**Functional Associations at Global Brain Level during Perception of an Auditory Illusion by applying Maximal Information Coefficient**

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**Abstract**

Maximal information coefficient (MIC) is a recently introduced information-theoretic measure of functional association with a promising potential of application to high dimensional complex data sets. Here, we applied MIC to reveal the nature of the functional associations between different brain regions during the perception of binaural beat (BB); BB is is an auditory illusion occurring when two sinusoidal tones of slightly different frequency are presented separately to each ear and an illusory beat at the different frequency is perceived. We recorded sixty-four channels EEG from two groups of participants, musicians and non-musicians, during the presentation of BB, and systematically varied the frequency difference from 1 Hz to 48 Hz. Participants were also presented non-binuaral beat (NBB) stimuli, in which same frequencies were presented to both ears. Across groups, as compared to NBB, (i) BB conditions produced the most robust changes in the MIC values at the whole brain level when the frequency differences were in the classical alpha range (8-12 Hz), and (ii) the number of electrode pairs showing nonlinear associations decreased gradually with increasing frequency difference. Between groups, significant effects were found for BBs in the broad gamma frequency range (34-48 Hz), but such effects were not observed between groups during NBB. Altogether, these results revealed the nature of functional associations at the whole brain level during the binaural beat perception and demonstrated the usefulness of MIC in characterizing interregional neural dependencies.

Keywords: EEG, Binaural beat, Network, Maximal information coefficient, Mutual information, musician

1. **Introduction**

The study of brain dynamics from noninvasively obtained large scale brain responses (such as M/EEG data) by using functional connectivity (or functional association, used here interchangeably) indices has become customary nowadays [[1](#_ENREF_1)] as novel insights into healthy brain functioning [[2](#_ENREF_2), [3](#_ENREF_3)], and its alterations with various brain disorders [[4](#_ENREF_4)] can be obtained by studying the brain’s complex network patterns [[5](#_ENREF_5), [6](#_ENREF_6)]. There exists a plethora of bivariate indices for this purpose [[7-10](#_ENREF_7)]. Although frequency domain based measures such as phase synchronization indices are among the most commonly used [[11](#_ENREF_11)], simpler time-domain measures such as correlation coefficient is also recommended to construct a brain’s functional network [[12](#_ENREF_12)]. However, correlation coefficient captures only linear association between neural signals, is prone to outliers in the data and its interpretations are not always straightforward [[13](#_ENREF_13), [14](#_ENREF_14)]. Information theory-based indices such as mutual information (MI) [[15](#_ENREF_15), [16](#_ENREF_16)] would be, however, more theoretically suitable for this purpose, as they assess a more general form, linear and nonlinear, of statistical association between two time series [[17](#_ENREF_17)], and detect, in principle, both amplitude and cross-frequency synchronization [[18](#_ENREF_18)]. Yet, MI is usually not the most preferred option to assess functional connectivity in neural data set with finite and limited data points (but see some recent references [[19](#_ENREF_19)]). Firstly, the calculation of MI depends on the reliable estimation of both the marginal and the joint probability density functions, which is known to be a very complicated task for short, noisy time series [[20](#_ENREF_20), [21](#_ENREF_21)]. Second, MI is non-normalized, which means that it is (theoretically) zero for completely independent signals but unlike most other FC measures it is not for completely dependent signals. Finally, MI detects both linear and nonlinear interdependencies, but its sensitivity to different types of relationships may be different. Recently, Reshef and colleagues [[22](#_ENREF_22)] have introduced a new index termed Maximal Information Coefficient (MIC), which is related to MI as it is the maximum normalized MI where the joint entropy between two time series, {*xi*(*k*)}and{*xj*(*k*)},is calculated on (almost) all possible grids of the joint space. MIC is normalized between 0 (for independent) and 1 (for identical signals) and is allegedly equitable (see Refs. [[23-25](#_ENREF_23)] for a detailed discussion on this issue), i.e., for a fixed signal to noise ratio, its value is the same for any type of relationship between two signals, thereby being similarly sensitive for all of them. Besides, the value of MIC for completely independent signals of limited size depends only on the number of data samples. Thus, the statistical significance of MIC can be determined and tabulated using surrogate data [[26](#_ENREF_26)].

 In this study, we applied this new measure to investigate the functional connectivity (FC) patterns between different brain regions during the perception of an auditory illusion, binaural beats (BB). BB occurs when two tones (e.g., 400 Hz and 410 Hz) with a very slight frequency mismatch (10 Hz) are presented separately to each ear (i.e. 400 Hz to left ear and 410 Hz to right ear) and the listener perceives a beat with a frequency equals to the frequency difference between the two ears [[27](#_ENREF_27)]. BB is an auditory illusion because the subjectively perceived beat is not physically present in the two tones presented to the listener. BB is produced when the carrier or base frequency is between 200-1000 Hz and the frequency difference between the two tones separately presented to two ears is lower than 40 Hz [[28](#_ENREF_28)]. Early invasive studies on cats showed that the BB effect is supposedly originated by the activities of neurons in the superior olives of the brainstem, inferior colliculus that are sensitive to phase shifts between two ears [[29](#_ENREF_29), [30](#_ENREF_30)]. However, in humans, it is suggested that in addition to subcortical brain regions, higher order cortical regions, seat of top-down cognitive processes, also play important role in the brain’s responses to the BB [[31](#_ENREF_31)][[32-34](#_ENREF_32)]. Not surprisingly, the impacts of BBs on human behaviour and psychological processes are found to be facilitatory [[35-37](#_ENREF_35)].

The first aim of this study was to apply the MIC measure to EEG signals recorded from human volunteers in order to reveal the functional associations between near and distant brain regions during binaural beat perception when stimulated by a range of BBs from 1 Hz to 48 Hz. The second aim was to investigate the differences between musicians and non-musicians in relation to BB stimulation. Musicians are an important group in this context as long-term musical training leads to substantial changes in both structure [[38](#_ENREF_38)] and functional auditory processes [[39](#_ENREF_39), [40](#_ENREF_40)], and therefore, musician’s brain is considered as an useful model of neuroplasticity [[41](#_ENREF_41), [42](#_ENREF_42)]. Further, long-term active training in music has been robustly associated with a heightened neural processing of auditory stimuli including both musical and non-musical sounds [[43](#_ENREF_43)], and this is taken as a signature of musicians’ improved ability of selective enhancement of auditory information [[44](#_ENREF_44)]. Therefore, it would be of interest to explore whether musicians’ brains showed a global pattern of functional associations that was characteristically different from those of nonmusicians and whether the difference was dependent on the specific frequency of BB stimulation.

1. **Materials & Methods**

2.1 *Participants*

Thirty-two healthy adult human volunteers participated in this study and were equally divided into two groups: musicians (*N*=16, 6 males, mean ± STD of age: 25.5 ± 3.18 years, all right handed) and non-musicians (*N*=16, 7 males, mean ± STD of age: 26.1 ± 3.82 years, 15 right handed). Musical expertise was measured by a questionnaire. The group of musicians had an average of 18.4 years (STD of 4.30 years) of active engagement with a musical instrument and 14 years (STD of 3.40 years) of formal training on a solo instrument; thirteen were self-reported professional musicians. On average, our musician participants practiced their principal instrument 21.59 hours per week (STD of 11.42 hours). The participants in the group of non-musicians had no formal training beyond the standard musical practice at school. All participants gave written informed consent before the experiment, and the experimental protocol was approved by the local Ethics Committee of the Department of Psychology, Goldsmiths.

*2.2 Stimuli*

Auditory stimuli were divided into 34 blocks of equal duration. Each block consisted of two conditions presented for 1 min each: the first was non-binaural beat (NBB) condition in which a tone of 200 Hz was presented to both ears, and the second was binaural beat (BB) condition in which a tone of 200 Hz was presented to the left ear and a tone of 200+*fbb* Hz was presented to right ear, thereby producing a frequency difference of *fbb* Hz between the two ears. Across blocks, *fbb* varied from 1 Hz to 48 Hz as follows: for the first twenty blocks, *fbb* increased from 1 Hz to 20 Hz with a step size of 1 Hz, and for the remaining fourteen blocks, *fbb* increased from 22 Hz to 48 Hz with a step size of 2 Hz.

*2.3 Experimental Procedure*

Participants sat in a semi-dark room and received the auditory stimuli by a Philips ear-headphone set with volume level adjusted by the participants at the beginning of the experiment and kept constant throughout the experiment. During the entire period of auditory stimulation, the participants were instructed to ignore the auditory stimulation while they watched a subtitled documentary film shown on a computer. This was primarily to ensure that the BB-related effects would be implicit, not requiring explicit attention, a procedure widely used in pre-attentive listening experiments [[45-47](#_ENREF_45)]. At the end of the experiment, the participants were asked to rate, on a 5-point Likert scale, their responses about the interestingness of the movie, the pleasantness of the auditory BB stimulation, and their overall alertness. No statistically significant differences were obtained between the two groups on any of these ratings (*Mann-Whitney U-test*, *p* > 0.05, two-tailed).

*2.4 EEG Recording*

Sixty-four channels EEG were recorded by Biosemi ActiveTwo system; the electrodes were placed according to the extended 10-20 montage. Four additional electrodes recorded horizontal and vertical eye movements. EEG signals were algebraically referenced to the mean of left and right earlobe electrodes. The sampling frequency was 512 Hz.

*2.5 EEG Analysis*

First, we down-sampled the data to 256 Hz in order to limit the file-sizes. Next, we applied a 0.5 Hz high-pass filter for removing slow drifts. Epochs containing large artefacts were removed (less than 2%) by visual inspection. Finally, blink artefacts were removed by Independent Component Analysis as implemented in the EEGLAB Toolbox [[48](#_ENREF_48)]. For each condition, we excluded the first and last 500 ms to eliminate any transient responses caused by the onset or offset of the auditory stimuli.

The functional association between any two EEG channels was measured by the MIC. Henceforth, we briefly describe the method.

 Given two EEGs *xi*(*k*) and *xj*(*k*) (*i,j*=1,..,64; *i*≠*j*, *k*=1,..,*n*), let (*qi*, *qj*) ∈*ℕ* 2/ *qiqj* < *nC* (0<*c*<1, -here, we take *c*=0.6 as in the original paper [[22](#_ENREF_22)]) be the number of elements in the two axes of a bi-dimensional grid *G*, and let

 (1)

denote the naïve estimation in G of the MI between both channels, obtained by estimating the marginal and the joint probability densities from this partition. Namely, *p(xi)* (resp. *p(xi)*) is calculated as the ratio between the number of points in each of the *qi* (resp. *qj*) boxes and the total number of samples, *n*.

 Then, MIC [[22](#_ENREF_22)] is defined as:

 (2)

where *IG* is the value of *MIC* over all possible ways of dividing the range of variance of *xi(k)* and *xi(k)* in *qi* and *qj* non-overlapping boxes, respectively; and max*G* indicates maximum over all possible values of (*qi,qj*). Defined in this way, MIC is normalized, as indicated above, between 0 (independence) and 1 (identical data).

 Note here that computing MIC is a computationally intensive procedure, as it requires the estimation of many MIs values; however, some efficient implementations have recently appeared in the literature [[49](#_ENREF_49), [50](#_ENREF_50)], which accelerates its calculation. We combined here a custom Matlab implementation using the parallel toolbox of Matlab ver. 8.5 with the C++ implementation included in MINERVA [[49](#_ENREF_49)] to calculate MIC.

We estimated Eq. (1) for each participant and BB-frequency in two time windows, the first 3 sec and the last 3 sec (i.e. 756 data samples) of both conditions. No statistical differences were observed between these windows, so the MIC values were averaged across the two windows.

MIC value for any electrode pair {*i,j*} would suggest a nonlinear association if it was higher than both the cut-off MIC value (=.1927) for completely independent signals of equal data length and the square of the Pearson’s correlation coefficient [[22](#_ENREF_22)]. The number of such nonlinear electrode pairs was expressed in proportion.

Statistical effects were considered significant at *p* < .05. Further, all reported effect sizes (*r*) were calculated after Rosenthal [[51, p.19](#_ENREF_51)] as follows: . The *r* values were interpreted after Cohen [[52](#_ENREF_52)] as follows: small effect, *r* = 0.10; medium effect, *r* = 0.30; large effect, *r* = 0.50.

1. **Results**

First, for each electrode-pair we normalized the MIC values for BB condition at each different frequency, *fbb* by subtracting the MIC values for corresponding NBB condition for each participant. Next, normalized MIC values were grouped into five groups of BB stimuli as follows: -BB (1 Hz ≤ *fbb* ≤ 4 Hz), -BB (5 Hz ≤ *fbb* ≤ 8 Hz), -BB (9 Hz ≤ *fbb* ≤ 12 Hz), -BB (13 Hz ≤ *fbb* ≤ 30 Hz ), and -BB (32 Hz ≤ *fbb* ≤ 48 Hz) based on the classical EEG frequency bands [[53](#_ENREF_53)]. Fig. 1A shows the mean normalized MIC values, averaged across all participants and all electrode pairs, for these five groups of BB stimuli. Any value significantly different from zero would indicate statistically robust differences of global functional associations during BB stimuli as compared to NBB. Across five frequency bands of BB stimuli, we observed that the average degree of functional associations at the global brain level was consistently lower for BB stimuli as compared to NBB. Five separate paired *t*-tests were conducted and the results are as follows: -BB: *t*(31) = -2.22, *p* = .034, *r* = .37; -BB: *t*(31) = -1.92, *p* = .06, *r* = .33; -BB: *t*(31) = -3.03, *p* = .005, *r* = .48; -BB: *t*(31) = -2.32, *p* = .027, *r* = .38; -BB: *t*(31) = -2.44, *p* = .021, *r* = .40). After applying Bonferroni correction for multiple comparison (*pcorr* = .01), only -BB (i.e. difference frequencies belonging to EEG alpha band) produced the most robust changes in the MIC values, and the effect size was medium to large. The scalp distribution of the normalized MIC values for the -BB was shown in Fig. 1B; although functional association was mostly decreased for BB condition across a wide range of brain regions, we also observed a dominant increase of functional associations over right fronto-central brain regions.

Next we calculated the number of electrode pairs showing nonlinear associations (see Sec 2.5 in *Materials and Methods*) and the results, expressed in proportion (varying from 0, no electrode-pair with nonlinear association, to 1, all electrode pairs are nonlinearly associated), are shown in Fig. 2 for the five groups of BBs. We observed a general trend towards decreasing nonlinear associations between near and distant brain regions with increasing frequency difference. One-way repeated-measures ANOVA revealed a main effect of BB (*F*(4,124) = 3.85, *p* = .025, Greenhouse-Geisser corrected), and post-hoc contrast analysis showed that the proportion of nonlinear links for the -BB stimulation was significantly different from its neighbouring frequency bands, i.e. from the -BB (*F*(1,31) = 14.441, *p* = .001, *r* = .93) and -BB stimulation (*F*(1,31) = 3.92, *p* = .05, *r* = .58).

Finally, we compared the two groups, musicians and non-musicians. We estimated the proportion of electrode pairs showing nonlinear associations for each group, condition and beat frequency difference, and the results are shown in Fig. 3. For BB condition, we found that non-musicians, as compared to musicians, showed stronger (*p* < .01) nonlinear associations between multiple and distant brain regions for BB frequency belonging to higher EEG frequencies, primarily in the high frequency gamma band (30-48 Hz). For BB belonging to upper alpha frequencies (10 Hz ≤ *fbb* ≤ 16 Hz), we did observe some differences between the two groups, but in the beta frequency range (18 Hz ≤ *fbb* ≤ 30 Hz) the differences between the groups disappeared. For NBB condition, we did not observe any significant differences between the two groups (*p* > .2)

1. **Discussion**

This study aimed to apply a recent measure of functional association, maximal information coefficient (MIC), to reveal the nature of complex associations between brain regions in healthy human adults during the perception of binaural beats presented over a wide range of various frequencies.

We found that as compared to non-binaural beat condition, all binaural beats produced a consistent and global decrease in the values of MIC. This implies that individual brain areas were less functionally associated with nearby and distant brain areas during the BB perception in general. This is in close agreement with a recent study [[54](#_ENREF_54)] which studied the degree of phase synchronization in intracranial recordings in patients during BB perception and found that the degree of synchronization decreases for most BB conditions, and interpreted the findings as a perturbation of ongoing spontaneous oscillatory brain responses. The most robust, in statistical sense, effect was observed BB was in the traditional alpha frequency band. It is the most studied among all brain rhythms and has a diverse role in brain functioning from memory to attentional processes [[55](#_ENREF_55), [56](#_ENREF_56)]. This is also the brain rhythm that emerges spontaneously in the brain and further shows a strict entrainment effect, i.e. the strength of alpha oscillations in the visual cortex is enhanced when stimulated by 10 Hz visual flickering stimuli [[57](#_ENREF_57)]. Although the entrainment of brain oscillations by BB is not always conclusively reported [[32](#_ENREF_32), [33](#_ENREF_33)], here we showed that the alpha-BB could significantly modulate the strength of the functional associations between brain regions. Interestingly, a recent study [[58](#_ENREF_58)] has reported larger interhemispheric coherence between the Heschl’s gyri (an area in the primary auditory cortex) in the EEG alpha-band (9-11 Hz) during both 10 Hz and 4 Hz binaural beat stimulation. This potentially suggests the potential role of alpha oscillations in auditory information processing [[59](#_ENREF_59)].

 Further, though there was a general decrease of association over a wide range of brain regions, certain brain regions in the right hemisphere like right fronto-central, right temporal, right occipital regions also demonstrated an increase of associations which are similar to a recent study [[58](#_ENREF_58)]. This co-occurrence of a widespread decrease of coupling and a localized increase of coupling may possibly suggest an intricate balance between global inhibition and local excitation, and further may allow sharper tuning to specific representations [[54](#_ENREF_54)] as well as flexible switching between them [[60](#_ENREF_60)].

Next we studied the nature of associations, especially focused on the nonlinear links between electrode regions as asynchronous couplings between neuronal populations are essentially nonlinear and play a fundamental role in forming neuronal transients and functional integration [[60](#_ENREF_60)]. The MIC is a very appropriate measure in this regard as it allows a simple way to find whether an association is linear or nonlinear, thereby avoiding the much more laborious and computationally intensive surrogate data analysis methods [[7](#_ENREF_7)]. We observed a clear separation between the two groups, musicians and non-musicians, in terms of the extent of nonlinear associations over the entire brain for BB belonging to high frequency gamma band. Surprisingly, musicians showed much less nonlinear coupling than non-musician. There are widespread evidences that musicians, as compared to non-musicians, show higher gamma band coupling, as measured by various FC indices, over distributed brain regions during listening to music [[39](#_ENREF_39), [61](#_ENREF_61), [62](#_ENREF_62)], yet our musicians showed reduced nonlinearity when stimulated by -BB. This apparent discrepancy could be explained by the fact that earlier studies studied functional connectivity (or associations as termed here) in the gamma band EEG signals (by filtering the raw EEG signals in the gamma band) but this study looked at the FC in the raw EEG signals but for BBs at the gamma frequency band. It could be that -BB led to a substantial increase of synchronized coupling in musicians as synchrony is related to linearity, thereby implying a larger driving effect by the gamma band binaural beats. However, a higher individual variability across musicians, as compared to non-musicians, was also observed in this linear and synchronous driving effect.

Let us discuss a few practical remarks and potential limitations of the current study. Here we presented the findings based on maximal information coefficient. It could be of interest to include some comparison with other association measures between electrode pairs. Earlier we applied phase synchrony based measures [[63](#_ENREF_63)], and do note that these measures are principally suitable for narrow-band signals but not for the broadband signals as studied here. A recent study [[8](#_ENREF_8)] has compared between various time domain measures like mutual information, different types of correlation coefficients on raw EEG data, and found mutual information to be most sensitive discriminating brain states. Second, our study was based exclusively on the stimulation induced brain responses and no behavioural responses were included. Indeed, a principal aim of the experiment was to study the implicit pre-attentive effects of binaural beat, i,e, effects that are obtained without any overt attention to the beat stimuli. Therefore, the participants watched a silent movie with subtitles during the entire period of auditory stimulation and were further instructed to ignore the background auditory stimulation. As mentioned earlier in the *Methods* that this procedure is widely used in pre-attentive listening experiments [[45-47](#_ENREF_45)], future studies however could reveal the impact of attention and any differences in the perception of binaural beat on the functional association patterns. Further, the higher frequency was always presented to the right ear, so any lateralization effect should be interpreted with caution [[64](#_ENREF_64)]. However, this is unlikely to influence the reported group-related differences because stimulation protocol was identical across all participants.

 Finally, a methodological comment on the MIC and its application to brain FC is in order. Indeed, a problem common to most current FC indices is that, while they may present high sensitivity to a certain type of relationship, they may be relatively insensitive (or even blind) to other types. Put in statistical terms, they have high statistical power as long as the type of relationship is the ‘correct’ one, but this power may drop significantly if it is not. Thus, for instance, Pearson correlation coefficient is statistically very powerful when it comes to detect linear correlations, yet it cannot detect nonlinear ones. This is problematic, because a change in the value of the index may be the result of decreased FC but also a consequence of a change in the character of the FC, from, e.g., linear to nonlinear, and both situations, which have potentially different meanings, could not be easily distinguished. This sacrifice of generality in return for higher sensitivity is also apparent in all those indices that require filtering the data (such as, e.g., most phase synchronization indices) to convert the signal from broad to narrow band, as the filtering process may have profound effects in the detection of FC (especially in the case of nonlinear cross-frequency correlations). Ideally, a “golden” index should be able to “quantify the strength of the statistical association between two variables without bias for relationships of a specific form”. One may add, additionally, that such a golden index should act ideally on the broadband data, with only the strict pre-processing between the originally recorded and the finally analysed data. We have explored here whether the recently developed MIC [[22](#_ENREF_22)] is a good candidate to allow some of the abovementioned flexibilities. Indeed, this lack of bias for a specific relationship, also termed equitability, was initially reported as one of the salient features of MIC [[22](#_ENREF_22)]. Since its publication, however, there has been much debate as to whether the MIC is actually equitable or not [[24](#_ENREF_24), [25](#_ENREF_25), [65-67](#_ENREF_65)]. Nevertheless, the present results seem to suggest that the MIC does possess some interesting features that make it a promising addition to the body of FC indices. Firstly, unlike MI, the MIC is normalized between 0 and 1, and its value for completely independent signals depend only on the number of data samples analysed rather than any individual feature of the data. Thus, even if MI is, as argued by some authors to be more equitable than MIC, the values of the former depend only on the statistical dependence between the signals rather than in their individual entropies. Secondly, by directly comparing MIC with the classical Pearson correlation coefficient, one can get important information into the type of interdependence (whether this is linear or nonlinear, as shown in Figure 3), an information that complements that of the strength of FC as indicated by the value of the index. Finally, as it acts on the unfiltered, broadband data, it is sensitive to the existence of both 1:1 and cross-frequency synchronization alike. Recent works [[50](#_ENREF_50), [68-71](#_ENREF_68)] have also shown that the original formulation of MIC can be modified to improve some of these features, such as its statistical power,. Note also that the study of suitable indices of association between data sets, which are sensitive to interdependence between the linear one, is a topic of great current interest [[71-73](#_ENREF_71)]. Among them, we decided to study the original derivation of MIC for the abovementioned reasons, but also for the availability, as commented in the Introduction, of tabulated estimators of statistical significance of its scores for different sample sizes. Altogether this reinforces the potential usefulness of this index in future applications for the study of functional association of complex neuronal datasets

In conclusion, this study showed that MIC was capable to quantify and to reveal the nature, linear or nonlinear, of functional connectivity pattern as observed at the whole brain level during binaural beat perception. The largest effects for the binaural beats were observed when the beats were at the alpha band, and further, the largest effects of musical training were observed when the beats were at the gamma band.

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*Figure 1.* A) Normalized MIC (BB-NBB) values as a function of BB frequency range (i.e. the range of frequency difference between the two ears), grouped on the classical EEG bands (delta,  [1-4 Hz], theta,  [5-8 Hz], alpha,  [9-12 Hz], beta,  [13-30 Hz] and gamma,  [32-48 Hz]). MIC values were averaged across all electrode-pairs and all participants. B) Scalp distribution of the normalized MIC values for -BB.

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*Figure 2*. Proportion of nonlinearly connected electrode-pairs or links as a function of the difference frequency. Results were pooled across all participants.



*Figure 3*. Proportion of nonlinearly connected electrode-pairs or links for two groups, musicians (red), and non-musicians (blue) as a function of the mismatch frequency. The shaded area represents 95% confidence interval.

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