

Visual and Audiovisual Effects of Isochronous Timing on Visual Perception and Brain Activity

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Understanding how the brain extracts and combines temporal structure (rhythm) information from events presented to different senses remains unresolved. Many neuroimaging beat perception studies have focused on the auditory domain and show the presence of a highly regular beat (isochrony) in “auditory” stimulus streams enhances neural responses in a distributed brain network and affects perceptual performance. Here, we acquired functional magnetic resonance imaging (fMRI) measurements of brain activity while healthy human participants performed a visual task on isochronous versus randomly timed “visual” streams, with or without concurrent task-irrelevant sounds. We found that visual detection of higher intensity oddball targets was better for isochronous than randomly timed streams, extending previous auditory findings to vision. The impact of isochrony on visual target sensitivity correlated positively with fMRI signal changes not only in visual cortex but also in auditory sensory cortex during audiovisual presentations. Visual isochrony activated a similar timing-related brain network to that previously found primarily in auditory beat perception work. Finally, activity in multisensory left posterior superior temporal sulcus increased specifically during concurrent isochronous audiovisual presentations. These results indicate that regular isochronous timing can modulate visual processing and this can also involve multisensory audiovisual brain mechanisms.

Keywords: cross-modal, multisensory, neuroimaging, prediction, timing

Introduction

Our senses are continuously bombarded by a plethora of events in our environment. These events often carry rich timing information that can be used to determine the relationship between inputs within or between different sensory modalities. This is apparent when listening to and observing music being played. By watching the lead violinist, we are better able to extract the stream of individual notes they play from the complex auditory input generated by the full orchestra. By listening to a soloist play, we are better able to predict the series of movements they will make than when watching a muted recording. In these 2 examples, synchronous audiovisual presentations enhance understanding of component events, in particular their underlying temporal structure (rhythm). Understanding how the brain extracts and combines both timing information from events within and between different sensory modalities has been little explored. Here, we focused on how audiovisual presentations manipulate brain responses to visual stimulus trains with different temporal structures.

Knowing when an event will occur can influence perception, resulting in both speeded reaction times (e.g., Coull and Nobre 1998; Davranche et al. 2011; Griffin et al. 2001) and improved accuracy for judging that event (Correa et al. 2004, 2005; Martens and Johnson 2005; Davranche et al. 2011). Much work on this topic has used temporal “orienting” cues that indicate the likely onset time for a target stimulus either symbolically or via the timing of another event (e.g., Bertelson 1967; Bertelson and Tisseyre 1968; Niemi and Näätänen 1981; Coull and Nobre 1998; Coull et al. 2000; Griffin et al. 2001; Nobre 2001; Correa et al. 2004, 2005; Martens and Johnson 2005; Davranche et al. 2011). Other studies have examined how the rhythm or global temporal structure of a stimulus train can provide temporal information regarding onset of a critical target event (e.g., Jones et al. 2002, 2006; Coull and Nobre 2008; Rimmele et al. 2011; Rohenkohl et al. 2011). For instance, trains of regularly timed (isochronous) stimuli that predict the onset of a final event can enhance perceptual judgment of that event in audition (Jones et al. 2002; Rimmele et al. 2011), although reportedly not in vision (Doherty et al. 2005). The apparent difference between the impact of isochrony on these 2 modalities might potentially reflect the better temporal resolution of audition than vision (Mabbott 1951), as shown for instance by timing judgments (e.g., Recanzone 2003; Merchant et al. 2008; Grondin and McAuley 2009) or by rhythm reproduction or recall (e.g., Glenberg et al. 1989; Glenberg and Jona 1991; Repp and Penel 2004; Kato and Konishi 2006; Mayer et al. 2009). Here, we manipulated isochrony for the timing of visual stimulus trains in a visual task, while also manipulating whether (task-irrelevant) synchronous sounds were present or not, using both behavioral and functional magnetic resonance imaging (fMRI) measures of brain activity.

Neuroimaging studies investigating processing of timing in the brain have consistently reported activations in a cortico-striatal network, including the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), insula and basal ganglia (e.g., Ferrandez et al. 2003; Coull et al. 2004; Livesey et al. 2007; Macar et al. 2006; Meck et al. 2008; Kosillo and Smith 2010; Harrington et al. 2011). Activity in all these regions is typically enhanced during isochronous beat-containing auditory stimuli, compared with less structured or more complex timing conditions (e.g., Grahn and Brett 2007; Bengtsson et al. 2009; Teki et al. 2011), with responses in the IFG and insula relating to beat perception strength (Grahn and McAuley 2009). The majority of such beat perception studies have focused on active monitoring of rhythms presented in audition, whereas here we instead examined the possible impact of isochrony for visual stimulus

trains. We note that some of the literature using temporal orienting cues, rather than isochronous trains, have already identified the involvement of left inferior parietal cortex in implicit timing tasks for vision (e.g., Assmus et al. 2003, 2005; Coull and Nobre 2008; Wiener et al. 2010; Cotti et al. 2011; Davranche et al. 2011).

Some effects of audiovisual timing manipulations have also been observed for a multisensory region of posterior superior temporal sulcus (pSTS; e.g., Calvert et al. 2000; Calvert 2001; Macaluso et al. 2004; Noesselt et al. 2007; Stevenson et al. 2010; Marchant et al. 2011). This region is thought to receive convergent inputs from auditory and visual cortices (Seltzer and Pandya 1989; Seltzer et al. 1996; Lewis and van Essen 2000) and is commonly reported as being activated during audiovisual integration (e.g., Calvert et al. 2000; Beauchamp et al. 2004; van Atteveldt et al. 2007; Stevenson and James 2009). For instance, activity in pSTS is typically greatest when audiovisual stimuli have simpler temporal structure, as most commonly manipulated by comparing synchronous to asynchronous stimuli (e.g., Calvert 2001; Macaluso et al. 2004; Noesselt et al. 2007; Stevenson et al. 2010; Marchant et al. 2011). In addition to whole-brain fMRI analyses, here we shall examine an a priori region of interest (ROI) in pSTS, to investigate any interaction effect between the impact of isochronous/random stream timing in vision and the presence/absence of concurrent auditory stimuli (audiovisual/vision-only). The coordinates for this pSTS ROI were taken from Noesselt et al. (2007), who utilized similar streams of simple flashes and beeps to those used here, while manipulating audiovisual synchrony in their study (see also Marchant et al. 2011, for use of the identical pSTS ROI). However, Noesselt et al. (2007) used only irregularly timed stimulus streams, whereas here we manipulated isochronous versus random timing for successive events within each stream.

Some impacts of timing have also been observed for sensory-specific cortices. Isochronous auditory stimuli with their highly predictable temporal structure can enhance activity in auditory cortices (Grahn and Brett 2007; Bengtsson et al. 2009), although Teki et al. (2011) reported attenuation. Activity in visual cortex can increase at the expected onset of a visual event (Buetti et al. 2010), which may reflect orienting of attention to the correct time point (Coull and Nobre 1998).

In the current study, we used trains of simple visual stimuli with either isochronous or pseudorandom timing. The behavioral task was to detect occasional higher intensity target events within each visual stream. The difference in intensity for such targets was titrated to avoid ceiling or floor effects in performance. The isochronous or pseudorandom timing of each visual stream gave no information about which item might be a higher intensity target, since intensity is fully orthogonal to timing. Nevertheless, we predicted that detection of intensity targets might be enhanced for the isochronous streams due to the predictable timing of events within them. As regards brain activity, we sought to test whether the timing network implicated in previous studies, involving parietal cortex, DLPFC, IFG, SMA, insula, and basal ganglia (Grahn and Brett 2007; Coull and Nobre 2008; Bengtsson et al. 2009; Kosillo and Smith 2010; Wiener et al. 2010; Cotti et al. 2011; Davranche et al. 2011; Teki et al. 2011), might be implicated in isochronous streams for vision. We further manipulated the presence/absence of concurrent (but task-irrelevant auditory) events, to test whether this might enhance any impacts of

isochrony on brain activations (for the above network, plus for pSTS) and potentially for any impacts of isochrony on visual target detection. Finally, given that timing manipulations can also affect sensory-specific cortex (for both visual and auditory cortex, see above), we examined regions of visual and auditory cortex that responded to our stimuli, testing whether their activity related to the impact of the timing manipulation upon sensory performance.

Materials and Methods

Participants

Seventeen volunteers (age range 19–35 years, 9 females) with no history of neurological or psychiatric illness by self-disclosure gave written informed consent to participate and were reimbursed for their time. All had normal or corrected vision and normal hearing by self-report. Data from one participant were removed due to excessive movements during scanning. This study was approved by the University College London Research Ethics Committee and conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Experimental Set-Up

Visual and auditory stimuli were presented using Cogent v1.25 (Vision Lab, University College London, UK; <http://www.vislab.ucl.ac.uk/>), running in MATLAB v6.5 (MathWorks Inc., Natick, MA) on a Windows PC. Visual stimuli were back-projected onto a screen ($30^\circ \times 26^\circ$) using a LCD projector (LT158; NEC) visible to the participant inside the scanner via a mirror mounted on the MR head coil. Auditory stimuli were presented via etymotic earphones (E-A-RTONE 3A Insert Earphone, E-A-R Auditory Systems, Acaro Company, IN), and ear defenders were worn to reduce background scanner noise. Participants made responses on a 1-button fiber-optic keypad with their right index finger.

Stimuli and Experimental Design

Each trial was 14 s in duration and comprised on average 57 rapid visual events (range 36–141), of which up to 6 were higher intensity targets (mean 3). The standard visual stimulus was a red central annulus (33 ms , 8° va diameter, 2° va aperture, 0.06 cd/mm^2), and the target stimulus was identical except brighter (by a mean \pm standard deviation of $0.17 \pm 0.86 \text{ cd/mm}^2$ across participants after individual titration). Target luminance was set for each participant prior to the main experiment to achieve approximately 75% hit-rate. Target events were restricted from occurring within 1.5 s from the start of a trial, end of the trial, or another target event. Visual stimuli were presented on a black background and a white central fixation cross (0.5° va, 2.31 cd/mm^2) remained visible throughout the experimental session (Fig. 1a). The intertrial interval was 2.01 s. Participants were instructed to make an immediate button press with their right index finger on detection of a brighter visual target.

A 2×2 factorial design manipulated the timing of visual events within each stimulus train (isochronous/random) and whether or not a synchronous auditory tone (30 ms including 5 ms onset and offset ramp, 1000 Hz, 64 dB(A)) accompanied all visual events on that trial. Four possible stimulus-onset-asynchronies (SOAs; 100, 200, 300, and 400 ms) were used between events. In the isochronous condition (ISO), all SOAs were identical throughout a trial, but different SOAs were used for different trials so there was an equal number of each SOA type presented overall (Fig. 1b). In the random condition (RAND), each of the 4 SOAs were equally likely to occur before each event (Fig. 1c). On half of the trials, the visual stimuli were presented alone (V: vision-only) and on the remainder of trials an auditory tone was presented in synchrony with each visual stimulus on that trial (VA: vision and audition, i.e., audiovisual). The auditory stimuli never provided any information about which visual event was a target because the same tone accompanied all visual events.

A total of 32 trials were presented for each of the 4 conditions (V_{ISO} , V_{RAND} , VA_{ISO} , and VA_{RAND}) per participant. Each participant performed

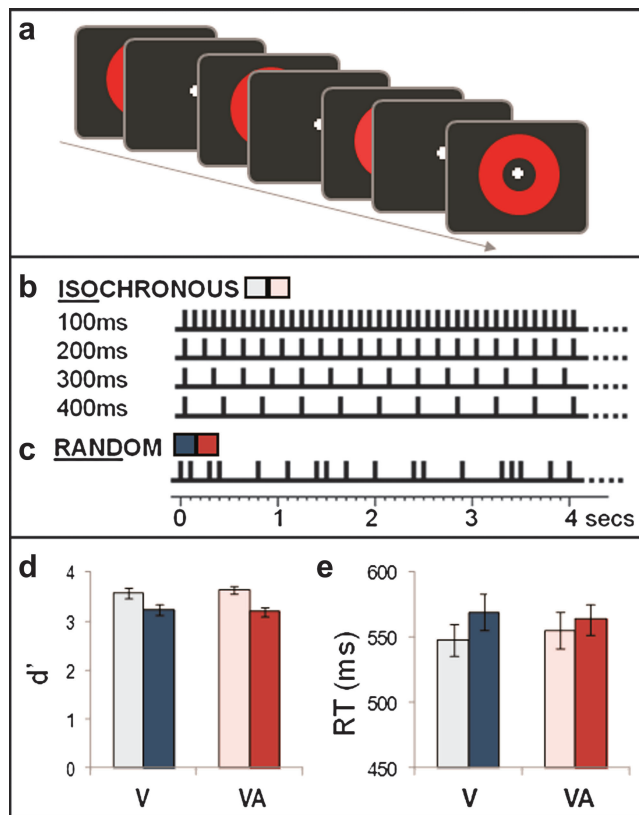


Figure 1. Schematic of visual task and behavioral performance measures. (a) Schematic of visual intensity-target detection task. (b and c) Timeline for stimulus onset during the 4 isochronous trial types (100, 200, 300, and 400 ms SOAs) and an exemplar random timing trial. (d) Visual target detection sensitivity (d') was enhanced and (e) RTs reduced by isochronous (light bars) compared with random timing conditions (dark bars), when visual stimuli were presented alone (V; blue bars) or accompanied by synchronous auditory tones (VA; red bars). Group means (± 1 standard error of the difference (s.e.d) for isochrony effect).

4 functional imaging sessions (~10 min each), each comprising 32 trials (8 trials per experimental condition) plus 4 null trials (14 s) presented in a pseudorandomised order. Prior to the experimental sessions, an in-situ practice was performed inside the scanner to familiarize participants with the task, set visual target luminance, and ensure that experimental auditory stimuli were clearly audible while the scanner was running. A 2-min fieldmap scan and a 12 min structural MRI scan were also conducted.

Behavioral Analysis

The first button press occurring within 1.5 s (response time window) after a target stimulus was classified as a hit (i.e., correctly detected target). The response time window matched the minimum period allowed between target events. The hit-rate was calculated by dividing the total number of hits by the number of targets presented across trials per condition. Any other button presses (not falling within the 1.5 s post-target response window) were classified as false alarm responses, and the total of these were divided by the total number of nontarget events to produce a false alarm rate. Signal detection analysis was then used to combine the hit-rate and false alarm rate measures into a formal measure of target detection sensitivity ($d' = Z(P_{\text{hits}}) - Z(P_{\text{false alarms}})$). Target detection sensitivity (d') and mean reaction time for hit responses (RT) were calculated for each of the 4 experimental conditions and then entered into 2×2 repeated measurement analyses of variance (ANOVAs) (stimulus timing \times presence of auditory tone). All statistical analyses on behavior were performed in SPSS v16.0 (SPSS Inc., Chicago).

Scanning Protocol

A Siemens 3T Allegra MRI (Siemens, Erlangen, Germany) with head coil system was used to acquire high-resolution T_1 -weighted anatomical

images (176 sagittal slices, field of view [FoV] = 256×240 mm FoV, 1 mm^3 voxel size); fieldmap images (double-echo FLASH, time echo $[TE]_1 = 10 \text{ ms}$, $TE_2 = 12.47 \text{ ms}$, $3 \times 3 \times 2 \text{ mm}$ resolution and 1-mm interslice gap); and T_2^* -weighted echoplanar functional images for blood oxygen level-dependent (BOLD) contrast (40 slices, 2-mm slice thickness and 1-mm gap, 3-mm resolution in plane, slice TE = 30 ms, volume time repetition = 2.4, 64×64 matrix). An EPI sequence with a sinusoidal readout and lower slew rates was used to reduce acoustic noise, although this was still audible throughout. Four task EPI sessions of 253 volumes were collected, and the first 6 volumes were discarded to allow for T_1 equilibrium effects.

fMRI Preprocessing and First-Level Analysis

The fMRI data were analyzed using statistical parametric mapping with SPM5 software (<http://www.fil.ion.ucl.ac.uk/spm>; see Friston et al. 1995). Scans from each participant were realigned using the first as a reference, unwarped incorporating fieldmap distortion information, spatially normalized into Montreal Neurological Institute (MNI) standard space (Evans et al. 1992, 1993), resampled to $3 \times 3 \times 3 \text{ mm}^3$ voxels and then spatially smoothed with a Gaussian kernel of 6 mm full-width at half-maximum, in accord with the standard SPM approach.

The 4 experimental trial types (stimulus timing \times presence of auditory tone) were modeled as separate regressors with a 14 s boxcar spanning the trial duration. A first-order parametric function was used to model activity associated with the different number of events within each trial, due to the varied SOA. A stick function regressor for button presses across all trials modeled variance due to target detection and associated motor responses. All regressors were convolved with the haemodynamic response function with both temporal and dispersion derivatives. Six head movemnt regressors created during the realignment preprocessing were also included.

First-level contrast images were generated for the main effects of timing and auditory presence, and the interaction between these 2 experimental factors (testing for a larger effect of auditory presence during isochronous than random streams). Contrast images were also created for each of the 4 conditions to be used in a second-level random-effects ANOVA for a conjunction analysis. Additionally, a contrast image for the main effect of task (collapsed across all 4 conditions) versus null trials allowed identification of peak voxel activations in sensory cortices (left/right occipital lobe, left/right superior temporal gyrus) responding to our stimuli during the task. First-level contrasts were estimated according to the general linear model for each participant.

Brain-Behavior Relation in Sensory Cortices

The participant-specific peak voxels for task trials versus null trials within the left and right occipital lobes and superior temporal gyri were taken to represent stimulus-responsive visual and auditory cortex for each participant. Beta parameter estimates for effects of isochrony versus random timing were extracted for such peak voxels. A participant-by-participant robust regression analysis (MATLAB robust-fit function, default bi-square option) was then performed, using the change in beta parameters values against the change in visual target sensitivity (d') for the main effect of timing (ISO > RAND) for each sensory region. A positive relationship was anticipated, to reflect greater enhancement in brain activity relating to better performance. Note that using the robust-fit function guarded against any such brain-behavior relations being driven by unrepresentative outliers.

Whole Brain Analysis

First-level contrast images for each participant were entered into a second-level random-effects analysis for statistical assessment across participants (Friston et al. 1995). Second-level t -tests were performed for main effects and interaction contrasts. A second-level repeated measures 2×2 ANOVA (stimulus timing \times presence of auditory tone) was generated, and a conjunction analysis was performed to assess regions with common activations for the effect of timing on vision-only trials ($V_{\text{ISO}} > V_{\text{RAND}}$) and on audiovisual trials ($VA_{\text{ISO}} > VA_{\text{RAND}}$). Voxel threshold was set at $p_{\text{unc}} < 0.001$ and only significant clusters surviving

correction for multiple comparisons ($n > 20$; $p_{FWE} < 0.05$) are reported for whole brain analysis. Peak locations for all significant clusters are reported in MNI space.

ROI Analysis

An a priori ROI analysis was performed on multisensory pSTS, as identified by Noesselt et al. (2007; see also Marchant et al. 2011). Noesselt et al. showed this region was modulated by the temporal properties of audiovisual stimuli contralateral to a peripheral visual stimulus. Given the central stimuli presented in the current study, an 8-mm sphere was centered on their peak voxel location in left ($x = -54$, $y = -50$, $z = 8$) and right ($x = 60$, $y = -48$, $z = 12$) pSTS. The average parameter beta values for each ROI were extracted for each participant using the MarsBaR toolbox (Brett et al. 2002) and entered into a 2×2 repeated measures ANOVA (stimulus timing \times presence of auditory tone) in SPSS, with post hoc t -tests performed.

Results

Behavioral Results

Stimulus timing influenced visual intensity-target detection sensitivity (d' ; $F_{1,15} = 51.1$, $P < 0.001$; Fig. 1*d*) and RTs ($F_{1,15} = 9.6$, $P = 0.007$; Fig. 1*e*). Visual sensitivity was improved and reaction times faster for the isochronous than the random timing condition. The presence of an accompanying tone did not significantly influence either visual performance measure.

fMRI Results

Presence of an Auditory Tone Activates Auditory Cortices

Unsurprisingly, auditory cortices along bilateral superior temporal gyri (STG; including both Heschl's gyri and the planum temporale) were more active during audiovisual than vision-only trials (left STG: cluster $p_{FWE} < 0.001$, 823 voxels, peak $t_{15} = 5.55$, $x = -54$, $y = -33$, $z = 12$; right STG: cluster $p_{FWE} < 0.001$, 750 voxels, peak $t_{15} = 8.60$, $x = 63$, $y = -24$, $z = 12$). No brain regions were more active during the vision-only trials.

Isochrony Activated Network of Timing Regions

Isochrony enhanced activity in bilateral IFG, insula, putamen and globus pallidus, left DLPFC, and left intraparietal sulcus (IPS) when compared with random timing (Table 1; Fig. 2*a-c*). A conjunction analysis between the simple effect of isochronous versus random timing on BOLD signal during the vision-only and audiovisual conditions ($[V_{ISO} > V_{RAND}]$ and $[VA_{ISO} > VA_{RAND}]$) confirmed common activation of the right anterior insula by isochrony regardless of sound presence/absence (cluster $p_{FWE} = 0.029$, 72 voxels, peak $t_{15} = 4.52$, $x = 30$, $y = 24$, $z = 6$; Fig. 2*d,e*). A similar pattern of activity was observed in the left anterior insula (Fig. 2*d,e*) but that cluster did not reach full statistical significance and is reported only for completeness (cluster $p_{FWE} > 0.05$, 8 voxels, peak $t_{15} = 4.08$, $x = -30$, $y = 21$, $z = 6$). No regions were preferentially activated for random versus isochronous stimuli.

Positive Brain-Behavior Relation for Main Effect of Timing in Sensory Cortices

Task-related (experimental trials $>$ null) peak voxels in bilateral visual (occipital lobe) and auditory (STG) cortices were identified for each participant (Table 2; Fig. 3) and beta parameter estimates extracted. There was a positive relation between change in behavioral performance (visual target d') and change in activity in the right occipital lobe (Fig. 3*d*) and bilateral STG (Fig. 3*a,b*)

Table 1

Brain regions more active during isochronous than pseudorandomly timed stimulus trains

	Cluster		Peak voxel			
	p_{FWE}	voxels	t_{15}	X	Y	Z
L DLPFC	0.017	31	5.09	-36	36	18
L IFG			4.72	-45	39	12
L insula (posterior)	0.024	29	4.75	-39	3	-3
L insula (anterior)	<0.001	59	5.69	-30	21	3
L putamen			4.75	-24	15	3
L intraparietal sulcus	0.017	59	4.79	-42	-42	36
R IFG	0.005	39	5.22	57	15	6
R insula (anterior)	<0.001	267	8.60	30	24	3
R insula (posterior)			5.08	42	6	0
R globus pallidus			4.57	18	0	3
R putamen			4.02	18	12	-3

Note: Main effect of isochrony $>$ random timing conditions, collapsed across presence or absence of an accompanying auditory tone. ($[V_{ISO} + VA_{ISO}] > [V_{RAND} + VA_{RAND}]$). Peak voxel locations reported in MNI coordinates. Thresholds: voxel $p_{unc} < 0.001$ and cluster $p_{FWE} < 0.05$.

for the main effect of timing (isochrony $>$ random; Table 2). There was also a trend toward the same positive linear relation in left occipital cortex (Fig. 3*c*). Participants with a greater isochrony-induced improvement in performance displayed greater activity enhancement in both visual and auditory sensory cortices for the same contrast. To better understand the relation between visual task performance and auditory cortex responses, we repeated the robust-fit regression analysis with the trials separated according to presence or absence of the auditory tone ($[V_{ISO} > V_{RAND}]$; $[VA_{ISO} > VA_{RAND}]$). The only remaining significant positive correlation in auditory cortex was observed for the right STG during the audiovisual conditions (slope = 1.51, step = -1.66, $t_{15} = 3.0$, $P = 0.047$).

Interaction between Timing and Presence of an Auditory Tone

Whole brain analysis for the interaction contrast ($[VA_{ISO} > VA_{RAND}] > [V_{ISO} > V_{RAND}]$) did not identify any regions showing a significantly greater isochrony enhancement in the audiovisual than vision-only condition. However, the a priori ROI in multisensory left pSTS previously identified to be modulated by audiovisual timing in Noesselt et al. (2007; 8-mm sphere centered at $x = -54$, $y = -50$, $z = 8$; Fig. 4*b*) did show a substantial trend toward an interaction effect ($F_{1,15} = 3.6$; $P = 0.077$) that is reported for completeness; as well as a significant main effect of timing ($F_{1,15} = 6.3$; $P = 0.024$). Post hoc t -tests confirmed that isochrony (vs. random timing) enhanced BOLD signal in left pSTS when visual stimuli were accompanied by an auditory tone ($t_{15} = 3.7$, $P = 0.002$) but not when presented alone ($t_{15} = 0.5$, $P = 0.619$, n.s.; Fig. 4*a*). Activity in left pSTS was highest during the multisensory isochronous condition than all others ($VA_{ISO} > V_{ISO}$: $t_{15} = 2.3$, $P = 0.035$; $VA_{ISO} > V_{RAND}$: $t_{15} = 2.1$, $P = 0.048$). Activity in the ROI in right pSTS also showed a main effect of timing ($F_{1,15} = 5.8$; $P = 0.029$; ISO $>$ RAND), but there was no trend toward an interaction with audiovisual synchrony ($F_{1,15} = 0.2$; $P = 0.668$, n.s.). This concurs with a left lateralisation for this multisensory integration site with centrally presented audiovisual stimuli (e.g., Calvert 2001; Micaluso et al. 2004).

Whole brain analysis for the opposite interaction contrast ($[VA_{ISO} < VA_{RAND}] > [V_{ISO} < V_{RAND}]$) identified a greater effect of random (vs. isochronous) timing in the audiovisual than vision-only condition for activity in the right STG (cluster $p_{FWE} = 0.030$, 25 voxels, peak $t_{15} = 6.75$, $p_{unc} < 0.001$, $x = 63$,

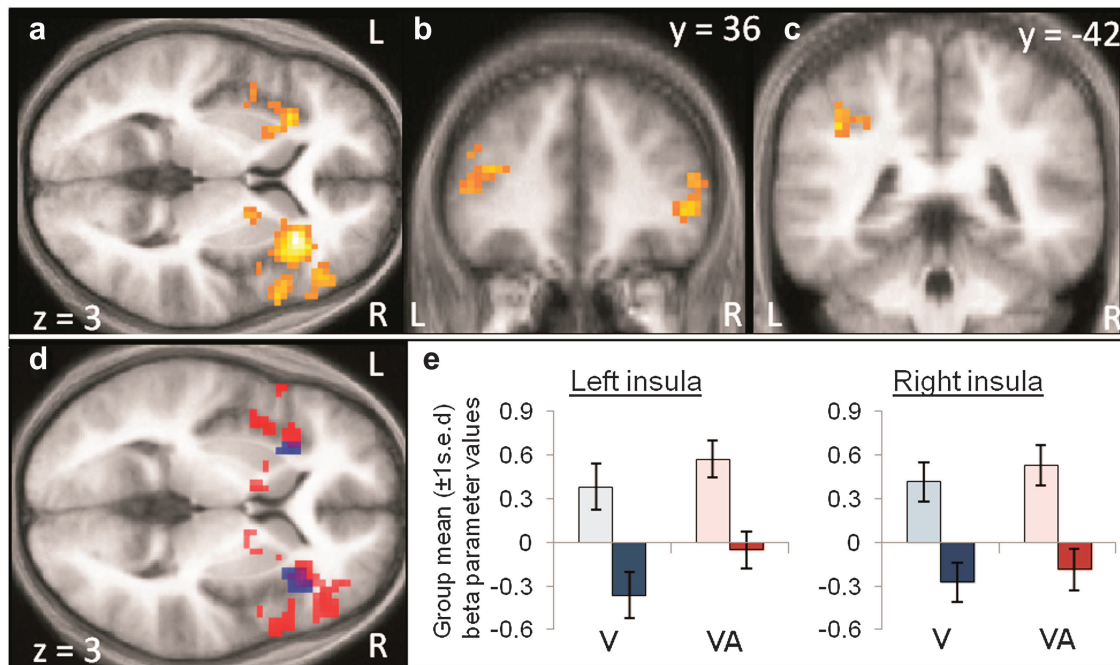


Figure 2. Brain activity enhanced by isochronous stimulus timing. (a) Isochrony versus random timing enhanced activity in bilateral IFG, insula, putamen, and globus pallidus; (b) in left DLPFC; and (c) in left IPS, when collapsed across visual (V) and audiovisual (VA) conditions. (d) Conjunction analysis confirmed overlap (purple shading) between isochrony enhancement effects on vision-only (V; blue shading) and audiovisual (VA; red shading) conditions in bilateral insula. (e) Cluster mean beta parameters (± 1 s.e.d) plotted for each condition (light bars = isochronous; dark bars = random). Thresholds: voxel $p_{unc} < 0.001$ and cluster $p_{FWE} < 0.05$ displayed on mean anatomical brain images.

Table 2
Task-related peak voxel location and robust regression with task performance for isochrony effect

Sensory cortices	Voxel position in MNI coordinates (mm)			Regression results			
	x	y	z	Slope	Step	t_{15}	P-value
L occipital lobe	-14.8 ± 7.8	-93.8 ± 5.0	5.0 ± 10.2	1.27	-0.27	1.5	0.083
R occipital lobe	16.8 ± 7.3	-91.1 ± 4.9	3.6 ± 12.8	2.20	-0.65	2.5	0.012*
L superior temporal gyrus	-55.5 ± 7.7	-18.9 ± 8.8	4.3 ± 4.5	1.89	-1.08	2.3	0.019*
R superior temporal gyrus	60.9 ± 5.1	-17.1 ± 7.9	5.4 ± 4.4	1.62	-1.17	1.9	0.041*

Note: Group mean (\pm standard deviation) task-related peak voxel locations in left and right sensory cortices reported in MNI coordinates. Robust-fit regression analysis results reported for participant-by-participant positive linear relation between change in beta parameter estimates from these peak voxels and change in visual target detection sensitivity (d'), for the contrast isochronous > random timing. * = significant regression ($P < 0.05$).

$y = -15, z = 0$; Fig. 4d). Post hoc paired t -tests (using extracted mean cluster beta parameter estimates) confirmed this was driven by significant enhancement of activity during presentations with random than isochronous timing when visual stimuli were accompanied by a synchronous auditory tone ($t_{15} = 5.3, P < 0.001$) but not when they were presented alone ($t_{15} = -0.5, P = 0.651, n.s.$; Fig. 4c). This presumably represents an auditory response to unpredictably timed sounds.

Discussion

This study investigated the influence of temporal structure (isochronous vs. random) for a visual stimulus train on visual intensity-target detection and brain activity; and any multisensory impact of adding sounds temporally coincident with each visual event. Highly regular isochronous timing enhanced visual target detection sensitivity and speeded detection responses, when compared with random timing. Temporal predictability also increased BOLD signals in an extended network that is

involved in temporal processing, including bilateral IFG, insula and putamen, and left IPS and DLPFC. There was a positive correlation between the participant-by-participant behavioral isochrony effect for target detection and the corresponding isochrony effect on activity in visual and auditory cortices involved by the task. It is noteworthy that “auditory” cortex, as well as visual, correlated with the impact of regular timing on “visual” performance, when concurrent sounds were present. Moreover, a multisensory ROI in the left pSTS showed highest activation during the isochronous than random timing specifically for the audiovisual condition.

The behavioral finding of enhanced visual target detection and speeding of reaction times in the current study, for isochronous versus random conditions, is in general accord with other studies showing that temporal predictability can aid visual task performance (Bertelson 1967; Bertelson and Tisseyre 1968; Niemi and Näätänen 1981; Coull and Nobre 1998; Coull et al. 2000; Griffin et al. 2001; Nobre 2001; Correa et al. 2004, 2005; Martens and Johnson 2005; Davranche et al.

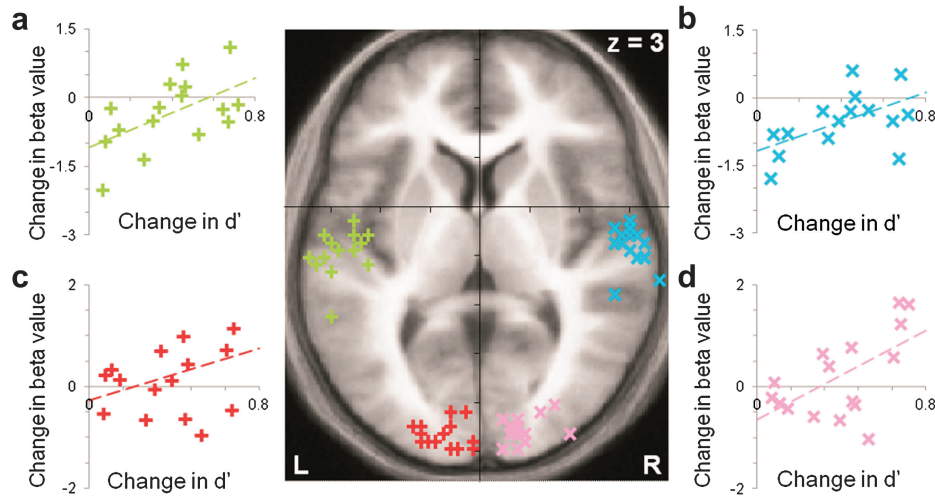


Figure 3. Positive linear relation between changes in performance and beta parameter estimates in sensory cortices for isochrony. Task-related peak voxels were identified in bilateral auditory (superior temporal gyrus, STG) and visual (occipital lobe) cortices per participant. Isochrony-induced voxel beta parameter change in (a) left and (b) right STG, or (c) left and (d) right occipital lobe are plotted against change in target detection sensitivity (d') for the same isochrony versus random timing contrast ($[V_{\text{ISO}} + V_{\text{ISO}}] > [V_{\text{RAND}} + V_{\text{RAND}}]$). One data-point plotted per participant ($n = 16$) with the dashed line representing the robust-fit linear regression result. Individual peak sensory task-related voxel MNI coordinates (x - and y -axis) are plotted in the central figure, collapsed in the z -axis, superimposed on a mean anatomical scan (at $z = 3$) for illustrative purposes. Please note that these sensory voxels were selected a priori, before examining the behavioral results; see main text.

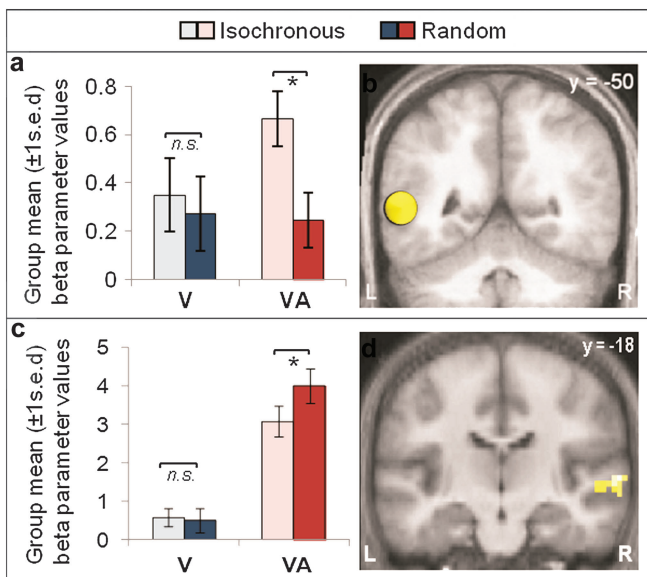


Figure 4. Auditory tone modulates impact of visual stimulus timing on pSTS ROI. (a) Multisensory ROI in left pSTS showed greater isochrony enhancement when visual stimuli were accompanied by a synchronous auditory tone (VA), but not when presented alone (V). (b) The 8-mm sphere ROI was centered at $x = -54$, $y = -50$, $z = 8$, a location previously identified to be modulated by temporal properties of long audiovisual stimulus streams (Noesselt et al. 2007; see also Marchant et al. 2011). By contrast, (c and d) whole brain analysis revealed a region in the right superior temporal gyrus (STG) that showed the opposite interaction pattern, with greater enhancement for random timing during the audiovisual (VA) than the vision-only (V) condition. (a and c) Group mean (± 1 s.e.d. for isochrony effect) beta parameter values plotted for each condition (light bar = isochronous; dark bars = random). (b) Shows ROI; (d) shows significant cluster from whole-brain analysis. Both are displayed on the mean anatomical image. * = Significant post hoc paired t -test ($P < 0.05$).

2011); but our study differs in several key respects. Here, performance was improved when visual targets were embedded within a highly regular (thus temporally predictable) extended isochronous stimulus train, compared with trains

with random timing. While several other studies have used a preceding sequence of events to build up a temporal expectation for the onset of target (Jones et al. 2002; Doherty et al. 2005; Rimmele et al. 2011), they did so for the final event in a predictable sequence, thereby defining which item was the target. In contrast, here we embedded target events at random positions within the sequence of an extended stimulus train while varying the temporal structure of that train. Unlike Doherty et al. (2005), we were able to show that temporal predictability can improve sensitivity to visual target events. Another key feature of our paradigm was that the property that defined visual targets (i.e., intensity) was fully orthogonal to the timing manipulation. Thus, the regular timing in the isochronous streams gave no information about which items were targets and which were nontargets, yet the regular temporal structure nevertheless still improved visual performance objectively.

Turning to brain activations for the isochronous versus pseudorandomly timed streams, parietal cortex, and a wider corticostriatal network were preferentially activated during the isochronous case. Parietal cortex has often been implicated in temporal orienting and temporal judgments (Coull and Nobre 1998, Coull et al. 2001; Assmus et al. 2003, 2005; Wiener et al. 2010; Cotti et al. 2011; Davranche et al. 2011) but is not commonly reported during (primarily auditory) beat perception studies. The enhanced response observed here in the IPS presumably reflects the highly predictable nature of visual event onset within the isochronous stimulus train. The left lateralisation of this IPS response would be in keeping with the present task involving only implicit temporal demands (for reviews, see Coull and Nobre 2008; Wiener et al. 2010), since our participants were never directed to concentrate on temporal structure of the stimuli but instead performed an orthogonal intensity-target detection task.

Activity in bilateral putamen, IFG, and insula was also enhanced during isochronous versus random stimulus timings, when collapsed across presence of an accompanying auditory tone. This fits with previously reported preferential responses

for these 3 regions during rhythmic stimuli containing strong beats, compared with complex or random timing for auditory sequences (Grahn and Brett 2007; Bengtsson et al. 2009; Grahn and Rowe 2009; Teki et al. 2011); but we now show this extends to a visual task. Moreover, we demonstrate that the same network is activated even when the role of timing is only implicit to the task performed, unlike the majority of previous beat-processing studies (Grahn and Brett 2007; Grahn and Rowe 2009; Teki et al. 2011).

The importance of the basal ganglia, which include the putamen and globus pallidus regions implicated here, in detection of temporal structure is indicated by reduced temporal perceptual performance by Parkinsonian patients (Artieda et al. 1992; Pastor et al. 1992; Rammsayer and Classen 1997; Harrington et al. 1998; Malapani et al. 1998; Grahn and Brett 2009; Wojtecki et al. 2011). Moreover, previous exposure to an auditory beat sequence has been shown to enhance activity in bilateral putamen during subsequent visual beat perception tasks (Grahn et al. 2011). So this structure may provide one common site where timing information from different senses may be combined (Buhusi and Meck 2005; Meck 2006).

The impact of isochrony on BOLD signal was also observed bilaterally in IFG and left DLPFC. These regions have often been recruited during timing tasks (e.g., Rao et al. 2001; Macar et al. 2002; Lewis and Miall 2003, 2006). It has been proposed that the right inferior prefrontal cortex is involved in general time measurement (Lewis and Miall 2006) or plays a monitoring role during temporal expectation (Vallesi et al. 2007); whereas the left frontal operculum has more specifically been implicated in temporal sequence discrimination (Schubotz et al. 2000; Schubotz and von Cramon 2001) and beat perception strength (Grahn and McAuley 2009). Bengtsson et al. (2009) reported increasing activation of both left IFG and DLPFC, as well as the insula, for stimuli with increasing temporal predictability during passive listening to auditory sequences.

The insula was the only region significantly enhanced by isochrony during both visual-only and audiovisual presentations here, as identified using a conjunction analysis. This would fit with previous studies reporting recruitment of the insula during temporal judgment tasks for both auditory (Ferrandez et al. 2003; Livesey et al. 2007; Morillon et al. 2009; Herdener et al. 2009) and visual stimuli (Rao et al. 2001; Nenadic et al. 2003; Herdener et al. 2009; see review Kosillo and Smith 2010), and in perception of rhythm for extended stimulus trains (Schubotz et al. 2000). Although observed bilaterally for the insula, the impact of isochrony here was somewhat stronger for the right insula, which is preferentially responsive to simple compared with complex auditory sequences (Grahn and Brett 2007). Here, we show this is also the case for visual stimuli, irrespective of whether they were presented alone or accompanied by a synchronous tone and when timing was implicit to the task performed (i.e., visual intensity-target detection).

There was no such main effect of isochrony on BOLD signal in sensory cortices but rather the strength of isochrony-induced enhancements in visual (occipital lobe) and auditory cortices (STG) correlated positively with the improvement in visual task performance (d') for isochronous streams. The intriguing correlation of auditory cortex with the impact of isochrony on the visual task was found only in the presence of concurrent sounds. We propose that these effects reflect sensory encoding of the regular temporal properties of the

isochronous streams, which went on to enhance performance in the (orthogonal) visual detection task. The involvement of auditory cortex when concurrent sounds were presented presumably indicates that the temporal structure of events in this additional (but task-irrelevant) modality was also encoded, even though the task-relevant target could only arise within the visual modality.

A ROI analysis in left pSTS (site taken from Noesselt et al. 2007) revealed a trend interaction, with preferential activation for stimuli with isochronous rather than random timing only when the inputs were multisensory (i.e., auditory tones present). Multisensory pSTS has long been implicated as an audiovisual integration site (e.g., see Calvert 2001; Beauchamp et al. 2004; Bischoff et al. 2007; Hein et al. 2007; Meienbrock et al. 2007; Stevenson and James 2009; Stevenson et al. 2010; Werner and Noppeney 2010; James et al. 2011). This region is thought to receive input from both sensory cortices (Seltzer et al. 1996; Lewis and van Essen 2000) and functional connectivity with these regions can be modulated by correspondence between multisensory inputs (Lewis and Noppeney 2010). The specific ROI location used here is influenced by the relative timing between auditory and visual stimulus trains (Noesselt et al. 2007; used by Marchant et al. 2011).

In the current study, synchronous central audiovisual presentation enhanced activity in the left pSTS region compared with unisensory presentation and this was more pronounced for stimuli with predictable than unpredictable timing. Furthermore, the impact of temporal predictability on this region was restricted to audiovisual presentation, not unisensory visual stimuli. Left lateralisation of the influence of temporal structure on pSTS would be in keeping with other audiovisual timing studies using centrally presented stimuli (Calvert et al. 2001; Macaluso et al. 2004). This might potentially reflect a similar impact of implicit timing on the left hemisphere, as observed for inferior parietal cortex (Coull and Nobre 1998; Wiener et al. 2010), except specifically constrained to multisensory stimulation.

One other region showed an impact of timing restricted to audiovisual presentations but for the reverse contrast. Random versus isochronous timing enhanced activity in the right STG but only when the visual stimuli were accompanied by synchronous tones. Teki et al. (2011) also reported heightened response to random compared with isochronous auditory stimuli in STG bilaterally but more posterior ($x = 66, y = -39, z = 3$) to our peak locus ($x = 63, y = -15, z = 3$). In a location more similar to that observed here ($x = 66, y = -22, z = 2$), Overath et al. (2007) reported increased activity in the planum temporale of the right STG that correlated with increasing entropy (decreasing predictability) for sequences of tones with different pitches. These results together with our current findings indicate enhanced BOLD signal in auditory cortex for conditions with more auditory disorder (i.e., higher unpredictability), apparently irrespective of whether this is defined in the temporal domain as used here or in the pitch domain for Overath et al. (2007). The planum temporale in the STG has been proposed as a computational hub for spectrotemporally complex auditory information (Griffiths and Warren 2002).

To conclude, isochronous (vs. random) temporal structure for stimulus trains enhanced detection of embedded unisensory visual intensity targets and increased activity in a cortico-striatal network and the IPS. A positive relation was observed between isochronous versus random behavioral effects on

visual target detection and activity in sensory cortices. Two regions showed an impact of timing limited to audiovisual presentations: predictable timing enhanced activity in multisensory pSTS, while random timing enhanced activity in the planum temporale. We believe this is the first evidence that the influence of temporal encoding in multisensory integration is not only restricted to the relative timing between inputs from different modalities, but it is also dependent upon the predictable nature of component events within each sensory modality.

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Notes

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