatial correlations in voxel intensities due to shared underlying anatomy and pathology (Friston et al., 1996).

In the field of diffusion-weighted imaging (DWI), VBA is being used increasingly to study white matter development, aging and pathology. The vast majority of these studies have involved quantitative measures derived from the diffusion tensor model, such as mean diffusivity (MD) and fractional anisotropy (FA) (Basser and Pierpaoli, 1996). Since these tensor-derived measures are scalar quantities, traditional VBA software packages (such as SPM (www.fil.ion.ucl.ac.uk/spm/) and FSL (www.fmrib.ox.ac.uk/fsl)) can be used to analyse the resultant 3D images. More recently, several diffusion-specific VBA approaches have been proposed that perform statistics on a tract skeleton (Smith et al., 2006) or surface (Maddah et al., 2011; Yushkevich et al., 2008; Zhang et al., 2010). By projecting local quantitative measures onto a tract skeleton or 2D surface, these methods aim to reduce the impact of imperfect image registration on anatomical correspondence. However, not all white matter tracts can be modelled by a skeleton or surface, and therefore these methods suffer from other problems related to inaccurate tract representation and projection (Bach et al., 2014).

Two issues relevant to VBA of white matter that have been largely neglected to date are as follows:

1. A white matter voxel can contain multiple populations of fibres, each belonging to a specific white matter tract with a unique function (a scenario often referred to as crossing fibres). Recent evidence suggests up to 90% of white matter voxels contain two or more fibre populations (Jeurissen et al., 2012). Ideally VBA of diffusion MRI should be able to attribute any significant effect to a specific fibre population in regions with crossing fibres.
2. White matter contains anatomical structures that are oriented and can span many voxels in the image. Spatially distant voxels can share the same underlying anatomy, yet adjacent voxels may share no anatomy (e.g. at a bundle interface). It is therefore reasonable to assume that correlations in quantitative measures can occur anywhere *along* a fibre tract, but not necessarily with all voxel neighbours isotropically (as is assumed to be the case in grey matter) (see Fig. 1).[1] This is based on the assumption that axons are likely to be affected by development, pathology or aging along their entire length.

Both issues 1 and 2 are problematic for appropriate smoothing and cluster-based statistical inference. A neighbourhood for traditional isotropic smoothing and cluster formation is ambiguous when adjacent voxels have multiple fibre populations, and ill-defined when adjacent fibre populations belong to different fibre tracts. Note that in the aforementioned surface- and tract-skeleton-based methods (Maddah et al., 2011; Smith et al., 2006; Yushkevich et al., 2008; Zhang et al., 2010), parameterisation of the tract enables smoothing and clustering with a more appropriate neighbourhood. However, 2D surfaces or 3D skeletons cannot appropriately represent all white matter tracts (e.g. fanning of the corpus callosum), and current methods do not account for crossing fibres.

In recent years, a number of quantitative measures have been proposed that can be assigned to a specific fibre population within a

[1] Note that this may not be true for lesions in diseases such as Stroke and Multiple Sclerosis. However, these lesions tend to be spatially heterogeneous and therefore less suited to multi-subject VBA.