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Article

Studying the effects of different anesthetics on quasi-periodic patterns in rat fMRI

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SUMMARY

Functional connectivity is defined as how regions of the brain are connected through similar patterns of activity. Quasi-periodic patterns (QPPs), semi-repeating patterns of activity throughout the brain during rest, are one measure of brain activity that has been found to contribute to functional connectivity. However, it has been shown that functional connectivity can be affected by neurological diseases such as Alzheimer's disease. Neurological diseases are often studied in rodent models when they are under anesthesia, which is known to change brain activity. Therefore, in this project, we aimed to observe the effects of three commonly used rodent anesthetics—isoflurane, dexmedetomidine, and a combination of both—on QPPs. This work was done by analyzing previously acquired functional MRI (fMRI) data from eight male Sprague Dawley rats using a 9.4 T MRI scanner. We then used a modified MATLAB script to run analyses on the imaging data. We hypothesized that dexmedetomidine and isoflurane would have inverse effects on the frequency of QPPs and QPP strength. This project has shown that these anesthetics may have different effects on QPP signals and that researchers should be aware of these potential effects when incorporating them into rodent disease model studies. Some of these effects may be at a greater level of strength or level of activation when compared to QPP results from other anesthetics. Other effects may be the result of variability between individual rats and how this may impact their results.

INTRODUCTION

The brain is the most complex organ of the human body. Its interpretation of senses and control over the body requires a lot of coordination and cooperation, not just from the body, but also within the brain. This is where functional connectivity plays a very important role. Functional connectivity is how the brain is connected through its activity and can also be described as how brain activity synchronizes in regions that are spatially distant from each other (1). In a technical sense, functional connectivity is measured through a correlation of activity at a given time; parts of the brain whose activities are highly correlated are said to be functionally connected (2). Multiple regions of the brain that are typically functionally connected at rest are often referred to as resting state networks (RSNs) (3). These RSNs are believed to be responsible for different types of cognitive processes, for example, the visual network and the auditory network are thought to be responsible for seeing and hearing, respectively (3). In this way, further study of functional connectivity between brain regions can help us better understand how the brain works and how its different regions work together. Functional connectivity is often measured using functional magnetic resonance imaging (fMRI) (2). fMRI is a useful imaging technique that allows us to capture activity in the brain as it changes over time. This activity is captured through the blood oxygen level dependent (BOLD) signal which makes use of the magnetic properties of oxygenated and deoxygenated blood as it is delivered to the active parts of the brain (4).

Certain neurological disorders, including Alzheimer's disease or depression, can lead to changes in functional connectivity (5). Neurological disorders have an immense impact on the life of the person with the disorder and the people around them. However, fMRI research can lead to the identification or treatment of neurological disorders that alter functional connectivity, such as attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, depression, and schizophrenia (6–11). In addition to functional connectivity, another measure of brain activity studied in this context is quasi-periodic patterns (QPPs) (12).

QPPs are a form of dynamic functional connectivity, which are observed by measuring similar activity between brain regions as it changes over time (12). QPPs are observed as semi-periodic waves of low-frequency neural activity that alternate between the default mode and task positive RSNs, networks that are active when the brain is not working on any certain task and when the brain is working on a task, respectively (13). These patterns of activity take the form of activation and deactivation between the two different networks and have been reliably detected in both humans and rodents (10, 12, 13). QPPs have been shown to contribute to functional connectivity, especially within the default mode and task positive networks (13). Researching QPPs helps us to understand functional connectivity, which can then help in researching related neurological disorders.

Often research on QPPs is done on rodents while they are under anesthetics, so that the animals stay still during the scan. However, it is known that anesthetics alter normal brain functions (14, 15). Therefore, a better understanding of how QPPs are affected by anesthetics in these rodent studies is needed for potential applications to human studies where anesthetics are often not used. Given the effects of anesthetics, their use in research trials could affect the resulting data and, consequently, how they are translated to humans. By studying both QPPs and how anesthetics affect them, we can gain a better understanding of anesthetic effects and the implications for translatable findings. The goal of this study was to observe, analyze, and quantify the differences in

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QPPs that arise from the use of different anesthetics in fMRI data taken from rats. Studying QPPs in rat brain fMRI data can help deepen our understanding of the brain's intrinsic activity and provide insights into the basic neurological mechanisms that produce QPPs, help us to investigate the effects of anesthetics on such mechanisms, and gain a better understanding of brain disorders.

The data being analyzed is fMRI data taken from eight rats. Each rat underwent three sequential scans during which they were anesthetized with isoflurane, dexmedetomidine, or a combination of dexmedetomidine with light isoflurane (isodex), respectively. Isoflurane is an anesthetic commonly used in animal studies that increases blood flow and blood pressure (16). Isoflurane also causes a decrease in heartrate (17). Dexmedetomidine, on the other hand, is an alpha-2 adrenergic agonist that inhibits the transmission of nerve impulses in the sympathetic nervous system (18). It decreases heart rate, myocardial contractility, oxygen demand, and cardiac output, while also constricting blood vessels and lowering blood flow (18, 19). Overall, dexmedetomidine works in opposition to isoflurane, with a focus on cardiorespiratory effects, and is often used in unison with isoflurane to help with sedation (20). We hypothesized that if isoflurane influenced QPPs, then dexmedetomidine would have an opposing effect, with isodex resulting in an intermediate effect. These effects were observed in the context of the number of QPPs during a scan and the strength of those QPPs. Our hypothesis was proven to be correct in some cases as isoflurane more often showed a higher number of QPPs, but a lower number of voxels (i.e., 3D units of space in a scan) exhibiting an intense level of activation within those QPPs; whereas dexmedetomidine tended to exhibit opposite effects generally with a lower number of QPPs and a higher number of voxels exhibiting an intense level of activation. The combination of both anesthetics sometimes showed results that were in between the results seen under isoflurane and dexmedetomidine alone. However, the results shown displayed a high level of variability across rats, which led to an inconsistency in observed trends and statistically insignificant differences across the anesthetic conditions.

RESULTS

In this study we looked at the strength and frequency of QPPs under three different anesthetic protocols to see how these anesthetics affected QPPs. We detected the QPPs by using an algorithm that iteratively identifies a pattern template from the fMRI scan and then quantifies how often this pattern occurs throughout the duration of the scan. To obtain our results, we first modified parts of a preexisting MATLAB script. The code allowed us to generate two separate figures as QPP metrics and figures for a single rat under each anesthetic condition (**Figure 1**). We used the correlation of the generated template to each point in the scan to calculate the number of QPPs within the scan (**Figure 1A-C**). To define which timepoints exhibited QPPs we used a correlation threshold of 0.2 (indicated by a red line), which is commonly used in the field as the standard correlation coefficient (r) threshold (15). We then used the template generated from the algorithm to study the activity of the voxels within the QPP pattern over four different timepoints of the QPP (**Figure 1D-F**). We used these results to determine the strength of the QPPs in each scan.

To quantify the strength of the QPP, a threshold for "intense" voxels was placed between 0.5 to 1 and -0.5 to -1. We set these numbers as the thresholds because they were the upper and lower quartiles of the possible range. QPP templates with a higher number of voxels in the "intense" ranges were defined as stronger QPPs. When it comes to the intense voxels in the positive number range (0.5 to 1), dexmedetomidine had the highest average number of voxels within that range, with an average of 369.375 voxels (**Figure 2A**). When it comes to the intense voxels in the negative number range (-1 to -0.5), dexmedetomidine had the highest average of voxels within that range as well (average of 382.25) (**Figure 2B**). Based on the hypothesis, we expected isoflurane to have the lowest number of intense voxels. While this visually appeared to be true with the intense negative voxels, a one-way ANOVA revealed no effect of anesthetic on the intense positively active voxels ($F(2,21) = 1.48$, $p = 0.2499$) or the intense negatively active voxels ($F(2,21) = 1.71$, $p = 0.2043$) (**Figure 2**).

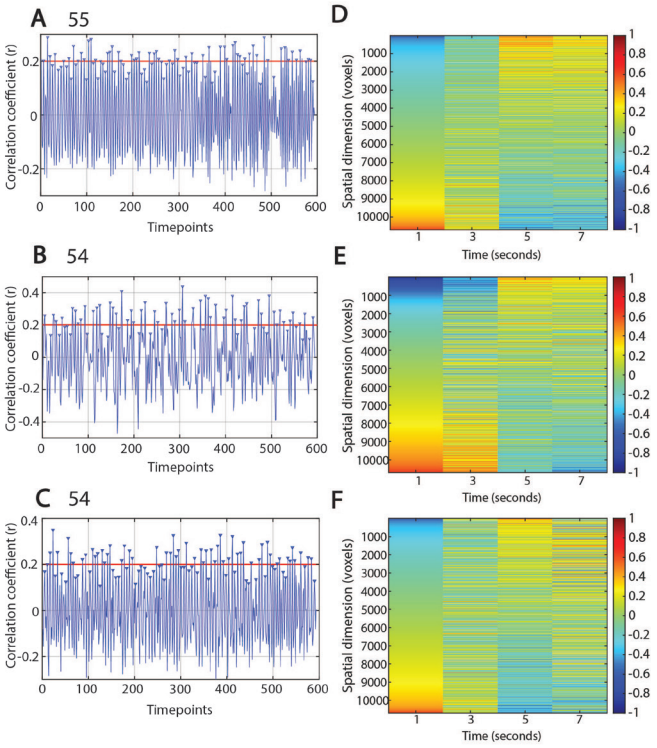

Figure 1. Code-generated figures displaying QPP information. Example from one subject of the two figures generated from the prewritten MATLAB script from which the data for this study was taken from a single subject. **(A-C)** The correlation time-course of the algorithm-generated QPP template and the fMRI scan. The red line represents the QPP threshold, which was set at 0.2. Only the flagged points above this line are counted as instances where QPPs occurred. The number in each panel represents the number of QPPs for that scan. **(D-F)** Visual representation of the activation level for all voxels within the QPP template. Each row represents a voxel in the brain and each column represents a timepoint within the QPP. The voxels at the first timepoint have been sorted from lowest level of activation to highest. The placement of a voxel in the other columns is aligned to its place in the first column. Data for the rat under **(A and D)** isoflurane, **(B and E)** dexmedetomidine and **(C and F)** isodex.

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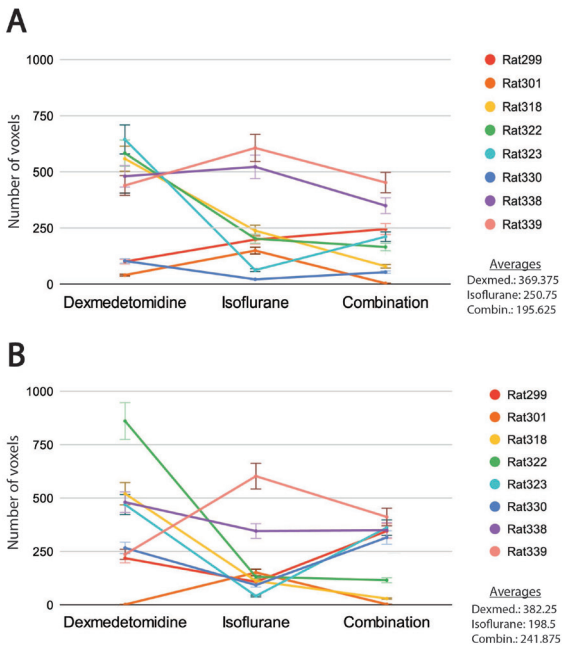

Figure 2. Number of voxels with intense levels of activation for each rat and anesthetic in the QPP template. Number of voxels with a high level of **(A)** positive and **(B)** negative activation in the QPP template. The threshold for "intense" positive voxels was defined as a range of 0.5 to 1 and -0.5 to -1 for "intense" negative voxels. Data for this figure was taken from a modified MATLAB script. Error bars represent the percent error at 10%.

We assessed the distribution of voxel activation levels within the first timepoint of each QPP template by plotting all of the activation values in a histogram (**Figure 3**). We also calculated the corresponding kurtosis value of each distribution (**Table 1**). Kurtosis is a measure of how normal a distribution is, with a value of 3 indicating a normal distribution (21). A narrower distribution of voxels across a histogram, represented by a kurtosis value greater than 3, means that more voxels have low activation (closer to zero) during the QPP. Likewise, having a flatter distribution, and a kurtosis value lower than 3, means that more voxels have higher activation during the QPP. With more voxels being at the extreme levels of activation, we would consider this to be a stronger QPP. Based on the hypothesis, we expected there to be a clear difference between the distributions under isoflurane and dexmedetomidine. Additionally, because isoflurane was shown to have less "intense" voxels, we expected more of the voxels to be in the "non-intense" range, leading to a narrower distribution in the histogram (**Figure 2**). The opposite was expected of dexmedetomidine scans. However, this was not always the case. Some histograms look similar to what was expected, where they have a narrow distribution for isoflurane and a flatter distribution for dexmedetomidine (**Figure 3E-F**). But there were also many histograms where this relationship between the level of intense activation and the distribution of voxel activation was not as expected. This is represented both in the individual kurtosis scores and the average values for each anesthetic (**Table 1**). The average kurtosis scores for isoflurane, dexmedetomidine, and isodex were 3.0727, 2.9477, and 3.0637, respectively, reflecting very little difference on the basis of anesthetic. These results show that the anesthetic used has very little effect on QPP strength.

To compare the number of QPPs in each group, the numbers obtained from the template correlation timecourse were used (**Figure 1A-C**). We graphed the number of timepoints above the 0.2 threshold for each scan as the number of QPPs (**Figure 4**). Because each rat was tested under each of the three anesthetics, there are three columns for each rat. When looking at each rat individually, isoflurane most often has the highest number of QPPs for said rat, with four out of the eight rats showing this pattern. But dexmedetomidine shows the highest number of QPPs for a rat only once. Isodex has the highest number of QPPs for an individual rat three times. Although isoflurane is the highest in this aspect, the gap between isoflurane and the next highest anesthetic for a rat is a marginal difference of either 1, 4, 5, or 17 QPPs. The highest number of QPPs from a rat under isoflurane is 67. These numbers are relatively small in comparison to isodex, where the highest number is 84. The lack of a consistent trend in the number of QPPs on the basis of anesthetic is further reflected by the results of a one-way ANOVA that showed the averages to be statistically insignificant ($F(2,21) = 0.38$, $p = 0.6896$).

DISCUSSION

This study has taken an important initial look at the effects of different anesthetics on QPPs. When it comes to the strength of the QPPs, the general trend was that on average, dexmedetomidine produced the strongest QPPs in both positive and negative levels of activation (**Figure 2**). For isoflurane, its average was the lowest in the number of voxels with negative levels of activation. But for isodex, the voxels with positive levels of activation ended up being in between dexmedetomidine and isoflurane (**Figure 2A**). These general trends show that, despite yielding statistically insignificant results, the different anesthetics could potentially have an effect on the strength of QPPs observed in each rodent, however, future analysis is needed to determine the effects this would have on functional connectivity and its presentation in various disease models. If a preference were to be given on which anesthetic is better to use or that reduces extraneous effects on the results of an experiment, no definitive answer can be given at this time. The data shows that there is considerable individual variability from the rats and the current sample size of testing in this project is too small to make the decision.

However, when looking at the distribution of activation levels within these QPPs, the anticipated trends were not maintained. Dexmedetomidine scans had a lot of intensely active negative and positive voxels, so we expected that the distribution across the histogram would be flatter because it contained more voxels that were within the intense activation ranges. The opposite was expected for isoflurane, that it would have a narrower distribution because there were less voxels within the intense range, so there would most likely be more near zero. However, this was only the case for two rats (**Figure 3E-F**). This analysis really highlights the individuality of the rats and makes it easy to notice particular trends in specific rats. For example, Rat 322 has a small peak in the number of voxels under dexmedetomidine in the high activation range (**Figure 3D**). This means that there are a higher number of voxels in the negative range, and this effect

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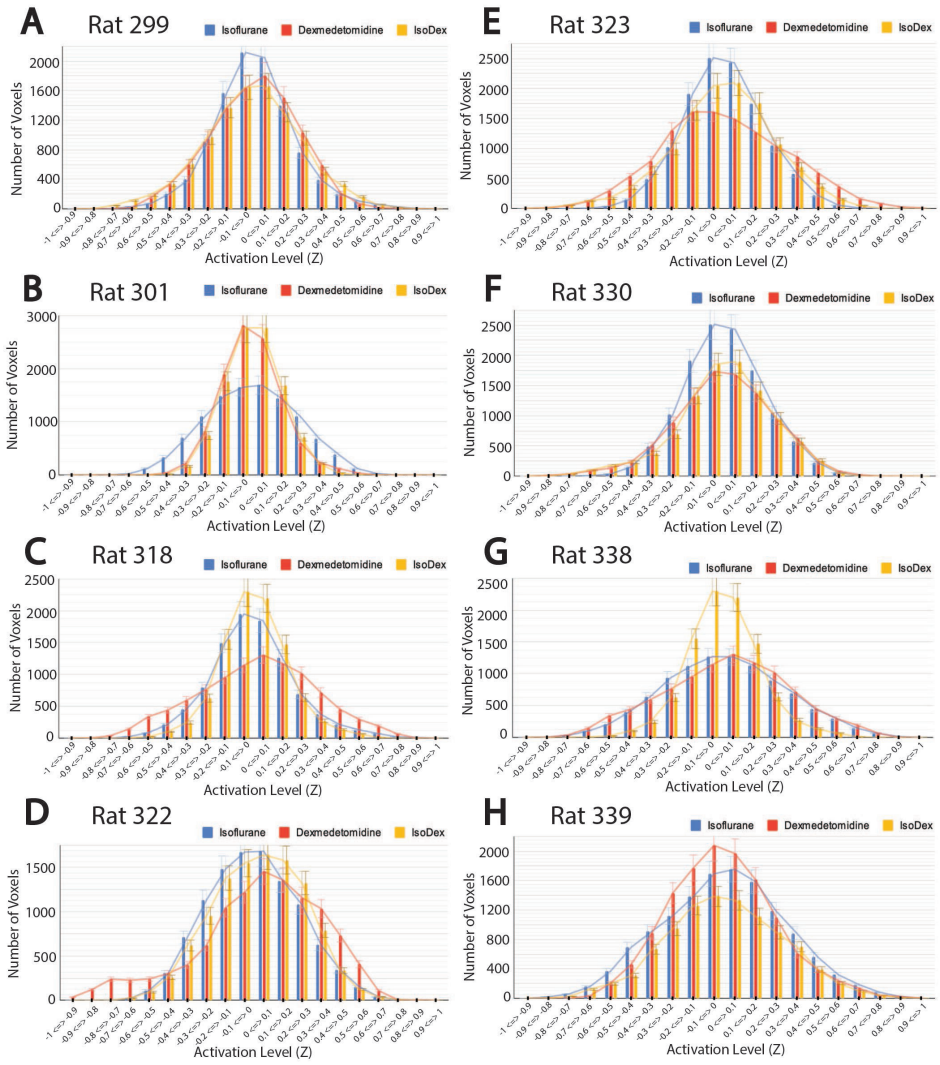

Figure 3. Voxel activation levels for each rat and anesthetic in the QPP template. Bins created with 0.10 intervals of activation levels from -1 to +1. Each panel corresponds to a different rat and displays the activation levels for the scans under isoflurane (blue), dexmedetomidine (red), and isodex (yellow). The activation values used to create this figure were extracted from the first timepoint of the QPP template observed. The error bars shown represent the percent error at 10%.

is seen in the line graph showing the number of voxels within the negative levels of activation (**Figure 2B**). So while larger trends may be apparent when looking at the overall strength of these QPPs across anesthetics, it is important to consider the role subject variability plays in these group animal studies. A future study that includes more animals would be better suited to study other properties of QPPs in more detail and observe the potential effects of anesthetics in a larger group size.

The number of QPPs for each anesthetic was also important for us to look at because while dexmedetomidine had the strongest QPPs in terms of activation levels, this was not the case when it came to the number of QPPs observed in each scan. Dexmedetomidine overall had lower numbers of QPPs for most rats. For example, for Rat 301, Rat 339, and Rat 318, dexmedetomidine had the least number of QPPs in that time span and isoflurane had the most for Rat 301, Rat 318, Rat 322, and Rat 330 (**Figure 4**).

In this study, we investigated the effects of various commonly used anesthetics on QPPs in rats. This work is important as it is known that anesthetics alter brain activity, but their effect on this particular form of brain activity was unknown. Therefore, it is important that the implications of anesthesia in this field are better understood so that the results of QPP studies in rats can be better interpreted and translated to human brain activity. The results of this study showed some inconsistent trends across anesthetics, emphasizing that these anesthetic effects should be considered when interpreting findings in rodents. Relatedly, this study also showcases the presence of individual variability within the dataset among larger group trends. Just like human beings, rats are also their own individuals. And so are their brains. Each rat was affected by the anesthetics differently. Although isoflurane scans had the highest number of QPPs in many rats, this still was not the case for all rats. This variability could have been caused not just by the general physiology

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	Rat 299	Rat 301	Rat 318	Rat 322	Rat 323	Rat 330	Rat 338	Rat 339
Isoflurane	3.8128	2.5994	3.6824	2.6867	2.9437	3.4658	2.6817	2.7092
Dexmedetomidine	2.8266	3.4467	2.5896	3.1513	2.7519	3.2292	2.5407	3.0455
Isodex	3.0823	3.0009	3.6841	2.6232	3.2296	3.4550	2.8236	2.6112

Table 1. Voxel activation level Kurtosis values. To quantify the differences observed in the voxel activation level histograms, kurtosis was measured for the activation values of the voxels for the first timepoint of the QPP **(Figure 3).** Kurtosis is a measure of how normal a distribution is, with a value of 3 indicating a normal distribution. A kurtosis value higher than 3 is indicative of a narrow distribution and a kurtosis value lower than 3 is indicative of a flatter distribution, with respect to the normal distribution.

of animal, but also the time of introduction of anesthesia and how fMRI scans can be easily affected by the smallest movements of the animal. Much like the trends observed when looking at the distribution of voxel activation within the QPPs, this further emphasizes the importance of considering individual variability when analyzing group datasets.

MATERIALS AND METHODS

Acquisition of fMRI Data

The imaging data used for this study was previously acquired on a 9.4 T animal MRI scanner by Dr. Wen-Ju Pan, a research scientist at Emory University in Atlanta, GA, USA. The protocol used to acquire this data was approved by the Emory University's Institutional Animal Care and Use Committee (IACUC). Our study did not involve any direct work with animals or the collection of any data from animals. The fMRI data used for the analysis in this study consisted of three 10-minute scans from eight male Sprague-Dawley rats, where each scan was acquired under one of the following anesthetics: isoflurane, dexmedetomidine, or a combination of dexmedetomidine with light isoflurane (isodex). During the isoflurane scans, animals were under 1.5% isoflurane via inhalation. For dexmedetomidine scans, a 0.025 mg/kg bolus of dexmedetomidine was injected subcutaneously and 10 minutes later followed by a 0.05 mg/kg/hr subcutaneous infusion of dexmedetomidine throughout the scan. For isodex scans, the same dexmedetomidine protocol was followed with the addition of 0.5% isoflurane being delivered to the animal during the scan. The preprocessing steps of these scans have been previously reported in other manuscripts that have used this dataset (22).

QPP Quantification

Quantification of the QPPs in each scan was performed using an output of the algorithm that detects the QPPs (12). As part of the QPP algorithm, a sliding window timecourse is presented, which displays the correlation values of each timepoint throughout the scan to the generated QPP template (**Figure 1A-C**). A standard threshold of 0.2 was set and all timepoints with a correlation coefficient greater than 0.2 were considered to be times at which QPPs occurred. The number of QPPs were determined manually for each scan and compared across anesthetic conditions for each rat (**Figure 4**). The figure displaying the results of this analysis was created using Google Sheets.

QPP Strength Analysis

A prewritten MATLAB script was used to visually display

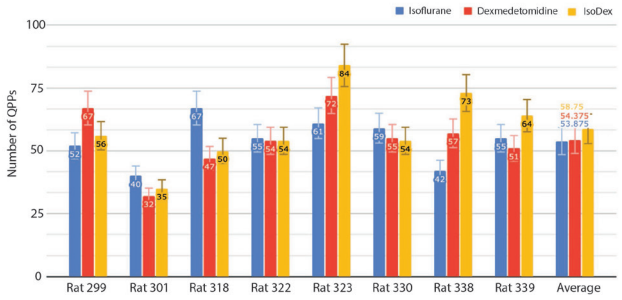

Figure 4. Number of QPPs per scan for each rat. Number of QPPs detected in each scan as generated from the prewritten MATLAB script (Figure 1). The numbers are presented for each rat's scan under isoflurane (blue), dexmedetomidine (red), and isodex (yellow). Error bars represent the percent error at 10%.

the generated QPP template used in the QPP algorithm (**Figure 1D-F**). This template depicts the activation level for the voxels over four different timepoints within the QPP. The activation level of each voxel was defined by subtracting the mean value from the activity (i.e., intensity) of each voxel and dividing it by the standard deviation (i.e., z-scoring). Additional code was written in MATLAB to quantify the number of voxels with activation levels that exceeded the determined thresholds. The threshold determining voxel activation levels to be "intense" were set to those greater than 0.5 and those lower than -0.5. The numbers of intensely active voxels were collected and used to create figures that displayed these values across rat and anesthetic as well as the distribution of activation levels for all voxels within the QPPs (**Figures 2, 3**).

Statistics

All statistical analyses, including one-way ANOVAs and kurtosis analyses, were performed in MATLAB.

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