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Learning to classify neural activity from a mouse model of Alzheimer's disease amyloidosis versus controls

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Abstract The mechanisms underlying Alzheimer's disease (AD) onset and progression are not yet elucidated. The extent to which alterations in the activity of individual neurons of an AD model are significant, and the phase at which they can be captured, point to the intensity of the pathology and imply the stage at which it can be detected. Using a machine-learning algorithm, we present a successful cell-by-cell classification of intracellularly recorded neurons from the B6C3 APPswe/PS1dE9 AD model, versus wildtypes controls, at both a late stage and at an early stage, when the plaque pathology and behavioral deficits are absent or rare. These results suggest that the deficits present in neuronal networks of both old and young transgenic animals are large enough to be apparent at the level of individual neurons, and that the pathology could be detected in nearly any given sample, even before pathologic signs.

Keywords: Alzheimer's disease; Amyloid-β; SVM; Classification; Machine-learning

1. Introduction

The resolution and the stage in which information on an Amyloid-β (Aβ)–related pathology can be detected in the brain are not well studied. An automated detection of neurons and neural assemblies that provides information about the pathology would be valuable for Alzheimer's disease (AD) research, and could assess the predictive power of various physiological features found in these mice, and constitute a set of parameters indicative of the pathology in the early stages.

Although the accumulation and aggregation of Aβ in the brain are postulated to be a central event in the pathogenesis of AD, different lines of evidence support the presence of a preclinical phase in the development of the disease, where Aβ abnormality begins before the onset of the clinical disease [1–4]. Other studies consider the soluble form of Aβ to be a major factor in cognitive decline [5,6]. Two crucial questions that could impact both the progress of the disease and early detection are whether any information about the pathology can be retrieved from individual neurons and whether this information is available in a pre-symptomatic stage.

It was recently shown that the coherence of neural activity in various cortical areas of the APP/PS1 transgenic (Tg^+) mice model *in vivo* is reduced compared to wildtype (WT) controls at different stages of AD [7–9]. It was proposed that this reduction in coherence of the network activity is linked to the malfunctioning of individual neurons. Recent evidence also showed a profound disruption of slow oscillations of cortical assemblies by pathological Aβ, that was elevated either chronically in the APP23 × PS45 mouse model, or acutely after exogenous administration [9]. Disruption to slow oscillations was also linked to tau pathology [10].

Although the aforementioned alterations were statistically evident at the group level, it is still not known how robust they are and whether they can be captured in individual cells at different stages of the pathological cascade. If a neuron-by-neuron classification based on physiological differences between APP/PS1 Tg^+ and WT mice is

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successful, it would imply that the effects are consistent across neurons, and that the detrimental effects of Aβ are evident in most neurons even before the appearance of significant plaque aggregation.

In this article, we describe how electrophysiological activity can be robustly classified when measured from APP/PS1 Tg^+ mice and littermate controls, using a support vector machine (SVM). Because they are data driven, automated algorithms for classification can be more accurate and more consistent than classification defined by human rules. Classification was applied on physiological features from three levels of cortical recordings *in vivo*: intracellular recordings, LFP (local field potentials), and ECoG (electrocorticogram). Although the LFP and the ECoG recordings reflect summation of electric activity over neuronal populations, intracellular recordings provide the physiological underpinnings of such activity. The physiological features used in this study pointed to reduced coherence and suggest an increased perturbation to neuronal activity. Recordings were obtained from animals from two age groups: young, before the emergence of significant Aβ plaque pathology and related behavioral deficits, and old, at an age when the cortex is burdened with Aβ plaques, and when various cognitive and behavioral impairments can be detected.

2. Methods

2.1. Data types

Data for classification were collected from recordings in the B6C3 APPswe/PS1dE9 transgenic mouse model (APP/PS1) and wildtype (WT) littermates. Supplementary Table 1 shows the ages of the animals used in all classifications. Classification results were obtained as elaborated below.

2.2. Data acquisition

Cortical activity was measured by three techniques: intracellular recordings, LFP, and ECoG.

2.2.1. Intracellular recordings

Each recording was made from an individual neuron from an APP/PS1 Tg^+ or WT mouse. Animals were from two age groups:

2.2.1.1. "Old" group: 9–19 months old

At this age, the cortex of the mouse model is burdened with Aβ plaques. We collected a total of $n = 19$ neurons: 13 WT, 6 Tg^+, from 12 and 6 animals, respectively.

2.2.1.2. "Young" group: 2–6 months old

This age range is before a significant onset of Aβ plaque pathology, whereas soluble Aβ is abundant in the cortex. We collected a total of $n = 26$ neurons: 15 WT (age: 3–6 months), 11 Tg^+ (age: 2–4 months) from 13 and 10 animals, respectively.

2.2.2. LFP of old group (9–19 months)

In this method, we recorded multicellular activity from a relatively small tissue volume in deeper layers of the cortex. A total of $n = 23$ recordings of LFP (12 WT, 11 Tg^+) were collected. After dura removal, LFP electrodes were inserted up to 300 μm below cortex surface.

2.2.3. ECoG recordings of the old group (9–19 months)

In this method, we recorded the multicellular activity of larger populations from superficial layers of the cortex. A total of $n = 23$ recordings of ECoG (12 WT, 11 Tg^+) were collected. ECoG electrodes were placed on top of the cortex above the dura.

LFP and ECoG were recorded in the same animals.

Fig. 1 shows examples of intracellular, LFP and ECoG recordings from APP/PS1 Tg^+ and WT, along with representative images of Aβ plaque pathology and cell staining from the two age groups.

2.3. Feature extraction and selection

We tested a series of features extracted from physiological parameters of recordings of APP/PS1 Tg^+ and WT mice in the two age groups. All the physiological features used by the classifiers are listed in Supplementary Table 2.

Each of the four classifiers used parameters from one dataset with one recording technique for the APP/PS1 Tg^+ and WT mice. These parameters captured different features of the recordings, and included the time-domain, and the frequency-domain from subthreshold or suprathreshold activity.

2.4. Classification setting

We trained a separate binary classifier on each of the data sets described in section 2.2 to solve the four classification "intracellular old", "intracellular young", "LFP", and "ECoG" problems. Each classification was done on the number of recordings (neurons/assemblies) in the respective dataset. The number of features used by each classifier is indicated in Supplementary Table 2.

The input for training each classifier was the set of electrophysiological features obtained for each of the examples (neurons/assemblies) in the respective dataset accompanied by a binary label indicating whether that example was a positive (Tg^+) or a negative sample (WT).

2.5. Classification algorithm

We used a linear SVM binary classifier [11]. Linear SVM is a supervised learning method which trains a hyperplane that maximizes the margin between the positive and negative samples. SVM inputs a set of labeled samples (x_i, y_i), where each sample is represented as a vector of input features $x_i \in R^d$, and is also labeled as positive (Tg^+) or negative (WT): $y_i \in \{+1, -1\}$.

SVM aims to solve the following optimization problem

$$\min_w \frac{1}{2}\|w\|^2 + C\sum_i \xi_i$$

$$\text{s.t. } y_i(w^T x_i + b) \geq 1 - \xi_i, \quad \xi_i \geq 0, \quad i = 1, \ldots, n$$