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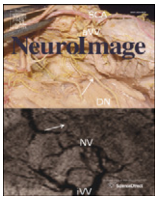

Probabilistic model-based functional parcellation reveals a robust, fine-grained subdivision of the striatum

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ABSTRACT

The striatum is involved in many different aspects of behaviour, reflected by the variety of cortical areas that provide input to this structure. This input is topographically organized and is likely to result in functionally specific signals. Such specificity can be examined using functional clustering approaches. Here, we propose a Bayesian model-based functional clustering approach applied solely to resting state striatal functional MRI timecourses to identify intrinsic striatal functional modules. Data from two sets of ten participants were used to obtain parcellations and examine their robustness. This stable clustering was used to initialize a more constrained model in order to obtain individualized parcellations in 57 additional participants. Resulting cluster time courses were used to examine functional connectivity between clusters and related to the rest of the brain in a GLM analysis. We find six distinct clusters in each hemisphere, with clear inter-hemispheric correspondence and functional relevance. These clusters exhibit functional connectivity profiles that further underscore their homologous nature and are consistent with existing notions on segregation and integration in parallel cortico-basal ganglia loops. Our findings suggest that multiple territories within both the affective and motor regions can be distinguished solely using resting state functional MRI from these regions.

Introduction

The striatum serves as the input structure of the basal ganglia, which are involved in motor control, attention, learning and decision-making. This functional versatility is subserved by inputs from thalamus, hippocampus, amygdala and many neocortical regions. Animal studies have shown that these inputs are topographically organized (Haber, 2003; Middleton and Strick, 2000; Alexander et al., 1986; Groenewegen, 2003) and more recent tractography studies have provided evidence that the same holds for humans (Lehéricy et al., 2004; Leh et al., 2007; Draganski et al., 2008; Tziortzi et al., 2013).

Such organization of inputs may reflect a division into functional subunits and discriminating these is important when studying corticostriatal connectivity specifically (e.g. in the context of development (Rubia et al., 2006), ageing (Hedden and Gabrieli, 2004) or pathology (Lawrence et al., 1998; Unschuld et al., 2013)) as well as whole-brain connectivity (Butts, 2009). Such a subdivision was found in a meta-analysis of 126 functional activation studies (Postuma and Dagher, 2006), showing a division into three parts, i.e. the dorsal caudate, ventral striatum and dorsal caudal putamen. Each showed specificity in the pattern of coactivation in task-based functional magnetic resonance imaging (fMRI). Di Martino et al. (2008) used these results as the basis for resting state functional connectivity analysis and found that seeds based on this subdivision showed distinct connectivity patterns, confirming the meta-analytic results. Barnes et al. (2010) identified participant-specific equivalents of these three striatal subunits by clustering the whole-brain connectivity profiles for voxels in the striatum.

Using a dataset comprising 1000 participants, Choi et al. (2012) generated a striatal parcellation, demonstrating a functional subdivision consistent with earlier results. Their approach was based on correlating striatal voxel timecourses with cortical surface-node timecourses. Voxels were assigned labels according to which network occurred most often among the top 25 correlated voxels. This resulted in a parcellation where the caudate was associated with frontoparietal and default mode networks, the accumbens was assigned to the limbic network and the putamen was split between frontoparietal, dorsal attention, default mode and somatomotor networks. Recently, Jung et al. (2014) reported parcellations based on correlation maps between striatal voxels and the rest of the brain. The parcellation was obtained using K-means clustering on the group averaged correlation maps for the caudate and putamen separately. This produced several different levels of parcellation and these were subsequently used to investigate the functional connectivity of clusters. They found that, even at fine-grained parcellations, the functional connectivity profiles of the clusters were distinct. In the caudate, these could be grouped into clusters associated with regions involved in cognition (dorsal caudate) and emotion (ventral caudate). Rostral putamen clusters were also associated with

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these types of areas, whereas the caudal putamen was mostly related to motor areas.

A limitation of the approach presented in Choi et al. (2012) is that it relies on the parcellation of cortex into networks, i.e. each voxel in the striatal mask is assigned to a cluster based on its correlation with a network. An implicit assumption in this heuristic is that these networks are disjoint. It is more likely that functional networks, like the ones used in Choi et al. (2012), represent a global mean configuration of functional connectivity. When looking at striatal function specifically, we are interested in all the configurations that feature striatal regions, which are not necessarily the same as the global mean configurations. K-means clustering, used in Jung et al. (2014), has the limitation that the number of clusters remains a free parameter to be tuned and has a bias towards evenly sized clusters. In addition, as the clustering was performed on connectivity profiles of the voxels, one needs to take care in interpreting the functional connectivity results of the clusters. Furthermore, the approaches in both Choi et al. (2012) and Jung et al. (2014) are group analyses, i.e. they do not provide single subject parcellations.

In this paper, Bayesian non-parametric (BNP) modelling is used to formulate a parcellation strategy to address these limitations. BNP models provide flexible and powerful analysis methods necessary for tackling difficult neuroimaging problems. For instance, Zhang et al. (2014) proposed an interesting non-parametric framework for analysing task fMRI data. BNP models steer clear of issues like choosing the number of clusters by letting them be determined by the data (for a general introduction to this type of model see (Gershman and Blei, 2012)). Andersen et al. (2012) employed such a framework to cluster the striatum. They used a graph-based clustering approach on the correlation matrix with a Chinese restaurant process (CRP) as a prior on cluster assignments. This approach has two main advantages over previous work, that is, it infers the number of clusters from the data and it only uses data from the striatum to perform clustering, permitting analysis of their relation with the rest of the brain in the same dataset. Using this approach bilateral striatal clusters were found, which could be grouped into the caudate, accumbens and putamen. However, no further analyses were performed to assess the functional relevance of the obtained clusters.

The approach we propose is that of an infinite Gaussian mixture model (IGMM), which allows us to generate a parcellation based solely on the striatal functional timecourses. In this mixture model, each voxel is assumed to belong to a cluster and voxels within a cluster are assumed to have the same underlying BOLD timecourse and voxel-specific noise structure. In contrast to Andersen et al. (2012), we use the distance-dependent Chinese restaurant process (dd-CRP) (Blei and Frazier, 2011) as a prior on cluster assignments. We chose this generalization of the CRP because it facilitates the incorporation of spatial constraints. This model is used to parcellate at the group level, a second model is formulated to tailor these parcellations to single subject data.

The incorporation of a spatial constraint is based on the following reasoning. The goal is to find functional modules and most connections between neurons are short range. Hence we assume that a functional unit is also spatially contiguous. A criticism might be that projections from external regions can terminate in non-adjacent regions (Cavada and Goldman-Rakic, 1991; Van Hoesen et al., 1981). However, this does not in itself argue for non-contiguous clusters as the full set of input and output connections might still be different for these termination sites. The assumption of contiguity can be checked by examining the cluster timecourses and their connectivity profiles. While one could also cluster without spatial constraint and enforce contiguity afterwards, employing a spatial constraint in the estimation is the more elegant and computationally efficient solution.

We show that our approach reveals functional clusters in the striatum representing specific elements within established cortico-striatal loops with identifiable single-subject representations. We confirm their functional relevance by looking at functional connectivity of these subject-specific clusters with the rest of the brain, which demonstrates their cluster-specific connection profiles.

Methods

Probabilistic model based clustering

Striatal voxels were clustered using an infinite Gaussian mixture model (IGMM), which is visualized as a graphical model in Supplementary Fig. S1. In our Gaussian mixture model, each voxel n is assigned to a cluster k and we draw a data point x_{nt} for each time t from a Gaussian with mean μ_{kt} and precision τ_{kt}. We placed a prior on the mean and precision in the form of a normal-gamma distribution with parameters μ_0, κ_0, a_0 and b_0. Note that we model timepoints as T independent draws from a one-dimensional Gaussian, as opposed to one draw from a T-dimensional Gaussian, where T is the number of timepoints. This has the advantages of computational efficiency and simplified group analysis.

A GMM can be turned into an IGMM by using the whimsically named Chinese Restaurant Process (CRP) as a prior on the cluster assignment. In the CRP analogy for our problem, voxels are customers, clusters are tables and cluster parameters, i.e. timecourse and noise parameters, are the dishes served at a table. In this restaurant, there are an infinite number of tables, each with their own dish, and as customers come in, they sit at a random table. The probability of choosing a table that already has seated customers is proportional to the number of diners at that table. The probability that they sit at an empty table is proportional to the concentration parameter of the CRP, which controls the expected number of clusters. While there are an infinite number of tables, the restaurant staff need only consider those that are actually occupied at any given point, bounding the maximum number of clusters to the number of customers.

The CRP prior assumes exchangeability, that is, it does not matter in what order customers enter the restaurant. We would like to incorporate a spatial constraint such that clusters are contiguous, however, which violates this assumption. The distance-dependent Chinese Restaurant Process (Blei and Frazier, 2011) (dd-CRP) is a generalization of the CRP that allows non-exchangeable elements. In the analogy for the dd-CRP, each customer picks one customer with whom they would like to sit, with probability proportional to how close they are. The concentration parameter of the dd-CRP then serves as an indication of how strongly customers keep to themselves. In this work, both the concentration parameter and distance between customers is encoded in an $N \times N$ matrix $\mathbf{A}$, where a_{ij} is the inverse distance between customers i and j and a_{ii} corresponds to the concentration parameter. The dd-CRP serves as a flexible prior, allowing us to incorporate a spatial constraint and infer the number of clusters.

In order to complete the model, we need to set the hyperparameters $\mathbf{A}$, μ_0, κ_0, a_0 and b_0. A spatial constraint was specified such that $a_{ij} = 1$ if i and j are adjacent, otherwise $a_{ij} = 0$. Voxels were considered adjacent if they shared a face or an edge and voxels were considered adjacent to themselves, that is, $a_{ii} = 1$ for all i. Data are assumed to be z-scored in the time domain. Therefore we set $\mu_0 = 0$, while keeping this a flat prior by setting κ_0 to an extremely small value. We place a vague prior on τ_{kt} by setting $a_0 = 2$ and $b_0 = 1$. The mean of this distribution is $\frac{a_0}{b_0} = 2$, corresponding to an expected within-cluster variance of 0.5.

In order to obtain single-subject representations of the group-level parcellation, we employed a more constrained model informed by the group-level results. In this model, we fix the number of clusters to that of the group results. Further regularization was provided by placing a spatial precision (inverse covariance) prior on the cluster timecourses. This prior precision was obtained by taking the inverse of the group level cluster covariance matrix. After initializing the parcellation to the group level parcellation, we employed Gibbs sampling to reassign customer links. This was applied to data from participants that were not used in the group-level inference. With the number of clusters fixed and each participant initialized the same way, this results in identifiable participant-specific versions of the group-level parcels. A more detailed description of both models, including derivations, can be found in the Methods S1.