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# Population-based beat-to-beat QT analysis from Holter recordings in the Long QT Syndrome

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## Abstract

The increasing dissemination of wearable ECG recorders (e.g. Holter, patches, and strap sensors) enables the acquisition of large amounts of data during long periods of time. However, the clinical value of these long-term continuous recordings is hindered by the lack of automatic tools to extract clinically relevant information (other than non-sinus and life-threatening rhythms) from such long-term data, particularly when targeting population-based research. In this work, we propose and test a new tool for analyzing beat-to-beat interval measurements and extracting features from Holter ECGs. Specifically, we assess the adaptation of the QT interval following sudden changes in heart rate in the primary long QT types (1 & 2). We find that in long QT syndrome type 2, certain QT adaptation patterns can indicate a higher risk for cardiac events.

## Introduction

The long QT syndrome (LQTS) is associated with an increased risk for cardiac events, and the literature well describes the various genotype-phenotype associations within the various types of mutations of this syndrome [1]. The standard clinical use of Holter recordings is limited to arrhythmia detection and quantification, and is not usually prescribed in patients suspected with the syndrome. Personal or family history of cardiac events and presence of a prolonged QTc interval on a standard 12-lead ECG are the foundations of a LQTS diagnostic. The analyses of ambulatory Holter ECGs are rather scarce in the LQTS despite the convincing findings about mutation-specific triggers of cardiac events [1]. The reported categories of investigated triggers are exercise, emotion, arousal, and sleep. Clinical investigations clearly

demonstrate that LQT2 subjects are more prone to experience events at sleep, while LQT1 subjects experienced events during exercise. Therefore, regulation of the QT interval and its adaptation to heart rate have been revealed as major arrhythmogenic mechanisms in the LQT1 [2] and the LQT2 syndrome [3].

Ambulatory Holter recordings contain, in general, a broad spectrum of heart rates. In this work, we extract QT variability and heart rate adaptation information from Holters of LQTS patients. We hypothesize that these measurements will deliver insights into the propensity of a patient to cardiac events. In our study, we designed and implemented novel computerized tools for extracting, quantifying, and presenting arbitrary measurements from Holter ECGs. We used this system to analyze beat-to-beat patterns of the QT interval from a large collection of Holter recordings. The comparisons were grouped by gender, LQTS genotype, and presence of cardiac events.

## Methods

### Data source

Holter ECG recordings and clinical information from healthy subjects and LQTS patients were extracted from the THEW initiative [4] and an NIH-funded study [5] conducted at the Heart Research Follow-up Program (Rochester, NY). We used a set of 192 Holter ECGs collected from healthy subjects, 138 Holters from subjects with LQT1, and 97 from subjects with LQT2. All available Holters from these studies were used, with the exception of subjects with pacemakers.

## Analyzing QT and RR intervals on a beat-to-beat basis

The Holters were annotated on a beat-to-beat basis using a validated computerized method [6] which delivered for each cardiac beat the RR interval, QT and QTpeak intervals, and other T wave morphology measurements. Measurements in the LQTS subjects were manually adjudicated during their original study. These Holter beat-to-beat measurements, along with clinical information (demographics, RX, and event history), were organized in a database system as shown in Figure 1. Using this system, we investigated how QT adapts to sudden changes in RR in the healthy, LQT1, and LQT2 subjects, while also investigating gender differences in these groups.

## Population-based assessment

Figure 1 shows the workflow we used to analyze beat-to-beat Holter annotations. The individual Holter annotations were converted to SQLite database files. These databases don't contain any new information, but make the existing measurements easy to sort, filter, search, or perform computations on. Pointers to the annotation databases are stored in a main database, which also contains tables of clinical information for each patient, and links the patients to their Holter annotations. Through a web interface, we are able to select Holters of interest based on patient characteristics (age, symptoms, etc.), and generate statistics from the Holter annotations of these patients. The web interface also includes a tool for creating ECG clocks [7] of any measurement in any population.

## Measuring instantaneous adaptation of QT intervals to heart rate

We extracted beat-to-beat  $\Delta$ QT and  $\Delta$ RR measurements from all Holters in the database, in order to compare their distributions between subjects who had a history of LQTS-

related symptoms and those who did not.  $\Delta QT$  and  $\Delta RR$  were computed as the changes in QT and RR compared to the previous heart beat, and QT was measured on the lead with the maximum average T wave amplitude (over the whole recording). Action potential duration may not fully adapt to a change in pacing rate for 2-3 minutes, but it does show some response instantly [8]. This partial, immediate change is what we hope to capture with our simple measurement of  $\Delta QT$  and  $\Delta RR$ . Each  $\Delta QT$ - $\Delta RR$  pair (i.e. each beat) will fall into one of the regions illustrated in Figure 2. We defined an area in this  $\Delta QT$ - $\Delta RR$  plane that we expect to be associated with high risk for cardiac events:

$$\Delta QT > 0.5\Delta RR + X \quad (1)$$

where X is a threshold such as 40ms. We arbitrarily considered this threshold to define abnormal QT responses that could be associated with an increased risk for triggering arrhythmias, shortening of the TQ interval. The factor of 0.5 was chosen empirically to roughly preserve the ratio of QT to RR for typical values. If, for example, RR decreases by 20ms, QT only needs to decrease by about 10ms to compensate. To enforce something different, such as stable beat-to-beat QTc, the scale factor could be changed to e.g. 0.2. We measured the percentage of beats satisfying Eqn. 1 in different groups of patients, and refer to this measurement as "PBX" (e.g. "PB40" for X=40ms). We expect patients with more beats in the defined region, i.e. with a high PBX value, to be more likely to have cardiac events. Beats flagged as 'unstable' by the annotation algorithm were excluded from the analysis.

## Statistical Analysis

Within each genotype-gender strata, percentages of heart beats satisfying Eqn. 1 were compared between subjects with and without a history of cardiac events using the nonparametric Kruskal-Wallis test. Further, the logistic regression model was used to estimate

odds ratios in the prediction of the existence of at least one cardiac event for genotype-gender strata.

## Results

### Study Population

The study population is described in Table 1, including gender, age, presence of beta-blockers at the time of the Holter recording, and presence of symptoms (at any time). There were no statistical differences in age ( $p=0.97$ ), gender ( $p=0.71$ ), beta-blocker treatment ( $p=0.36$ ), or symptoms ( $p=0.56$ ) between the LQT1 and LQT2 cohorts.

	LQTS type 1 n = 138	LQTS type 2 n = 97	Healthy n = 192
Gender (M/F, % female)	37/101, 73%	29/68, 70%	95/97, 51%
Age (years)	33±14	33±14	38±16
Beta blockers (%)	72%	69%	
Symptoms (%)	67%	71%	

Table 1: Study population. All recordings contain at least 15,000 heart beats. N represents the number of recordings. In LQT1, there were 127 unique subjects, and in LQT2 there were 83 unique subjects.

### Measuring rapid adaptation of QT intervals to heart rate change

In Figure 3, we present the  $\Delta\text{QT}$ - $\Delta\text{RR}$  density plot of beats in several cohorts to visually identify patterns specific to LQT2 patients with ( $n=72$ ) and without ( $n=29$ ) events. In the subjects without events,  $\Delta\text{QT}$  and  $\Delta\text{RR}$  appear to be somewhat correlated. In subjects with

events, the correlation breaks down. In particular, subjects with events have increased  $\Delta$ QT- $\Delta$ RR variability in the top left and bottom right quadrant, revealing a stronger lack of QT adaptation to previous RR. We focus our analysis on the beats in the top left quadrant, i.e., where there is a lack of QT shortening following heart rate acceleration. In Table 2, we report the percentage of beats present in a region where  $\Delta$ QT is much longer than  $0.5 \cdot \Delta$ RR. The marker suggested by Eqn. 1 seems to be valid in LQT2 males, while this difference in QT response to RR was not present in LQT2 females or LQT1 subjects (and hence LQT1 was not plotted in Figure 3).

	n	Events (%)	No events (%)	p value
Healthy	192		2.6 $\pm$ 2.8	
male	95		2.3 $\pm$ 2.2	
female	97		2.9 $\pm$ 3.3	
LQT1	138	3.8 $\pm$ 3.2	4.2 $\pm$ 3.7	0.968
male	37	2.7 $\pm$ 2.3	2.5 $\pm$ 1.9	0.949
female	101	4.2 $\pm$ 3.4	4.8 $\pm$ 4.1	0.896
LQT2	97	9.3 $\pm$ 6.8	5.9 $\pm$ 4.2	0.027
male	29	11.5 $\pm$ 7.1	4.4 $\pm$ 4.1	0.002
female	68	8.5 $\pm$ 6.4	6.9 $\pm$ 4.0	0.666

Table 2: Percentage of heart beats (avg $\pm$ std) with  $\Delta$ QT >  $0.5\Delta$ RR+50msec (i.e. PB50). p values compare subjects with and without a history of cardiac events.

We computed gender-specific logistic regression models for LQT2 patients. In males, using PB40 as the single input parameter yields a model with a C-statistic of 0.8 (C=0.8). As expected, the parameter reached significance (OR: 1.2, 95% CI: 1.0-1.4, p=0.047), implying that for males with LQT2, the odds of experiencing an adverse cardiac event was 20% higher for each additional 1 percentage point increase in PB40. However, the same parameter by itself



did not yield a significant model in LQT2 females ( $p=0.498$ ). When considering multivariate analysis, two input parameters were used: PB40 *and* PB50. The resulting model for LQT2 females had  $C=0.8$ , and both parameters reached significance ( $p<0.001$  for both). Interestingly, OR for PB40 was 0.28 (95% CI: 0.13-0.60), while OR for PB50 was 4.65 (95% CI: 1.9-11.4). That is, the parameters, though both intended to be indicative of high risk for events, are associated with *opposite* effects on the outcome (history of events), possibly indicating that  $X=50\text{ms}$  was an especially high risk threshold.

## Discussion

The access to beat-to-beat measurements of the heart rate (RR intervals) and QT intervals over prolonged periods of time (24 hours) delivers new insights into the QT/RR relationship that may not be observed in a conventional clinical setting or protocol [9]. Most reported analysis of QT-RR dynamics studied the slope of this relationship as an independent marker of risk [2, 10], while the analysis of the response of QT to previous RR has been primarily directed toward the modeling of the QT hysteresis effect [11] to reveal abnormal regulation leading to arrhythmogenesis.

In our work, we hypothesized that the LQTS patients with events have a higher occurrence of abnormal beat-to-beat responses to heart rate variations, setting up the stage for arrhythmogenic cascade. We designed the proposed method to measure this lack of QT adaptation in LQTS patients. The computer tool developed here provided a quantitative measure of the number of beats (or percentage of beats, in reference to one full-day recording) associated with an abnormal response of QT to heart rate (Figures 2 and 3).

In the LQT2 syndrome, patients may have propensity to develop arrhythmias at rest and following strong emotion, i.e., when their heart rate is vagally driven, and slow heart rate leads to pronounced QT prolongation and therefore more propensity to arrhythmia-triggering following

heart rate changes. For this reason, we expected our technique to work well at identifying the LQT2 patients with a history of events. Our results confirm this hypothesis for males, while in female LQT2 patients this observation was less clear (see Table 2). Kim et al. [3] showed that LQT2 female patients had a higher probability of cardiac events triggered by arousal than males, but the susceptibility to this trigger was modulated by the location of the mutation (pore, transmembrane, etc.). More investigation of the phenotype-genotype association in our cohort of patients could help explaining the observed gender differences.

In LQT1 patients, exercise is the primary trigger for life-threatening arrhythmias. Sustained increased heart rate and a lack of adaptation (shortening) of the QT interval duration could degenerate into life-threatening ventricular arrhythmias. However, in our study, we did not find any statistical difference between LQT1 patients with and without events. The logistic models we tested also did not reveal any association between our ECG measures and the presence of events. This may be explained by the lack of high heart rates captured in the LQT1 Holters used in this study, for which the upper quartile of HR did not exceed 110bpm in any subject.

In future work, we will experiment with other measures of  $\Delta QT$  and  $\Delta RR$ , e.g. taking a longer RR history into account, including ectopic beats in the analysis, or utilizing different features (such as symmetry) of the 2D distributions we already computed. We will also be improving the HEQS system to make it more accessible to all types of users, which will allow the Holter database to be used for other studies such as ischemia and arrhythmia detection. For clinicians who are unfamiliar with SQL queries, visual query building tools such as Metabase [12] would be welcome additions to the system. For all users, storing frequently-used queries and database views can make the learning and query building processes much faster. Ideally, most common tasks will be possible through a point and click interface, without explicitly writing full queries.

## Conclusions

We have developed a unique tool for the investigation of long-term ambulatory ECGs. This tool enables easy presentations of arbitrary ECG features using various novel visualizations with beat-to-beat resolution. We then presented an example based on QT interval adaptation in patients with the long QT syndrome, for the purpose of risk estimation. This study required the extraction of beat-to-beat  $\Delta QT$  and  $\Delta RR$  values from over 400 Holters, or approximately 50 million heart beats. Calculating the percentage of beats satisfying  $\Delta QT > 0.5\Delta RR + X$  revealed significant differences between LQT2 males with and without cardiac events using  $X=50ms$  ("PB50"), and measurement at multiple thresholds (PB40 and PB50) revealed differences in LQT2 females with and without events.

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## Figure Captions

### Figure 1

High-level overview of the Holter ECG Query System (HEQS). This tool enables the analysis of individual Holter ECGs as well as population-based data mining.

### Figure 2

$\Delta$ QT- $\Delta$ RR plane with four areas defining categories of cardiac beats as “adapting” or “not adapting” to HR. Beats with  $\Delta$ QT- $\Delta$ RR values falling into the green areas are associated with QT following expected adaptation to heart rate. Beats in the top left (red area) are expected to increase risk for cardiac events, as QT is getting longer while RR is getting shorter. The central dark gray region includes  $|\Delta$ QT| and  $|\Delta$ RR| < 10 msec; beats in this region were neglected in our analyses.

### Figure 3

#### Subcaptions

(a) Healthy, n=194

(b) LQT2 w/o events, n=29

(c) LQT2 w/events, n=72

#### Main caption

Figure 3: Heat map of  $\Delta$ QT- $\Delta$ RR measured in three different cohorts. Red indicates many beats had a given  $\Delta$ QT- $\Delta$ RR relationship, and blue indicates very few beats did. The region in which  $\Delta$ QT and  $\Delta$ RR varied by <10ms was cropped from the center of each plot, as beats with very little change in QT or RR are not expected to carry useful information. The white dashed lines represent  $X=40$ ms and  $X=50$ ms in Eqn. 1. Resolution is limited by the relatively low sample rate of our Holters (180-200Hz). Six short-duration Holters (<15,000 beats) were included in these plots.

Figure 1

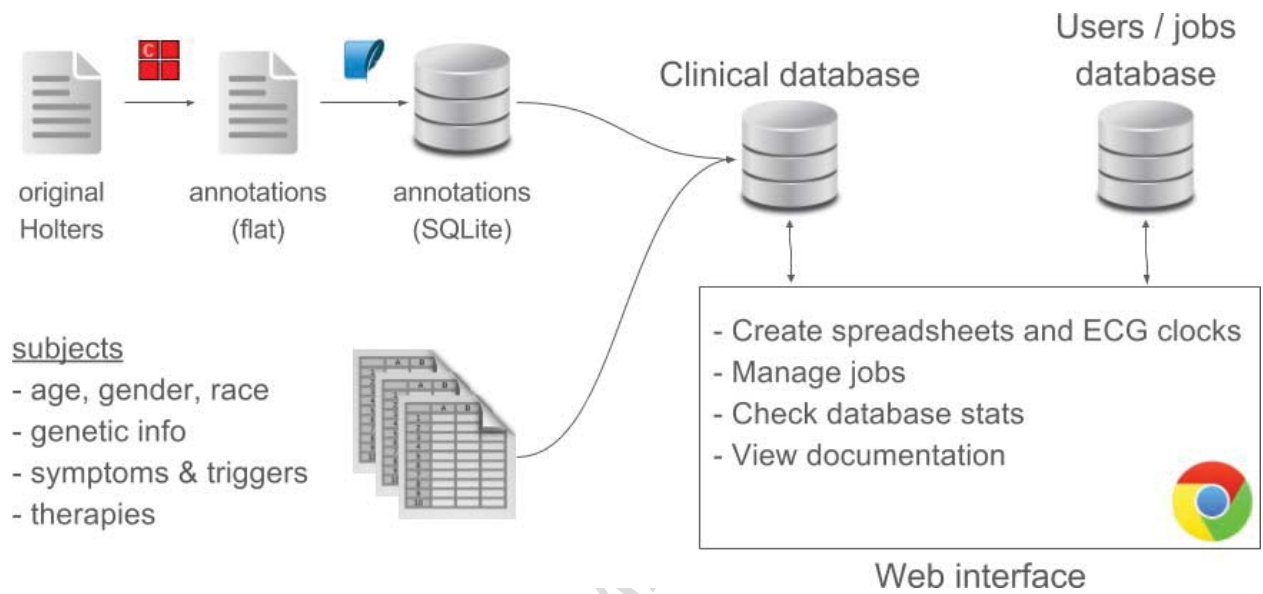


Figure 2

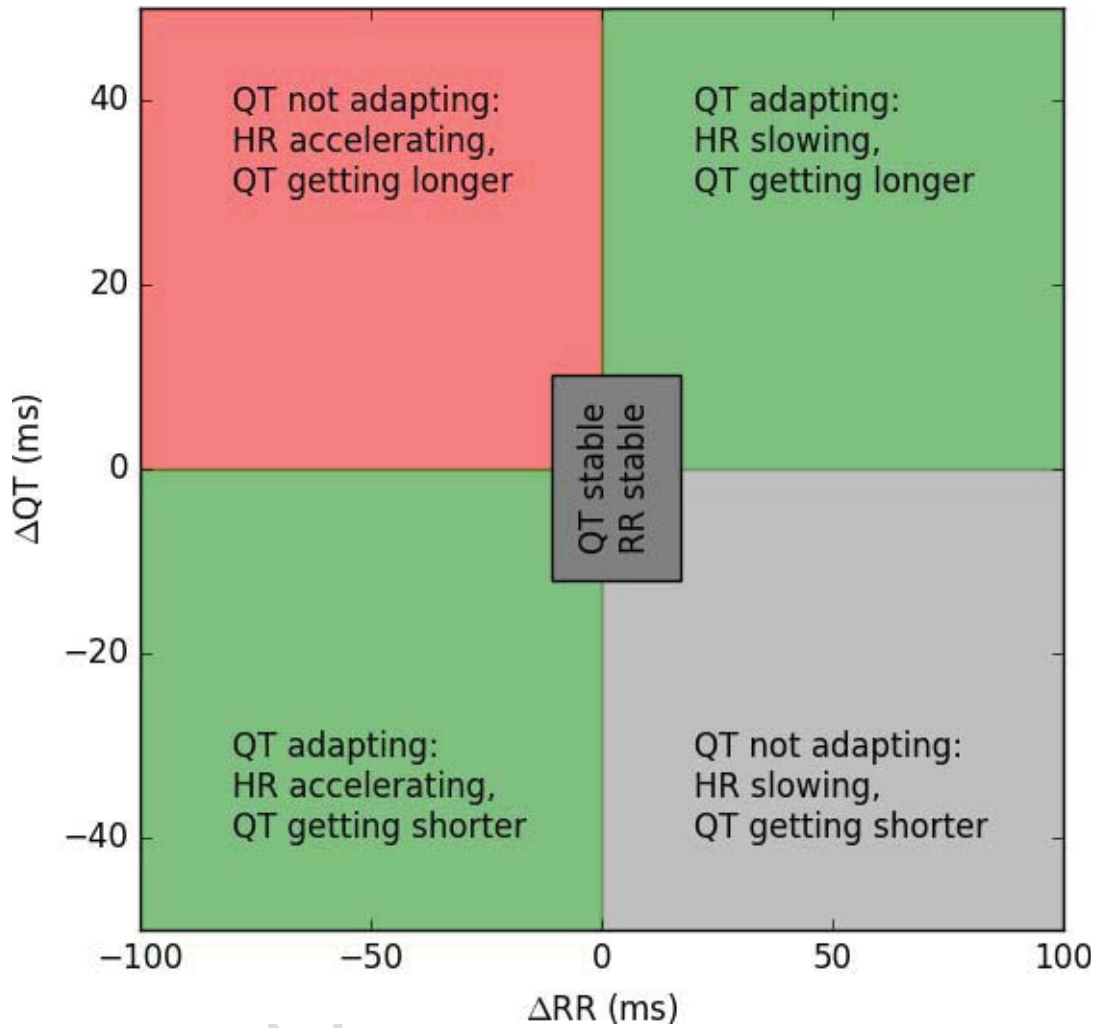




Figure 3A

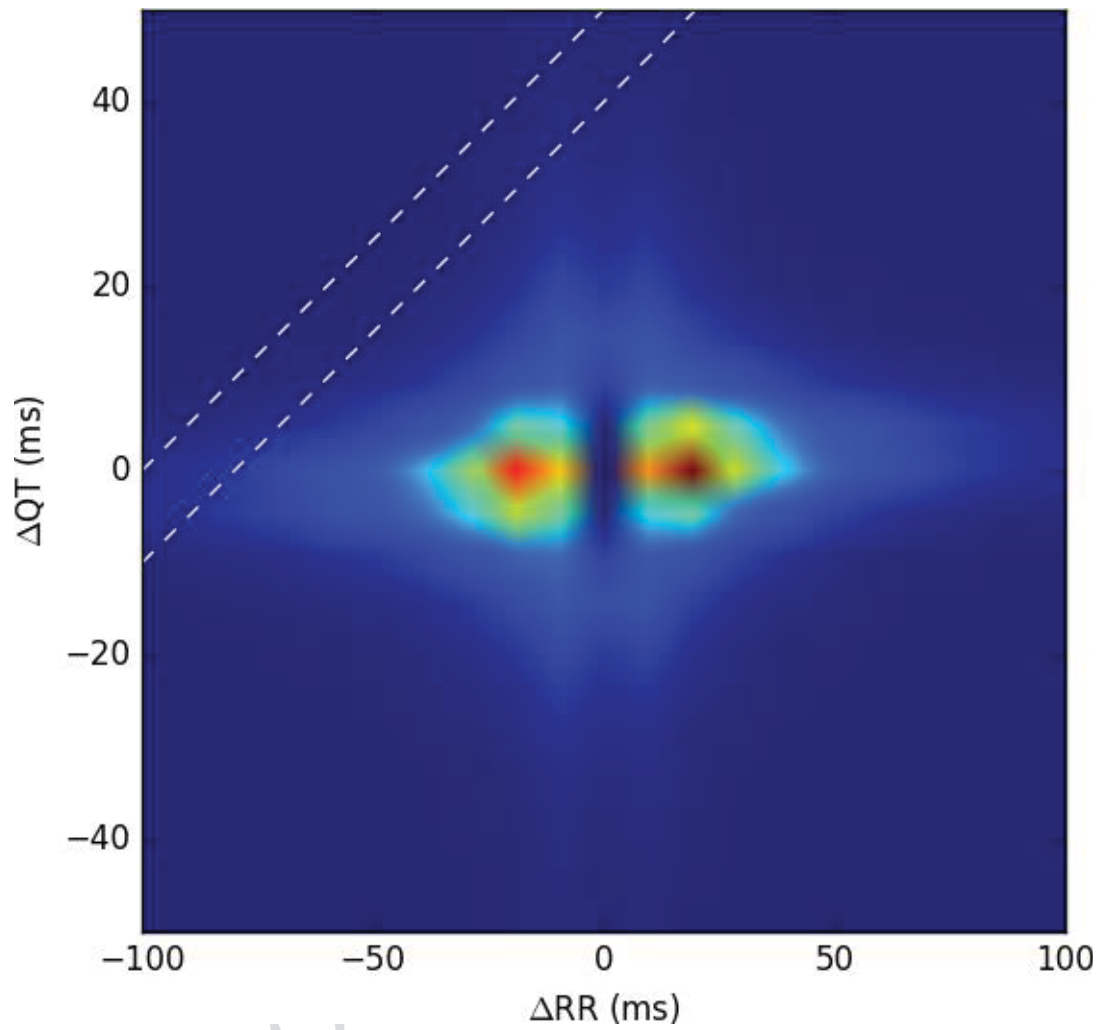


Figure 3B

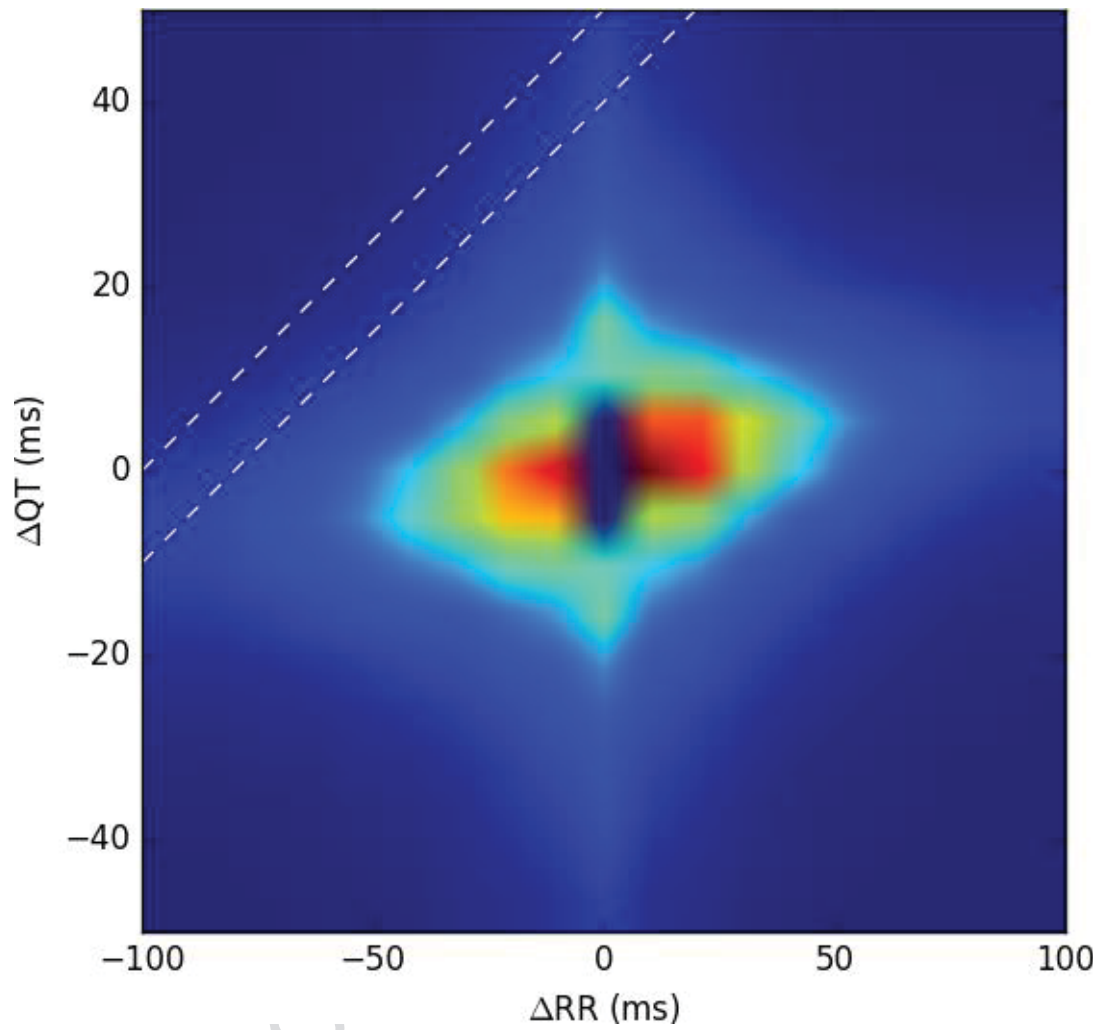


Figure 3C

