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A cross-validated cytoarchitectonic atlas of the human ventral visual stream

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ABSTRACT

The human ventral visual stream consists of several areas that are considered processing stages essential for perception and recognition. A fundamental microanatomical feature differentiating areas is cytoarchitecture, which refers to the distribution, size, and density of cells across cortical layers. Because cytoarchitectonic structure is measured in 20-micron-thick histological slices of postmortem tissue, it is difficult to assess (a) how anatomically consistent these areas are across brains and (b) how they relate to brain parcellations obtained with prevalent neuroimaging methods, acquired at the millimeter and centimeter scale. Therefore, the goal of this study was to (a) generate a cross-validated cytoarchitectonic atlas of the human ventral visual stream on a whole brain template that is commonly used in neuroimaging studies and (b) to compare this atlas to a recently published retinotopic parcellation of visual cortex (Wang et al., 2014). To achieve this goal, we generated an atlas of eight cytoarchitectonic areas: four areas in the occipital lobe (hOc1-hOc4v) and four in the fusiform gyrus (FG1-FG4), then we tested how the different alignment techniques affect the accuracy of the resulting atlas. Results show that both cortex-based alignment (CBA) and nonlinear volumetric alignment (NVA) generate an atlas with better cross-validation performance than affine volumetric alignment (AVA). Additionally, CBA outperformed NVA in 6/8 of the cytoarchitectonic areas. Finally, the comparison of the cytoarchitectonic atlas to a retinotopic atlas shows a clear correspondence between cytoarchitectonic and retinotopic areas in the ventral visual stream. The successful performance of CBA suggests a coupling between cytoarchitectonic areas and macroanatomical landmarks in the human ventral visual stream, and furthermore, that this coupling can be utilized for generating an accurate group atlas. In addition, the coupling between cytoarchitecture and retinotopy highlights the potential use of this atlas in understanding how anatomical features contribute to brain function. We make this cytoarchitectonic atlas freely available in both BrainVoyager and FreeSurfer formats (http://vpnl.stanford.edu/vcAtlas). The availability of this atlas will enable future studies to link cytoarchitectonic organization to other parcellations of the human ventral visual stream with potential to advance the understanding of this pathway in typical and atypical populations.

Introduction

The ventral visual pathway, a stretch of cortex including the ventral aspects of the occipital and temporal lobes, is a key processing stream involved in visual perception and recognition (Goodale et al., 1991; Mishkin et al., 1983; Grill-Spector and Weiner, 2014). A major neuroscientific goal is to understand the anatomical infrastructure composing this pathway. A classic microanatomical feature defining an area is cytoarchitecture – or the spatial arrangement of cell bodies and types in the six-layered cortical ribbon (Amunts and Zilles, 2015; Brodmann, 1909; Campbell, 1905; Smith, 1907; v.Economo and Koskinas, 1925), which is considered to be tightly linked to the functional properties of an area. To characterize the distribution and density across cortical layers, which is the main criterion to delineate boundaries between cytoarchitectonic brain areas, postmortem brains are stained to differentiate cell bodies of neurons and glial cells from

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other compartments of the cortical tissue (e.g. myelinated nerve fibers, axons, dendrites). Even though established more than a century ago, a large majority of present neuroimaging studies still relate their findings to Brodmann's (1909) classic cytoarchitectonic parcellation.

While influential, there are several limitations to Brodmann's and other classical approaches (Bailey and Bonin, 1951; Brodmann, 1909; Campbell, 1905; Smith, 1907; v.Economo and Koskinas, 1925) used to define brain areas based on cytoarchitectonics (Zilles and Amunts, 2010). First, classical approaches lack important information regarding the inter-subject variability of cytoarchitectonic structures. Second, the criteria used for histological distinctions were not clearly defined and researchers identified boundaries based on visual inspection of histological sections. Consequently, definitions of cytoarchitectonic boundaries depend on subjective judgments made by particular observers, leading to contention among researchers regarding the location of boundaries, especially in higher sensory and association cortices. Third, the cytoarchitectonic areas that were identified with this approach were typically summarized by schematic drawings indicating their approximate location on the brain. As such, they are often oversimplified. Further, there is no precise method to project these schematics onto actual anatomical brain volumes obtained by modern magnetic resonance imaging (MRI) techniques to allow for comparison to other brain parcellation methods (Amunts et al., 2013; Glasser et al., 2016; Glasser and Van Essen, 2011; Yeo et al., 2011; Zilles and Amunts, 2009). A common solution to project these areas onto anatomical MRIs has been to manually approximate locations of these cytoarchitectonic areas relative to cortical folding patterns (e.g. Talairach and Tournoux, 1988, Scholtens et al., 2015; van den Heuvel et al., 2015). This, however, results in considerable subjectivity and uncertainty in localizing cytoarchitectonic areas.

To overcome the problems of classical approaches, methodological advancements in the last 20 years have yielded new methods enabling more accurate delineation of cytoarchitectonic areas in the human brain (Schleicher et al., 2005, 1999, 1998). The main advantages of these modern techniques are that (1) the definitions of areal boundaries are observer-independent and statistically testable, and (2) properties of each cytoarchitectonic area are determined based on the analysis of histological structure of multiple brains. Specifically, an observer-independent algorithm identifies locations along the cortical ribbon in which the density and layering of cell bodies across the cortical depth (referred to as gray level index, GLI), show a significant change (Schleicher et al., 1999, 1998). For a cytoarchitectonic boundary to be accepted, it has to be consistently found in neighboring serial sections and across brains. Finally, cytoarchitectonic areas identified in histological sections are registered to the anatomical MRI volumes of each brain taken prior to histological processing. This not only identifies the precise location of a cytoarchitectonic area in each brain, but also corrects for shrinkage artifacts associated with histological processing (Amunts et al., 2000).

Using this approach, eight cytoarchitectonic areas have been identified in the human ventral visual stream (hOc1-hOc4v: Amunts et al., 2000; Rottschy et al., 2007, FG1-FG4: Caspers et al., 2013; Lorenz et al., 2015, see Fig. 1). Additionally, a probabilistic atlas of these cytoarchitectonic areas has been incorporated into the SPM toolbox (Eickhoff et al., 2005). However, it is unknown how well these probabilistic maps predict the location of these cytoarchitectonic areas in new subjects, and whether cytoarchitectonic parcellations correspond to other parcellations of the human ventral visual stream (e.g., Glasser et al., 2016; Wang et al., 2014).

To fill these gaps in knowledge we (1) generated a cross-validated probabilistic atlas of cytoarchitectonic areas in the human ventral visual stream extending from the occipital lobe through ventral temporal cortex (VTC) and (2) compared the cross-validated cytoarchitectonic atlas to a recently published retinotopic atlas of human visual cortex (Wang et al., 2014).

Importantly, we tested how different alignment approaches affect the accuracy of the generated atlas. Specifically, we generated atlases using three different methods: (1) an affine volumetric alignment (AVA) to the MNI305 brain, (2) a nonlinear volumetric alignment (NVA) to the Colin27 brain, and (3) cortex-based alignment (CBA), which aligns brains based on cortical folding patterns (Fischl et al., 1999; Frost and Goebel, 2012a, 2012b) to a common brain. Here we used the FreeSurfer average brain, which is an average cortical surface of 39 independent living participants. We quantitatively assessed the performance of the different methods by (1) evaluating the consistency of cytoarchitectonic areas across brains and (2) quantifying how well each method predicts the location of cytoarchitectonic areas in new brains using an exhaustive leave-one-out cross-validation procedure. Recent reports find a strong coupling between cytoarchitectonic boundaries relative to macroanatomical landmarks in ventral occipital-temporal cortex (Lorenz et al., 2015; Rottschy et al., 2007; Weiner et al., 2014) and provide evidence that cortex-based alignment improves the inter-subject registration of two cytoarchitectonic areas within the human occipital lobe (Fischl et al., 2008). Thus, we hypothesized that registering brains using alignment methods that use macroanatomical features would increase the inter-subject consistency of cytoarchitectonic areas and produce a more precise group atlas of cytoarchitectonic areas of the human ventral visual stream compared to affine volumetric alignment that does not use macroanatomical landmarks.

Methods

Definition of cytoarchitectonic areas (cROIs)

Cytoarchitectonic regions of interest (cROIs) were defined previously from a sample of 11 postmortem (PM) adult brains (5 females; Amunts et al., 2000; Caspers et al., 2013; Lorenz et al., 2015; Rottschy et al., 2007). Each cROI was defined in 10 PM brains. hOc1-hOc4v, as well as FG1 and FG2, were defined on the same 10 brains. FG3 and FG4 were defined on 9 of these brains and in one additional PM brain, resulting in 11 brains in total. The brains were obtained from the body donor program of the Institute of Anatomy at the University of Düsseldorf. Donors had no neurological or psychiatric diseases, except one case with transitory motor disease (for details see Table 1 in Amunts et al., 2000; Caspers et al., 2013; Rottschy et al., 2007). Within 8–24 h after death the brains were removed and fixated in 4% formalin or Bodians's fixative for a time period of at least six months. Before the brains were histologically processed, each brain was scanned at a Siemens 1.5 T scanner (Erlangen, Germany). A high-resolution anatomical image of the whole brain was acquired, using a T1-weighted 3D-FLASH sequence (1 mm isotropic, TR = 40 ms, TE = 5 ms, flip angle = 40°). Following that, the brains were embedded in paraffin, serially sectioned in oblique close to coronal sections of 20 μm and every 15th slice was stained for cell bodies (Merker, 1983). Detailed methods of histology and 3D reconstruction have been described previously (Amunts et al., 2005; Amunts et al., 1999; Zilles et al., 2002).

Characteristics of ventral visual stream cROIs

There are four cROIs in the occipital lobe:

Human occipital cytoarchitectonic area 1, **hOc1** (Amunts et al., 2000), is located in the calcarine sulcus (Fig. 1a – dark green). This area closely matches functionally defined area V1 (Abdollahi et al., 2014; Hinds et al., 2009; Wohlschläger et al., 2005) and corresponds to Brodmann area 17 (Brodmann, 1909). hOc1 is characterized by a clear layered structure with prominent layer IV, which is further subdivided into sublayers, small cells in layer III and V, and a dense layer VI (Amunts et al., 2000).

Human occipital cytoarchitectonic area 2, **hOc2** (Amunts et al., 2000), surrounds hOc1 both inferiorly and superiorly. It has a thinner layer IV compared to hOc1, a cell dense layer III, and shows a