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REFERENCING SCHEMES AND THEIR EFFECT ON OSCILLATIONS AND BROADBAND POWER SPECTRAL SHIFTS IN STEREOELECTROENCEPHALOGRAPHY

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ABSTRACT: Choosing a referencing scheme for stereoelectroencephalography (SEEG) is complicated by the varying depth of contact locations and, consequently, the different tissue that is being recorded from. In order to better understand how changes in electrophysiology related to movement are affected by the choice of reference, we examined how 16 different referencing schemes effected alpha (8 - 13 Hz) and beta (13 - 30 Hz) oscillations and high-frequency broadband (HFB) power (65 - 115 Hz). We found the choice of referencing scheme has more complicated effects than previously described and recommend using different referencing schemes as a methodological tool to optimize brain-computer interface (BCI) performace.

INTRODUCTION

Stereoelectroencephalography (SEEG) measures electric potential as a differential between two voltage measurements, a reference and a recording, like all methods of measuring electric potential. SEEG recording contacts are implanted so that each contact is typically in a different layer of gray matter, in white matter or in a subcortical structure whereas electrocorticography (ECoG) contacts are placed above the dura usually mostly covering a small number of gyri. This causes SEEG to have relatively large variations in the statistical properties of the signals because of different brain-to-electrode impedance from the relative lipid contact in the tissue, compartmentalization of intracellular & extracellular solutes and formation of a fluid sheath around the SEEG shaft as well as sampling brain areas with more diverse cytoarchitecture and functional specialization.

In order to study the effects of referencing on SEEG recordings, we focused on well-replicated results; spatially focal high-frequency broadband (HFB) power increases in primary motor cortex, beta (13 - 30 Hz) power decreases across much of primary motor cortex and alpha (8 - 13 Hz) power changes (increases and decreases) during movement [1] [2] [3]. HFB changes are theorized to facilitate action selection and gate action selection respectively [4]. HFB has been shown to be closely correlated with increases in firing rates in single units [5] and beta oscillations have been shown to be modeled accurately as traveling waves [6]. Alpha power changes related to movement-related in primary motor cortex are not as well understood but likely relate to the mirror neuron system [7]. Although the function of this rhythm is not as well described, it is observed reliably. Thus, the electrophysiological characteristics of these signals are relatively well understood, so we chose them to compare the effect of different referencing schemes. Previous work has explored how a subselection of these referencing schemes effect HFB and alpha (8 - 12 Hz) movement-related signal and found that more local rereferencing methods, like bipolar and Laplacian rereferencing, increased decodability of oscillations whereas more global rereferencing, like common average referencing, increased decodability of HFB [8]. In this study, we explored why this tradeoff occurs and how including other rereferencing strategies can give us a fuller picture in order to inform reference selection for brain-computer interface (BCI) applications.

MATERIALS AND METHODS

Ethics Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Mayo Clinic under IRB number 15-006530, which also authorized sharing of the data. Each patient/representative voluntarily provided independent written informed consent to participate in this study as specifically described in the IRB review (with the consent form independently approved by the IRB).

Patients: Thirteen patients (6 females, 11 - 20 years of age) from Mayo Clinic were included in this study. These data are publicly available from a previous publication [9]. These patients underwent placement of 10 - 20 sEEG electrode leads to characterize epileptogenic brain areas

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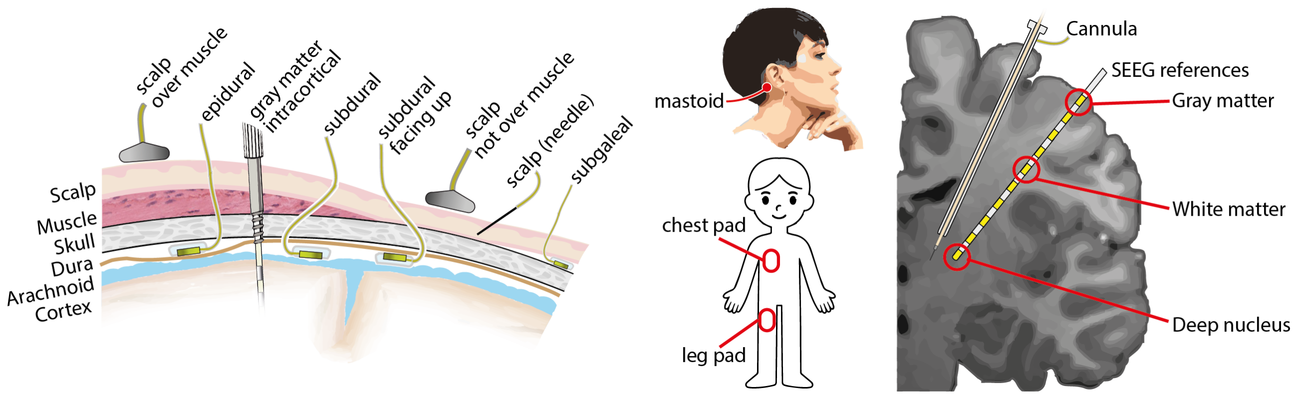

Figure 1: Native referencing options during SEEG recordings. Generally, the aim is for the reference to have the same environmental electrical noise so that it is removed by the differential amplifier. If the reference contains signal, such as from the brain or muscles, this signal will be present in all recording channels, so an electrically inactive location is ideal.

for treatment of drug-resistant partial epilepsy.

Task: Patients were visually cued to move their hand, tongue or foot for three seconds alternated with the same period of rest as in [9]. The task was administered using BCI-2000 [10].

SEEG Recording: The data was recorded with a g.HiAmp amplifier (gTec, Schiedlberg, Austria). Recordings were sampled at 1,200 Hz including electromyography (EMG) measured from the forearm flexors/extensors (hand), base of chin (tongue) and anterior tibialis (foot).

Referencing: SEEG data was recorded with a native reference as close to the recordings as possible to eliminate common noise. Of the common choices for referencing online recordings shown in Fig. 1, we chose a low-amplitude white matter contact since it has the same electrical environment as the other recording contacts, does not have signal from muscle activation and has low-amplitude neural signal. After the signal was recorded, a new reference signal was generated in 16 different ways:

1. Native: the original white-matter reference
2. Average: an average of all the channels (Fig. 2a)
3. Lead average: an average of all channels on a single lead (Fig. 2a)
4. Headbox average: an average of all contacts being amplified by the same headbox (Fig. 2a)
5. Bipolar: the next neighboring contact (Fig. 2a)
6. White matter: the average of all contacts predominantly located in white matter (Fig. 2b)
7. Laplacian: the average of two neighboring contacts or the single neighbor for the ends of the electrode
8. Position: the weighted average of two contacts on either side or as many as there are (Fig. 2c)
9. Distance: the average of all the contacts weighted by the distance to the recording contact (Fig. 2d)
10. Low PSD: an average of the 50% of contacts with power spectral density (PSD) below 45 Hz most frequency below the mean PSD (Fig. 2e)
11. Low RMS: an average of the 50% of contacts with the lowest root mean square (RMS) amplitude (Fig. 2f)
12. Low PSD per lead: same as low PSD but per lead
13. Low RMS per lead: same as low RMS but per lead
14. Low PSD per headbox: same as low PSD but per headbox
15. Low RMS per headbox: same as low RMS but per headbox
16. PCA: the first (largest) principal component using all channels as observations and samples over time as features (Fig. 2g)

Locality analysis: In order to determine how much each re-referencing scheme caused correlation between channels, or spread the signal, Pearson's r was computed on the time-series data. We report the median Pearson's r correlation across samples aggregated by epoch, including both movement and rest periods, from -500 ms to 1500 ms relative to the start of the period.

Movement-rest analysis: The time-series data was converted into power spectral density using Welch's method with 1024 points per segment and a 75% window overlap between segments using Hann windowing. An activation r^2 metric was computed as in [9] using the following equation:

$$r^2 = \frac{(\overline{m} - \overline{r})^3}{|\overline{m} - \overline{r}|\sigma^2_{m \cup r}} \frac{N_m N_r}{N^2_{m \cup r}}$$

where $\overline{m}$ is the mean PSD for movement, $\overline{r}$ is the mean PSD for rest, $\sigma_{m \cup r}$ is the variance of both movement and rest PSDs and N_m, N_r and $N_{m \cup r}$ are the number of movement epochs, rest epochs and the combined sum, respectively. This signed metric to quantifies the difference between the mean of the movement PSDs across epochs

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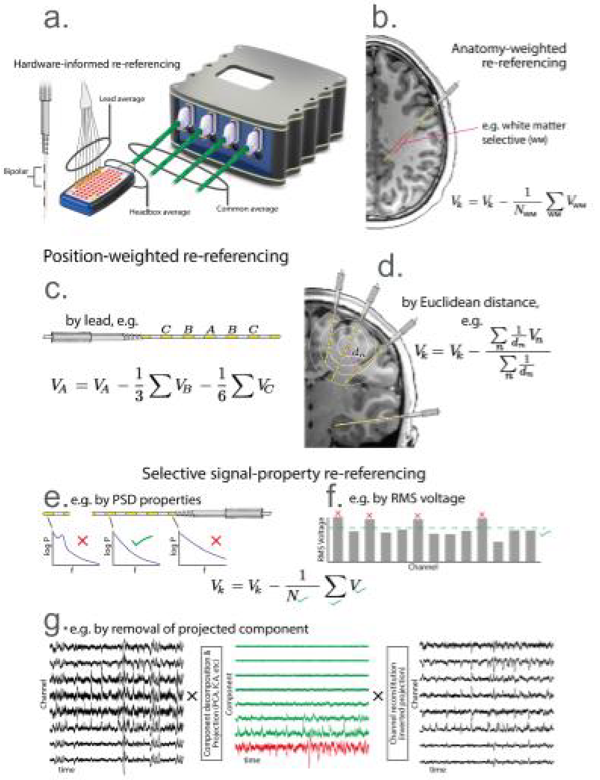

Figure 2: Many of the re-referencing options for after the recording has been digitized. Average and bipolar referencing tend to be used more commonly but there are many other options.

compared to mean rest PSDs across epochs relative to the variances of PSDs across epochs of movement and rest seperately. Power spectral density was averaged in 5 Hs bins. The best r^2 in the alpha, beta and HFB ranges for were then found separately for each patient and effector (hand, tongue and foot). Time-series data were also filtered with a fourth order Butterworth 2 Hz on either side of the peak oscillation frequency for beta and from 65 to 115 Hz in bandwidths of 10 Hz for HFB to visualize the time-course of changes observed in the PSDs.

RESULTS

SEEG contacts that were modulated with movement generally had the pattern of an increase or decrease in alpha power, decreased beta power and increased HFB during movement, as shown in Fig. 3. Power decreased in some recording contacts in every patient in the beta range (Fig. 3, gray box), where blue indicates a decrease in power during movement relative to rest. Similarly, power increased in the HFB range (Fig. 3, black box) for some recording contacts in every patient, where the yellow color indicates an increase in power during movement relative to rest. The number of contacts with beta power decreases was more than the number of contacts with HFB increases. Alpha power changed for at least one contact in every patient as well (Fig. 3, white box) but was less consistent in direction. The patterns of spectral differences were similar between average and bipolar references, and this was generally the case for all re-reference schemes.

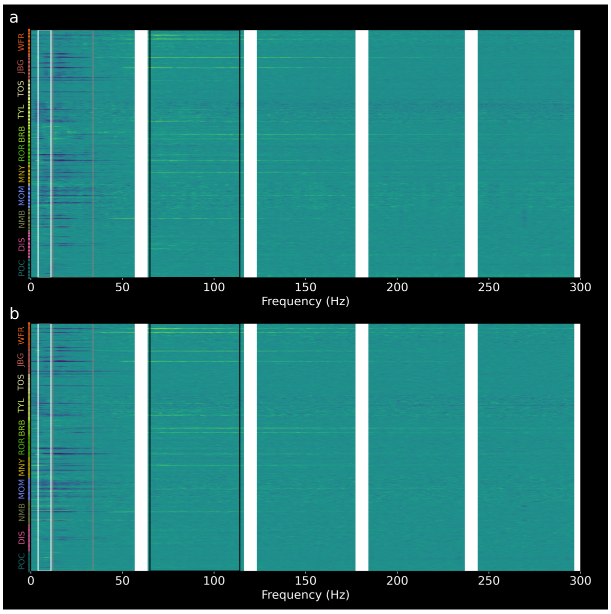

Figure 3: r^2 activation maps of the signed ratio of the difference between the mean PSD across epochs of movement and rest relative to the variance unique to movement and rest for average (a) and bipolar (b) references. In both references, there are contacts with beta power decreases during movement and high-frequency broadband power increases during movement but only at electrode contacts positioned at brain areas that are modulated with hand movement. The all the recording contacts for all patients are shown on the y-axis with each electrode shaft striped using alternating dark-light colors. The frequency of the PSD is shown on the x-axis, with boxes around alpha in white, beta in gray and HFB in black.

We found that more local re-referencing methods, such as bipolar and Laplician, had lower correlations between channels while more global re-referencing methods, such as using an average reference, had greater correlations. Here, we are referring to referencing schemes that include more recording contacts in the signal used as a reference for a given contact as more global and referencing schemes that include fewer contacts as more local. The greater amount of yellow off the diagonal in each of the plots in Fig. 4a is summarized as an average in Fig. 4b. Laplacian and bipolar referencing schemes had the least correlation between recording contacts and that correlation was near the diagonal suggesting that neighboring contacts on the same electrode shaft contributed most to that correlation. Average referencing had an intermediate amount of correlation between channels which was spread out less near the diagnonal than Laplacian and bipolar correlations, suggesting that the signal spread was less local to an electrode shaft. Native referencing had by far the most correlation between recording contacts, including relatively large correlations between contacts on different electrode shafts, suggesting that signal from the

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chosen white matter reference contact was largely present in all of the recording contacts.

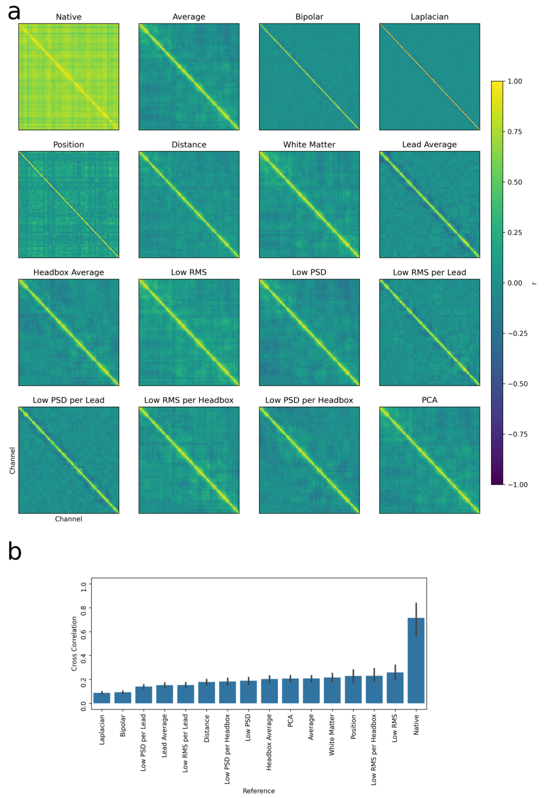

Figure 4: a. Correlation plots between channels computed pairwise are shown for each referencing scheme. The autocorrelation on the diagonal is always one. Off the diagonal, correlation implies that recording contacts are detecting the same source so minimizing this increases the specificity of the location of the source of the signal when interpretating the data. b. The average off-diagonal correlation across patients.

Next, we quantified how referencing schemes effected r^2 values in the alpha, beta and HFB ranges across the patients and for the three different effectors (hand, tongue and foot) as shown in Fig. 5. The recording contact with the most movement-related modulation was determined using the maximal absolute value r^2 in the frequency range of each spectral feature. The mean of all these values across references was then subtracted from each r^2 to get δr^2. We found movement related changes in the oscillatory frequencies, alpha and beta, were better detected by more local referencing schemes (Fig. 5a and b). More global referencing schemes, on the other hand, better differentiated movement-related changes in HFB (Fig. 5c). However, was considerable variation across patients and effectors; bipolar or Laplacian referencing was not the best choice for detecting oscillations in many cases (different patients and effector combinations) and average referencing was not the best choice for detecting HFB in many cases.
We looked into the effect of the referencing scheme on beta and HFB power using data from an example patient (Fig. 6). As shown in Fig. 6a, the HFB increase that peaked immediately after movement onset was maximal at the fourth most superficial contact. The neighboring contacts also had a peak in HFB, causing the bipolar reference to diminish this HFB increase after movement. In Fig. 6b, beta oscillations were observed to constructively interfere at the contact with the greatest movement-related changes before the movement onset and descructively interfere during the movement. The result was that bipolar referencing caused the difference between beta power before movement (during the rest period) to have a larger difference compared to beta during the movement. In Fig. 6c, the amount of time shown is reduced to show few enough cycles that the phase can be seen. The opposite phase in the recording contact most modulated by movement compared to the neighboring contact, shows the constructive interference increasing beta power during rest for bipolar referencing.

DISCUSSION

For each patient and effector, there was a relatively local source of HFB activity during movement and a relatively diffuse distribution of alpha and beta oscillations during rest as previously described [2]. This was generally best captured using bipolar or Laplacian referencing for oscillations and average referencing for HFB. This was because, when the recording contact was positioned in line with the source of the activity, oscillations constructively interfered, increasing the signal-to-noise ratio. HFB, on the other hand, does not interfere like oscillations do and so was better captured by an average reference scheme. There was considerable variability depending on position of the recording contact and the tissue types of each contact and its neighbors. These differences cause different referencing schemes to be preferred and dispreferred in a pattern that is unique to each case, suggesting that referencing is a tool that can be used to optimize the detection of signal in the data by compensating for some of these effects, especially in applications such as BCI where interpretation of the signal is secondary to performance.

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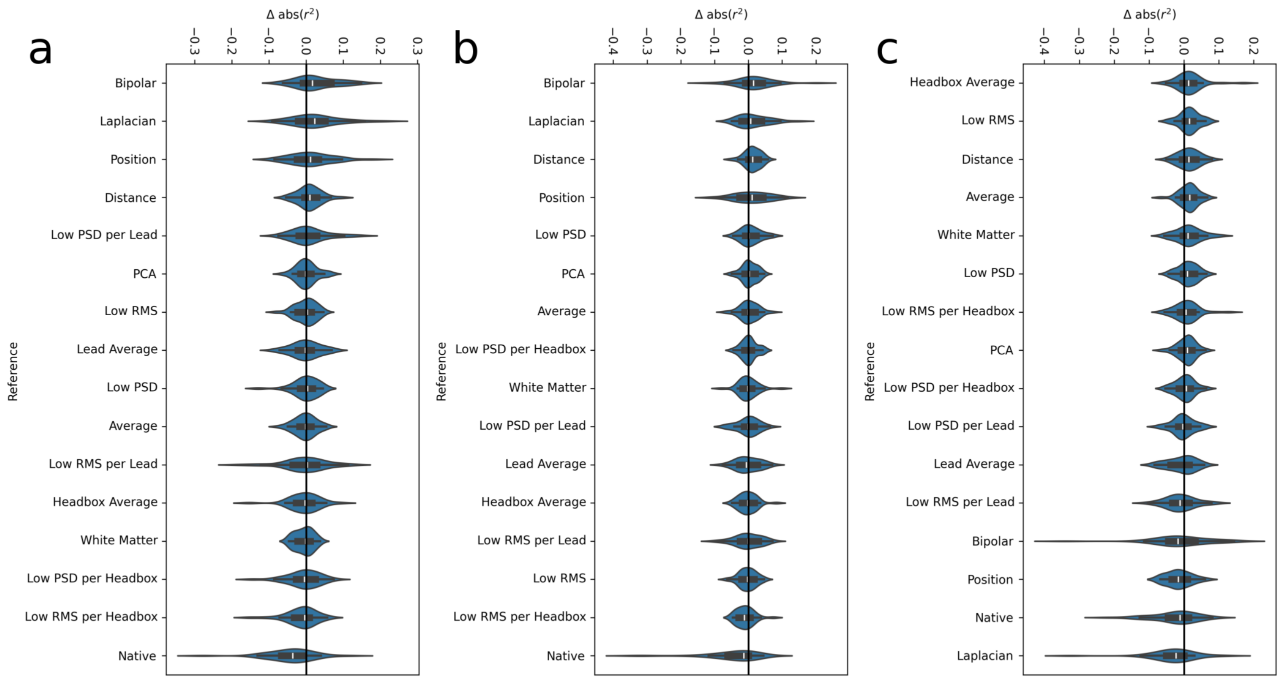

Figure 5: The change in r^2 metric for different referencing schemes are shown for alpha (a), beta (b) and HFB (c). More local referencing strategies such as bipolar and Laplacian cause larger differences between the rest and movement conditions, as measured by r^2 for oscillations (alpha and beta). More global referencing schemes, such average referencing, cause larger differences for HFB. However, there is such great variability between patients and effectors such that this approach is not optimal in many cases.

CONCLUSION

There is considerable variability in the r^2 activation metric between patients and effectors compared to the variability between referencing strategies. We interpret this to be due to effects of the position and orientation of the electrode recording contacts relative to neural sources of activity which depend on the trajectory of the electrode shaft and the micro-organization of the brain. In general, using Laplacian or bipolar referencing to study oscillations and average referencing to study HFB yields better signal-to-noise, however, this is not the case much of the time so referencing strategy should be used as a tool to optimize data interpretation.

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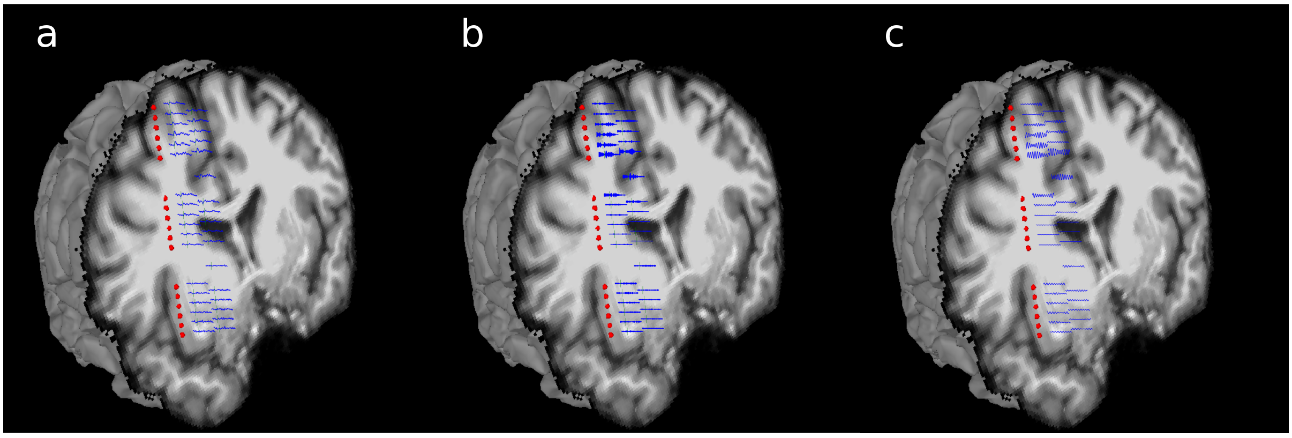

Figure 6: a. HFB activity around movement onset (green vertical line) for an example recording. Activity using an average reference is shown to the right of the recording contacts (red spheres). HFB with a bipolar reference is shown to the right of that, interleaved between the two contacts being referenced. The HFB signal decreases as distance increases from the spatial location with maximal modulation during movement. Since the HFB modulation in the movement-related contacts that are shown only contributes a small amount to the average reference, the reference signal has low HFB. The difference between a maximally active contact and the reference is greater than the difference between that maximally active contact and its neighbor which is also has HFB activation. b. Time-series data filtered in the beta range is shown for average reference to the right of contacts and bipolar reference to the right of that. When oscillations are aligned in phase, they constructively interfere as in the pre-movement period for the 5th and 6th most superficial contacts. Whereas, when the phases are opposite, as in the next most superficial bipolar pair, they destructively interfere. This is shown with fewer points in time in (c) in order to see this effect.

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