Distinct interacting cortical networks for stimulus-response and repetition-suppression

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Non-invasive studies consider the initial neural stimulus response (SR) and repetition suppression (RS) – the decreased response to repeated sensory stimuli – as engaging the same neurons. That is, RS is a suppression of the SR. We challenge this conjecture using electrocorticographic (ECoG) recordings with high spatial resolution in ten patients listening to task-irrelevant trains of auditory stimuli. SR and RS were indexed by high-frequency activity (HFA) across temporal, parietal, and frontal cortices. HFASR and HFARS were temporally and spatially distinct, with HFARS emerging later than HFASR and showing only a limited spatial intersection with HFASR; most HFASR sites did not demonstrate HFARS, and HFARS was found where no HFASR could be recorded. β activity was enhanced in HFARS compared to HFASR cortical sites. θ activity was enhanced in HFASR compared to HFARS sites. Furthermore, HFASR sites propagated information to HFARS sites via transient θ:β phase-phase coupling. In contrast to predictive coding (PC) accounts our results indicate that HFASR and HFARS are functionally linked but have minimal spatial overlap. HFASR might enable stable and rapid perception of environmental stimuli across extended temporal intervals. In contrast HFARS might support efficient generation of an internal model based on stimulus history.
ubiquitous finding in neuroscience is that neural responses to repeated stimuli are reduced compared to initial stimulus presentation, the phenomenon of repetition suppression (RS). RS has been shown in both single-unit studies in the monkey cortex\textsuperscript{1–3} as well as noninvasive studies in humans using different techniques (for a review, see ref. \textsuperscript{4}). Several explanations for RS have been put forward, including adaptation or habituation, sharpening of representations, and reduction of prediction errors\textsuperscript{5–12}. This reduction of responses to frequently occurring stimuli is associated with an enhanced response to unexpected events, establishing a mechanism for change detection\textsuperscript{13,14} with the probability of stimulus events accounting for a large proportion of neural variability\textsuperscript{5}. Most hypotheses on the mechanisms responsible for RS assume that what is suppressed is the stimulus-induced response. That is, the same neurons or networks that are initially responsive to the stimulus are the ones which are less active when the same stimulus repeats. Noninvasive studies in humans report that RS and stimulus response (SR) overlap, but these methods cannot distinguish nearby cortical activity.

A critical question remains whether RS is restricted to reducing the SR, in which case SR and RS should co-occur in the same electrodes (henceforward SR+ and RS+ sites), as suggested by scalp EEG and MEG recordings. Alternatively, SR and RS could be dissociated, but the circuits exhibiting SR and RS are intermingled and not resolvable by low-resolution scalp recording. This potential dissociation could be measured using a direct cortical recording of broadband high-frequency activity (HFA, 80–150 Hz), which is the key response frequency in previous ECoG (electrocorticography) studies\textsuperscript{15–19} studying SR and RS.

Here, we utilized the high temporal and spatial resolution of direct cortical recordings from subdural ECoG electrodes to compare SR+ and RS+ signals in ten patients presented with trains of task-irrelevant auditory stimuli while attending a visual slide show to probe the natural nature of RS. We show that while SR and RS both engage frontal, parietal, and temporal regions, they can be dissociated temporally and spatially in HFA. Critically, HFA SR+ and RS+ sites are distinctly modulated by $\theta$ and $\beta$ low-frequency activity, respectively, with mutual information flow from SR+ to RS+ sites.

Results

For easy reference, the results sections correspond to the similarly enumerated sections of the methods section.

I – Stimulus response. We studied 412 channels (95 channels over frontal, 202 channels over temporal, and 115 channels over parietal regions across all subjects (see Fig. 1b)). Ninety-one channels showed a significant HFA modulation to auditory tones (of which 84 showed a stimulus response without RS, SR+ and RS–; Fig. 1b, c). Stimulus response occurred between 17–393 ms (SRmax at 113 ms, $p < 0.001$) over multiple cortical regions (11 channels over frontal, 53 over temporal, and 20 over parietal regions, see Fig. 1b and Table 1), manifested as an increase in HFA power. None of the RS+ channels in our study showed a significant reduction of the HFA relative to the pre-stimulus period in response to the first standard.

II – Repetition suppression. RS (defined as both a significant FN standard and significant negative trend ($r$ value) from S1 to S3) was found in 31 channels (of which 24 channels did not show SR, SR–+SR– Fig. 1d and Table 1) between 48–436 ms following stimulus onset (SRmax at 265 ms, $p < 0.001$, Fig. 1e). Channels designated as SR+RS+ showed no trend towards a stimulus response (average $p = 0.41$, SD = 0.1) even with a liberal, uncorrected significance criteria. We found three channels showing RE (both a significant FN standard and significant positive $r$ value), in the parietal ($N = 2$) and the temporal ($N = 1$) cortex. None of these channels showed significant SI (i.e., they were SR–RE+ channels).

III – Comparison of stimulus response and repetition suppression. About 115 channels exhibited SR and/or RS. Of these, only seven channels showed both (designated SR+RS+). The remaining showed only SR (SR+RS–, 84 channels, Fig. 2a) or showed RS without SR (SR–RS+, 24 channels, Fig. 2b). We first confirmed that the lack of SR in SR+RS+ sites is not due to reduced sensitivity caused by high baseline variance ($c^2$) in these channels compared to other sites (baseline $–200–0$ ms, $F(3,408) = 0.37$; $p = 0.78$; SR+RS–: mean $c = 0.0012$, std = 0.0004; SR+RS+: $c^2 = 0.0008$, std = 0.0008; SR–RS+: $c^2 = 0.0017$, std = 0.0002; $c^2 = 0.0009$, std = 0.0037). We also estimated the BF to determine the amount of evidence for a change over baseline separately for each channel at each time point. Bayes factor analysis provided strong support to lack of stimulus response in SR+RS+ channels ($BF_{mean} = 0.12$, $BF_{min} = 0.098$, $BF_{max} = 0.19$; Fig. 2c) and SR–RS– channels ($BF_{mean} = 0.17$, $BF_{min} = 0.15$, $BF_{max} = 0.21$), while strong evidence for stimulus response was observed in SR+RS+ channels ($BF_{mean} = 570.03$, $BF_{min} = 289.7$, $BF_{max} = 7590$), and in SR+RS– channels ($BF_{mean} = 54.54$, $BF_{min} = 34.5$, $BF_{max} = 506.19$). We additionally estimated the BF to determine the amount of evidence for repetition suppression separately for each channel. We estimated the RS effect in each S1, S2, and S3 sequence as the summed difference between HFA activity, see Table 2. Post hoc tests revealed stronger $\beta$ in SR+RS+ ($BF_{mean} = 158.75$, $BF_{min} = 154.5$, $BF_{max} = 161.9$) than RS– ($BF_{mean} = 314.72$, $BF_{min} = 312.7$, $BF_{max} = 319.4$) in these channels. We determined the amount of evidence for repetition suppression separately for each channel. We found support for no repetition suppression, neither in SR+RS– ($BF_{mean} = 0.23$, $BF_{min} = 0.21$, $BF_{max} = 0.26$) nor SR–RS– channels ($BF_{mean} = 0.23$, $BF_{min} = 0.22$, $BF_{max} = 0.25$). However, we observed positive evidence in SR+RS+ channels ($BF_{mean} = 315.72$, $BF_{min} = 172.7$, $BF_{max} = 1928.4$) and in SR+RS– channels ($BF_{mean} = 16.52$, $BF_{min} = 4.49$, $BF_{max} = 376$; Fig. 2d). Temporal parameters also distinguished SR and RS channels. We found that RS peaked significantly later than SR in SR+RS+ ($SR_{peak} = 158$ ms, $RS_{peak} = 230$ ms, $t_{0.05} = 2.55$; $p = 0.04$, Fig. 2e) and all SR+RS– and SR–RS+ channels combined ($SR_{peak} = 167$ ms, $RS_{peak} = 253$ ms, $t_{0.05} = 3.62$; $p < 0.001$, Fig. 2e).

IV – Comparison of dominant band power. We then asked whether SR and RS sites dissociate in spectral characteristics. Power spectral-density (PSD) showed an interaction between factors Channel Type ($SR+RS–$, $SR–RS+–$, $SR–RS–$, $SR+RS+$) and Frequency Bands ($\theta$, $\alpha$, $\beta$) ($F_{1243} = 3.2$; $p = 0.013$; Fig. 3a). $\theta$ and $\beta$ activity differed significantly between channel types but not $\alpha$ activity, see Table 2. Post hoc tests revealed stronger $\theta$ power ($P_{0}$) in SR+ than SR– channels ($P_{0,SR+RS–} > P_{0,SR–RS–}$; $t_{106} = 2.51$; $q = 0.04$; $P_{0,SR+RS–} > P_{0,SR–RS–}$; $t_{106} = 2.37$; $q = 0.0297$; $P_{0,SR+RS–} > P_{0,SR–RS–}$; $t_{106} = 2.41$; $q = 0.0297$; and a trend towards $P_{0,SR+RS–} > P_{0,SR–RS–}$; $t_{106} = 1.99$; $q = 0.082$; $t_{106} = 1.99$ denotes the $t$ value which the observed $t$ values had to exceed to be considered significant). In contrast, $\beta$ activity showed stronger power for RS+ than SR– channels ($P_{0,SR+RS–} > P_{0,SR–RS–}$; $t_{106} = 2.37$; $q = 0.0297$; $P_{0,SR+RS–} > P_{0,SR–RS–}$; $t_{106} = 1.99$; $q = 0.082$; $t_{106} = 1.99$ denotes the $t$ value which the observed $t$ values had to exceed to be considered significant).
Cross-frequency coupling. Within channel low frequency-HFA phase-amplitude coupling (PAC, Fig. 3c, d) showed no main effects of channel type or frequency band ($F_{\text{channel type}} = 0.28; p = 0.59$, $F_{\text{frequency band}} = 1.5; p = 0.22$), but a significant interaction ($F = 4.79; p = 0.03$), reflecting stronger SR–RS+ HFA coupling to $\beta$ than $\theta$ phase and vice versa in SR+–RS– channels (Fig. 3e).

SR+–RS– channels showed increased post-stimulus (116–270 ms) phase:phase coupling of $\theta$ SR+ and $\beta$ RS+ ($\kappa_{\text{crit}} = 0.0043; \kappa_{\text{max}} = 0.019; p < 0.00001$, Fig. 3f) indicating significant interaction (Fig. 3g, h). Phase concentration coefficient $\kappa$ differed significantly across frequency band pairs between 160–261 ms ($F_{\text{crit}} = 3.95$ denotes the critical $F$ value which the observed $F$ values had to exceed to be considered significant; $\max F_{2,288} = 8.27; p < 0.00001$), due to stronger $\theta\beta$ coupling ($\kappa_{\theta\beta} = 0.0091$) than $\theta\alpha$.

The distinct SR and RS cortical sites raise the question of whether SR+–RS– and SR–RS+ sites interact. SR+–RS– and SR–RS+ electrodes showed increased post-stimulus (116–270 ms) phase-phase coupling of $\theta_{SR+}$ and $\beta_{RS+}$ ($\kappa_{\text{crit}} = 0.0043; \kappa_{\text{max}} = 0.019; p < 0.00001$, Fig. 3f) indicating significant interaction (Fig. 3g, h). Phase concentration coefficient $\kappa$ differed significantly across frequency band pairs between 160–261 ms ($F_{\text{crit}} = 3.95$ denotes the critical $F$ value which the observed $F$ values had to exceed to be considered significant; $\max F_{2,288} = 8.27; p < 0.00001$), due to stronger $\theta\beta$ coupling ($\kappa_{\theta\beta} = 0.0091$) than $\theta\alpha$.

Table 1 Summary of channels.

| Patient | HFA SR-RS+ channels (temporal/frontal/parietal) | HFA SR+–RS– channels (temporal/frontal/parietal) | Total no. of electrodes |
|---------|-----------------------------------------------|-----------------------------------------------|-------------------------|
| I       | 3 (1/2/0)                                     | 22 (13/5/4)                                   | 60                      |
| II      | 3 (0/0/3)                                     | 17 (8/1/8)                                    | 59                      |
| III     | 5 (2/0/3)                                     | 11 (8/1/2)                                    | 52                      |
| IV      | 4 (2/0/2)                                     | 2 (0/1/1)                                     | 56                      |
| V       | 2 (1/1/0)                                     | 13 (7/3/3)                                    | 60                      |
| VI      | 1 (0/0/1)                                     | 3 (2/0/1)                                     | 15                      |
| VII     | 3 (1/0/2)                                     | 5 (4/0/1)                                     | 26                      |
| VIII    | 1 (1/0/0)                                     | 0 (0/0/0)                                     | 16                      |
| IX      | 2 (0/2/0)                                     | 2 (2/0/1)                                     | 53                      |
| X       | 0 (0/0/0)                                     | 9 (9/0/0)                                     | 15                      |
| total No | 24 (8/5/11)                                   | 84 (53/11/20)                                 | 412                     |

Fig. 1 Stimulus response and repetition suppression show different spatial profiles. a shows the auditory oddball paradigm. While the occurrence of deviants was unpredictable, $S_1$, $S_2$, and $S_4$ were always predictable. b shows the spatial distribution of HFA SR+–RS– (green) and SR+–RS+ (magenta) channels as marked dots against the background of a standard schematic brain using MNI coordinates that was also used for surgical planning. The remaining electrodes are marked by small white dots. c shows the HFA amplitude modulation of SR+ channels over time averaged across electrodes. The shaded area denotes the standard error across channels. d shows the spatial distribution of HFA SR+–RS+ channels (blue) analog to b. Channels with magenta circles represent SR+–RS+, as in b. e Modulation of repetition-suppression ($F$ values) in SR–RS+ channels. The dashed blue line represents the significance threshold of $F$ values. The shaded area denotes the standard error across the channels.
coupling (κθ: α = 0.0004; t = 3.25; p = 0.0016), and αβ coupling (καβ = 0.0009; t = 5.03; p < 0.0001 Fig. 3i, j).

VII – Information propagation. Between-sites mutual information (MI) analysis revealed early SR+ activity between 89–192 ms to be predictive of later RS+ activity between 190–226 ms (MIcrit = 0.85 bits; MImax = 0.86 bits at 141 ms of SR+ and 210 ms of RS+ time series; p < 0.00001. Fig. 3k) suggesting information propagation from SR+ to RS+ sites.

Discussion
Numerous studies report that the response to sensory stimuli decreases with repeating stimulation, a phenomenon known as repetition suppression (RS) or stimulus-specific adaptation14. Noninvasive studies report substantial spatial overlap of stimulus response and repetition suppression, but such studies are limited in spatial resolution19. Thus, these methods are not well suited to examine whether RS reflects a stimulus response which gets reduced upon repeating stimulation, or might be a separate phenomenon of activity reduction relative to baseline in sites lacking stimulus response. This type of RS might reflect a short-term memory mechanism, independent of stimulus response. Here, we used intracranial EEG data in the context of repeating tones to measure the temporal, spatial, and spectral features of both phenomena. Unlike previous studies studying RS, we did not limit our analyses to channels showing stimulus response, and found many sites showing exclusively SR and sites showing exclusively RS. Moreover, SR and RS exclusive sites also showed distinct spectral
characteristics. SR sites showed higher $\theta$ power and $\theta$:HFA phase–amplitude coupling (PAC) than sites with no SR, and RS sites showed stronger $\beta$ power and stronger $\beta$:HFA PAC than sites showing no RS. Finally, we show that the two processes interact - the two types of sites show phase-phase coupling between their dominant theta and beta frequencies. Further, HFA SR peaks earlier than HFA RS effects, and HFA SR predicts HFA RS.

Stimulus response was evident in all three lobes measured (frontal, parietal and temporal), manifested in high-frequency activity. All three regions also showed RS, with an amplitude decrease to repeated stimulation. Previous ECoG studies have
shown adaptation of high-frequency activity, mostly located in the temporal and parietal cortex\textsuperscript{21}, and here we show that lateral frontal cortex sites adapt to frequent auditory repetition as well, which has only been shown for low frequencies\textsuperscript{22,23}.

What could be the mechanisms driving SR with no apparent RS? Under the traditional explanation of RS as a process of adaptation which recovers with time\textsuperscript{24}, SR without RS might reflect sites with recovery times shorter than our inter-stimulus intervals, such that full recovery has been attained. Indeed, previous findings suggested variability in adaptation time constants\textsuperscript{24}. The time constant of neuronal populations can be seen as reflecting the temporal resolution of the representation of the environment. Differences in resolution might allow distinguishing processing of coarse and fine-grained details\textsuperscript{24}. Previous studies in vision show that the phase of \( \theta \) activity across frontal and parietal regions is related to rhythmic sampling predicting visual detection performance\textsuperscript{25,26}. Here, HFA SR+ modulated by \( \theta \) activity (as evidenced by an increase in PAC), independent of RS, could be a mechanism to detect sensory evidence independent of context information or expectations.

An alternative explanation suggested by a reviewer is that SR–RS+ channels reflect the summed response of neurons excited by the stimulus and show repetition suppression (i.e., genuine SR+RS+) and of neurons that are a-priori inhibited by the stimulus. These inhibited neurons would “cancel out” the apparent SR in our mesoscopic recording of LFPs, making it look as if RS is present without SR. Without extensive single neuron measurements, it is difficult to rule out this possibility. However, we suggest that this possibility is less likely, considering the different spectral characteristics of SR+ sites and RS+ sites. If apparent SR–RS+ channels represent a composite signal of genuine SR+RS+ and inhibited neurons, then SR–RS+ channels should show comparable spectral signatures as other SR+ channels (namely SR+RS− and SR+RS+). However, both in the \( \theta \) and the \( \beta \) range, SR–RS+ channels show a spectral signature which resembles other SR− channels (SR−RS−) and differs from SR+ channels. Specifically, in the \( \theta \) range, SR–RS+ channels show \( \theta \) power that is lower than in SR+RS− or SR+RS+ channels and is not different from channels neither responding to the stimulus nor showing repetition suppression (SR–RS−). In the \( \beta \) range, SR–RS+ channels also show different \( \beta \) activity compared to SR +RS− channels. Additionally, we found very few sites with a negative stimulus response to the first stimulus in a series, suggesting that inhibition is a rare response to the stimuli.

Within the classical notion of RS, it is harder to explain the finding of RS without an initial SR. One possibility is that rather than simple adaptation, repetition suppression without stimulus response reflects direct top-down inhibitory prediction signals. This is consistent with the conjecture that top-down prediction effects are carried by activity in the beta band. Previous studies argued that feedback signals are distributed across cortical layers and segregated by spectral content\textsuperscript{27,28}. They suggested that feedback signals target deep (infragranular) layers of the cortex with activity in the \( \beta \) band. In addition to enhanced \( \beta \) band activity, repetition suppression sites showed enhanced \( \beta \)-HFA PAC. Hence, repetition suppression embedded in \( \beta \) activity might reflect an internal model based on stimulus history.

RS can be explained by neural sharpening\textsuperscript{8,12,29,30} due to the fall-out of neurons that are not optimally tuned to stimulus features with repetition. Repeated sensory evidence strengthens intracortical inhibitory connections. This lateral interaction\textsuperscript{31} may cause a decrease in the population response (inhibitory sharpening\textsuperscript{12}). Even though we cannot directly test neural sharpening, lateral interactions can be an explanation for the SR +RS− vs SR–RS+ sites. This sharpening may also be influenced by top-down inhibition as a component of hierarchical predictive coding.

Predictive coding (PC) schemes mostly assume that the stimulus response itself is suppressed when it is predicted, indicating that the evaluation of a stimulus likelihood precedes or occurs simultaneously with the bottom-up response to the stimulus, so that only deviations from prediction are registered. The current results show that RS effects followed SR in time, overlapping in time with only the late part of the stimulus response. This is consistent with prediction-error-like effects as the mismatch negativity (MMN), which overlaps in time the late part of the auditory N1 response from 100 ms after stimulus onset\textsuperscript{32}. Thus, even if predictions are formed a-priori, they seem to affect mainly the later stages of processing.

The SR+ and RS+ ensembles showed distinct spectra and spatial and temporal layout, yet were not disconnected—activity in the \( \theta \) and \( \beta \) range exhibited significant phase-phase coupling and HFA showed information transfer from SR+ to RS+ sites, which was local in time. The phase coupling signals originate from separable sites and were found exclusively between \( \theta \) and \( \beta \), suggesting that the \( \theta \)-\( \beta \) cross-frequency phase coupling effects are not due to waveform shape\textsuperscript{33}. Phase coupling might enable temporally precise coordination of neuronal processing by establishing systematic spike-timing relationships among functionally distinct oscillatory assemblies enabling functional integration and coordination\textsuperscript{34,35}. The functional meaning of this coupling in the present case remains to be investigated.

Another sign of communication between the sites is that HFA in the SR+ sites reduced the uncertainty of HFA responses in the RS+ sites. MI is based on information theory\textsuperscript{36} and formally characterizes the information content of neural responses and interactions between these responses. In previous studies, MI has been applied to multiunit recordings and local field potentials in nonhuman primates\textsuperscript{25,37–39} and intracranial data in human\textsuperscript{40}. Importantly, MI makes no assumptions about the content of the signal itself but only that it changes as a function of time. The strength of this approach is that it characterizes the nonlinear relationship between two different neural responses. We found a clear exchange of information from SR+ to RS+ sites but not vice versa. Under the assumption that the repetition suppression reflects the process of top-down model predictions, this result supports the notion that stimulus responses (or prediction errors under the PC framework\textsuperscript{41}) inform the generation of the internal model. Taking together the finding of phase-phase coupling between \( \theta \) and \( \beta \) activity, the fact that each band respectively

### Table 2 Comparison of PSDs between channel types SR+RS−, SR–RS+, SR–RS−, and SR+RS+ channels, respectively, each for the three frequency bands \( \theta \), \( \beta \), and \( \alpha \) based on the interaction between both factors.

| Power spectral-density (PSD) | F     | p     |
|----------------------------|-------|-------|
| SR+RS−                     |       |       |
| \( \theta \)               | 35.9  | 33.4  |
| \( \beta \)                | 19.5  | 21.9  |
| \( \alpha \)               | 30.7  | 30.2  |
| SR–RS+                     | 34.3  | 36.1  |
| SR+RS+                     | 19.1  | 21.5  |
| SR–RS−                     | 30.5  | 31.5  |
| SR+RS+                     | 36.3  | 0.3   |

\( F_{3,40} = 3.37 \) \( p = 0.012 \)

\( F_{3,40} = 2.76 \) \( p = 0.04 \)

\( F_{3,40} = 0.3 \) \( p = 0.82 \)
modulated the local HFA amplitude in its region (PAC), and the finding of directional M1 between of SR+ to RS+ sites, supports the proposal of cross-talk between bottom-up (θ) and top-down (β) effects.

**Limitations.** Repetition effects were investigated in depth in previous studies in vision and audition across different species using a large repertoire of recording techniques. These studies are often motivated by behavioral repetition priming, showing that repetition leads to improved identification of stimuli. Repetition-suppression is assumed to reflect statistical learning and contributes to sensory memory update by tracking stimulus history. Most repetition suppression studies compared responses between a first and second presentation which show the strongest repetition suppression effects in non-invasive recordings. Several previous studies showed local PAC as in our study (phase of low frequency and amplitude of higher frequency of the same broadband signal) across species and different recording techniques. However, since PAC supports information processing, genuine coupling in contrast to spurious correlations must be shown. Spurious coupling can result from filtering non-sinusoidal signal and creating artificial coupling at distinct frequencies, especially in local PAC. However, commensurate with phase-phase coupling, PAC is more likely genuine if the higher frequency is exclusively coupled to only one of two distinct low frequencies originating from separable neuronal processes. We indeed found a double dissociation of HFA SR+ coupled to θ but not β and vice versa for HFA RS+ in the temporal interval of coupling between θ and β. This differential coupling finding provides evidence for two distinct processes.

In our study, we focused on the repeated and hence predictable part of the auditory stimulation. How repetition and expectation suppression interact is still debated. Our paradigm does not allow us to conclusively dissociate between repetition independent of expectation. However, recent evidence suggests that subjects are less likely to apply overt expectations (even when available) when the stimuli are not task-related (as was the case in our study), suggesting that when attention is directed elsewhere, expectation vanished despite robust repetition suppression being still evident.

**Conclusion**

Our critical finding is that SR and RS dynamics were temporally and spatially distinct. Our results highlight the role of distinct processes in computing a stimulus response and feedback signals which are functionally linked but do not completely overlap.

**Methods**

**Patients.** Ten patients (mean age 32, SD = 9.74) undergoing pre-surgical monitoring for drug-resistant epilepsy with subdural electrodes participated in the experiment after providing their written informed consent. Recordings took place at the University of California, San Francisco (UCSF) (five patients) and at the Dept. of Epileptology (Krankenhaus Maria), Bielefeld University (five patients) and were approved by the local ethics committees. Data from these patients were preprocessed in an analogous manner as reported. Data from these patients were approved by the local ethics committees. Data from these patients were preprocessed in an analogous manner as reported.

**Stimuli.** Participants listened to stimuli consisting of 180 ms long (10 ms rise and fall time) harmonic sounds with a fundamental frequency of 500 or 550 Hz and the 3rd harmonics with descending amplitudes (6→9→12 dB relative to the fundamental). The stimuli were generated using Cool Edit 2000 software (Syntrilium, USA). They were presented from loudspeakers positioned at the foot of the subject’s bed at a comfortable loudness.

**Procedure.** While reclined in their hospital bed, participants watched an engaging slide show while sound trains were played in the background. Sound trains included high probability standards (p = 0.8; f0 = 500 Hz) mixed with low probability deviants (p = 0.2; f0 = 550 Hz) in blocks of 400 sounds, with a stimulus onset asynchrony (SOA) of 600 ms. Hence, in each block, 320 standard tones and 80 deviant tones were presented. In different blocks, the order of the sounds was either pseudorandom, with a minimum of three standard tones before a deviant (irregular condition), or regular, such that the standard stimulus was repeated exactly four times before a deviant was presented (S-S-S-S-D-S-S-S-S-D-...., Fig. 1a). Thus, in the regular condition, the fourth standard tone was fully predictable whereas in the irregular condition, the fourth stimulus was either a standard or a deviant, and prediction was not possible. The current report examines the responses to the repeating standards. The deviation-related responses from the subset of the subjects recorded at UCSF was previously reported.

**Data recording and preprocessing.** ECoG was recorded at UCSF using electrode grids equipped with 64 platinum-iridium-electrodes, arranged in an 8 × 8 array with 10 mm center-to-center spacing (AdvTech Medical Instrument Corporation, Racine, Wisconsin). At The Mara, Bielefeld, ECoG was recorded via electrode strips (single strips or parallel arrangement of strips; white dots in Fig. 1b, d represent all electrode locations) using a Nihon Kohden amplifier (Tokyo, Japan). Electrodes were positioned based solely on clinical needs. The exposed electrode diameter was 2.3 mm. The data at UCSF were recorded continuously throughout the task at a sampling rate of 2003 Hz. At The Mara, the sampling rate was 2000 Hz in the case of four subjects and 1000 Hz in one subject. We used Matlab 13b (Mathworks, Natick, USA) for all offline data processing. After visual inspection, we excluded channels exhibiting ictal activity or excessive noise from further analysis. In the remaining “good” channels (see Table 1), we then excluded time intervals containing artificial signal distortions such as signal steps or pulses by visual inspection. Finally, we re-referenced the remaining electrode time series by subtracting the common average reference from the good channels from each channel time series. The resulting time series were used to characterize brain dynamics of responses to repeated auditory stimulus presentation. For high-frequency signals, we band-pass filtered each electrode’s time series in the high-frequency range (80–150 Hz). All filtering was done with zero-shift infinite impulse response (IIR) filters (Butterworth filter of order 4; bi-lateral function in matlab). We obtained HFA by calculating the analytic amplitude A(t) by Hilbert-transforming the filtered time series. We smoothed the HFA amplitude time series such that the amplitude value at each time point t is the mean of 10 ms around each time point t. Filtering was done for each trial (1–5 s to 2 s around stimulus onset—sufficiently long to prevent any edge effects during filtering).

**Data analysis.** We conducted the following analysis steps explained in detail below. First, we defined stimulus response of the HFA (I-Stimulus-responsive activity modulation). Next, we parameterized response attenuation of cortical HFA responses to repeated standard tones using a time-resolved ANOVA (II – Repetition-suppression). We then compared the temporal and spatial profile of stimulus response and repetition suppression (III – Comparison of stimulus response and repetition suppression). Next, we tested to what degree the HFA SR and RS are associated with low-frequency activity (IV – Cross-frequency modulation). We then tested whether HFA SR and RS were modulated by distinct neuronal populations in low frequencies (V – Cross-frequency modulation) and for functional integration between low-frequency neuronal populations (VI – SR-RS integration). Finally, we assessed information flow between SR+ and RS– channels using time-resolved mutual information to test for the directionality of information propagation (VII – Information propagation).

1. **Stimulus-responsive activity modulation.** We identified stimulus-responsive channels SR+ showing a significant HFA modulation following the onset of standard stimuli using the following steps. We first averaged stimulus-locked HFA responses across all standard trials. To apply a sensitive measure which takes into account that HFA responses can occur with a delay and/or can be transient, we then calculated the average baseline activity of the HFA (I-Stimulus-responsive activity modulation). Next, we parameterized response attenuation of cortical HFA responses to repeated standard tones using a time-resolved ANOVA (II – Repetition-suppression). We then compared the temporal and spatial profile of stimulus response and repetition suppression (III – Comparison of stimulus response and repetition suppression). Next, we tested to what degree the HFA SR and RS are associated with low-frequency activity (IV – Cross-frequency specific modulation). We then tested whether HFA SR and RS were modulated by distinct neuronal populations in low frequencies (V – Cross-frequency modulation) and for functional integration between low-frequency neuronal populations (VI – SR-RS integration). Finally, we assessed information flow between SR+ and RS– channels using time-resolved mutual information to test for the directionality of information propagation (VII – Information propagation).
the false discovery rate) in any of the five intervals were classified as showing a significant HFA modulation following the standard stimuli and were denoted as SR+, whereas the remaining channels were labeled as SR−. To determine the amount of evidence for a change over baseline, we compared HFA values at each time point with HFA values in the baseline interval separately for each channel across trials, using Bayes factor (BF; for bf.m toolbox in MATLAB http://klabhub.github.io/bayesfactor). BF >3 is considered strong evidence for a difference (the difference is three times more likely than no difference) and BF <1/3 supports null effects [69,70].

II – Repetition-suppression. RS is defined as attenuated amplitude to repeated stimulus presentation. Hence, this definition is twofold: (i) a change of which is SR− monotonically decreasing with the number of repetition presentations. While (i) refers to statistical differences in brain response with repetitions, (ii) assumes a specific model of response attenuation. We thus grouped trials according to the number of standards in a train in three groups (S1, S2, and S3) since only the first three standards in a train can be expected in both conditions. To parameterize the amplitude modulation with stimulus repetition (i), we ran a one-way ANOVA with a factor number of standards for each electrode (with trials as a random variable), regardless of whether it was SR− or SR+, at every time point, both in the regular and irregular condition. This leads to an F value time series (main effect: $F_{\text{S standard}}$) for each channel in each condition. Significant F values only define differences between numbers of preceding standards but not the exact model of monotonic decrease of neural responses. We tested (ii) the model of a monotonic neural amplitude decrease across the number of repetitions. For each electrode, at each time point, we calculated the Pearson correlation between the mean HFA and the number of sequential preceding standards, yielding a time series of $r_{\text{RS}}$ for each trials (r) for each channel time series. We compared each channel $r$ value and r value against a surrogate distribution constructed under the null assumption of no difference or no correlation, respectively. This surrogate distribution was constructed by randomly reassigning the labels (S1, S2, and S3) to the single trials in across trials yielding one PSD for each channel. We then averaged across three trials showing intervals with the conjunction of both significant r values were considered as showing significant RS+ or RS− channel time series. The temporal interval of coupling between low-frequency networks as determined in the previous step IV, we divided both the $\theta$ and $\beta$ cycle separately in 50 equally spaced bins ranging from $-\pi$ to $\pi$ and computed the average HFA for all trials within a 45-degree window centered on every phase bin. The resulting HFA histograms—each containing 50 values—were averaged separately for SR+ and RS+, separately for $\theta$ and $\beta$ activity. We then calculated the normalized Kullback–Leibler divergence (KLD) of the observed distribution against a uniform distribution to quantify how strongly the observed distribution of HFA of SR+ and RS+ were modulated by the phase of the $\theta$ or $\beta$ activity. The obtained KLD within a 2-way ANOVA with the factor channel type ($\text{SR}^+ \text{ or}$ SR) and frequency band ($\theta$ or $\beta$). The interaction effect of the ANOVA describes the double dissociation of HFA of SR+ and RS+ PAC to $\theta$ and $\beta$ networks, respectively.

IV – Comparison of dominant band power. We estimated the power spectral density (PSD) in each trial (collapsing across all S1, S2, and S3 separately) for SR+ and RS+ channels using Welch’s method based on the FFT. Specifically, for each channel, we calculated PSD as a function of frequency (1–30 Hz, 1 Hz steps) in each trial in temporal intervals of 100 ms (due to the short SOA of 600 ms) between $-0.1$ to 0.3 s in steps of 50 ms. The resulting PSD values were compared across trials yielding one PSD for each channel. We averaged across channels ($\theta$ (4–8 Hz) and $\beta$ (8–12 Hz)) and compared the resulting power estimates across channels using a two-way ANOVA with the factors channel type ($\text{SR}^+ \text{ or}$ SR−, $\text{SR}^+$, $\text{SR}^-$, and $\text{SR}^+$), and cross-frequency coupling (PAC) is a mechanism that has been proposed to coordinate the timing of neuronal firing within local neural networks (see ref. 73 for a review). We utilized conventional cross-frequency coupling metrics to test for differences in coupling of HFA to low-frequency bands in $\text{SR}^+$ vs $\text{SR}^-$ channels. We calculated the instantaneous phase for low-frequency activity (see below) for each $\text{SR}^+$ and $\text{RS}^-$ channel time series. In the temporal interval of coupling between low-frequency networks as determined in the previous step IV, we divided both the $\theta$ and $\beta$ cycle separately in 50 equally spaced bins ranging from $-\pi$ to $\pi$ and computed the average HFA for all trials within a 45-degree window centered on every phase bin. The resulting HFA histograms—each containing 50 values—were averaged separately for SR+ and RS+, separately for $\theta$ and $\beta$ activity. We then calculated the normalized Kullback–Leibler divergence (KLD) of the observed distribution against a uniform distribution to quantify how strongly the observed distribution of HFA of $\text{SR}^+$ and $\text{RS}^+$ were modulated by the phase of the $\theta$ or $\beta$ activity. The obtained KLD was compared with 1000 permutations leading to a two-way ANOVA with the factors channel type ($\text{SR}^+$ or SR) and frequency band ($\theta$ or $\beta$). The interaction effect of the ANOVA describes the double dissociation of HFA of $\text{SR}^+$ and $\text{RS}^+$ PAC to $\theta$ and $\beta$ networks, respectively.

V – Cross-frequency coupling. The interplay between activity at distinct frequencies is proposed to be regulated via cross-frequency phase coupling (CFC) [74] and via phase–amplitude cross-frequency coupling (PAC; see below) [75,76]. Phase–amplitude cross-frequency coupling (PAC) is a mechanism that has been proposed to coordinate the timing of neuronal firing within local neural networks (see ref. 73 for a review). We utilized conventional cross-frequency coupling metrics to test for differences in coupling of HFA to low-frequency bands in $\text{SR}^+$ vs $\text{RS}^-$ channels. We calculated the instantaneous phase for low-frequency activity (see below) for each $\text{SR}^+$ and $\text{RS}^-$ channel time series. In the temporal interval of coupling between low-frequency networks as determined in the previous step IV, we divided both the $\theta$ and $\beta$ cycle separately in 50 equally spaced bins ranging from $-\pi$ to $\pi$ and computed the average HFA for all trials within a 45-degree window centered on every phase bin. The resulting HFA histograms—each containing 50 values—were averaged separately for SR+ and RS+, separately for $\theta$ and $\beta$ activity. We then calculated the normalized Kullback–Leibler divergence (KLD) of the observed distribution against a uniform distribution to quantify how strongly the observed distribution of HFA of $\text{SR}^+$ and $\text{RS}^+$ were modulated by the phase of the $\theta$ or $\beta$ activity. The obtained KLD was compared with 1000 permutations leading to a two-way ANOVA with the factors channel type ($\text{SR}^+$ or SR) and frequency band ($\theta$ or $\beta$). The interaction effect of the ANOVA describes the double dissociation of HFA of $\text{SR}^+$ and $\text{RS}^+$ PAC to $\theta$ and $\beta$ networks, respectively.

VI – SR–RS integration. We hypothesized that while the amplitude of HFA is modulated by the phase of the low frequencies within a population (PAC) [76], CFC is prevalent across populations in low frequencies might be achieved via CFC [74,75,76]. CFC is defined by a nonrandom phase difference between oscillations, enabling topically precise coordination or integration among functionally distinct oscillatory networks [77]. We tested whether oscillatory rhythms in different frequency bands $f_1$ and $f_2$ either $\theta$, $\alpha$, $\beta$, or $\delta$—are aligned and whether this interaction is modulated in time. To that end, we calculated the instantaneous phase of $\text{SR}^+$ and $\text{RS}^-$ channel time series and binned phase time series in intervals of one cycle of the $f_1$ (133 ms for $\theta$ and 100 ms for $\alpha$) centered on time points between $-200$ to $300$ ms following stimulus onset in each trial. In each frequency interval in each trial, we divided the $f_1$ cycle into 50 equally spaced bins ranging from $-\pi$ to $\pi$ and registered the $f_1$ phase at each bin. This was done for each pair of $\text{SR}^+$ and $\text{RS}^-$ channels, excluding $\text{SR}^+$-$\text{RS}^-$ channels within each single recording session and separately for each participant, in which we found both $\text{SR}^+$ and $\text{RS}^-$ channels. This results in an $f_1$ phase distribution at each $f_1$ phase and each time point for each pair. For each distribution, we calculated the concentration coefficient $\kappa$ (reciprocal value to variance)

$$\kappa = \frac{1}{\sigma^2}$$

across all $f_1$ phase angles at each $f_1$ phase at each time point. $\kappa$ time series of each $\text{SR}^+$-$\text{RS}^-$ channel pair were baseline corrected by subtracting the mean $\kappa$ values in 1000 permutations leading to a one-way ANOVA with the factors channel type ($\text{SR}^+$ or $\text{RS}^-$), and frequency band ($\theta$, $\alpha$, $\beta$, or $\delta$). The obtained $\kappa$ was compared against a surrogate distribution. In 1000 runs, we shifted phase time series in each trial and each channel separately and calculated $\kappa$ values. To correct for multiple comparisons, $\kappa$ values were assigned to each $\kappa$ value within the surrogate distribution and corrected by applying the FDR procedure. We then compared $\kappa_{0.0}$ with $\kappa_{0.0}$ and $\kappa_{0.0}$ time series. To parameterize the difference in $\kappa$ across coupling, we ran a one-way ANOVA with factor frequency pairs ($\theta$, $\alpha$, and $\beta$) and $\kappa$ time series. The obtained $\kappa$ was compared against a surrogate distribution. In 1000 permutations leading to a one-way ANOVA, $\kappa$ values were assigned to each $\kappa$ value within the surrogate distribution and corrected by applying the FDR procedure. We then compared $\kappa_{0.0}$ with $\kappa_{0.0}$ and $\kappa_{0.0}$ time series. To parameterize the difference in $\kappa$ across different $\delta$ time series, we tested whether $\theta$ values were assigned to each $\kappa$ value within the surrogate distribution and corrected by applying the FDR procedure. We then compared $\kappa_{0.0}$ with $\kappa_{0.0}$ and $\kappa_{0.0}$ time series. To parameterize the difference in $\kappa$ across different $\delta$ time series, we tested whether $\theta$ values were assigned to each $\kappa$ value within the surrogate distribution and corrected by applying the FDR procedure.
between −0.1 and 0.4 s for trial-averaged HFA.

\[
\text{MI} = \frac{H(R|S) + H(S|R) - H(RS, SR)}{-\log(2)\text{MI value}}
\]

(4)

Where H(R|S) and H(S|R) stands for the entropy of the SR+RS- channel and SR−RS+ channel, respectively, and H(RS, SR) designates their joint entropy. The denominator standardizes each value by the maximal achievable information value. We iterated through all intervals around each point of RS+ and SR− channels resulting in a matrix of MI values quantifying which temporal interval of the HFA time series of SR+ channels predicts the HFA time series of SR− channels and vice versa for each pair of channels. We then averaged the MI across all pairs of channels. We then compared each MI-value against a surrogate distribution. This surrogate distribution was constructed by randomly shifting SR+ and SR− time series of single channels and averaging across subjects in 1000 permutations. In each run, we repeated the same analysis as outlined above. This leads to 1000 surrogate MI values. The resulting p values for the MI values relative to the surrogate distribution were corrected by applying the FDR.

**Reporting summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this article.

**Data availability**

The datasets generated and/or analyzed during the current study are available in the Open Science Foundation repository (https://osf.io/ceut7/view_only=16da8766ce03458ca25ade4945972d8c).

**Code availability**

Custom MATLAB 2013b code used for preprocessing and analysis is available as a GitHub repository (https://github.com/repetitionsuppression/ECoGRepetitionSuppression), which includes system requirements and dependencies.

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**Code availability**

Custom MATLAB 2013b code used for preprocessing and analysis is available as a GitHub repository (https://github.com/repetitionsuppression/ECoGRepetitionSuppression), which includes system requirements and dependencies.
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