available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Unconscious contextual memory affects early responses in the anterior temporal lobe

Maximilien Chaumon[a,b,*], *Dominique Hasboun*[a,b,d], *Michel Baulac*[a,d], *Claude Adam*[a,b,d], *Catherine Tallon-Baudry*[a,b,c]

[a]*Université Pierre et Marie Curie, UPMC Univ Paris 06, Paris, France*
[b]*CRICM, CNRS UMR 7225 INSERM UMRS 975, Paris, France*
[c]*MEG-EEG Center, Hôpital de la Pitié-Salpêtrière, Paris, France*
[d]*Epileptology Unit, Neurology department, Hôpital de la Pitié-Salpêtrière, Paris, France*

ARTICLE INFO

Article history:
Accepted 23 May 2009
Available online 6 June 2009

Keywords:
Contextual cueing
Visual search
Implicit memory
Implicit learning
Inferior temporal cortex
Intracranial recording
Epilepsy

ABSTRACT

Memory and perception are two tightly interrelated cognitive processes, but the neural level of their interaction remains a matter of debate. Proponents of a late interaction emphasize feedback memory effects on visual processing, whereas others suggest that feed forward processing is affected by memory. In the visual domain, unconscious memory for stable relations among objects is known to influence visually-guided behavior. Recent evidence suggest an early interaction between this form of unconscious memory and visually-driven neural activity: the brain dissociates stable and unstable spatial relations at surprisingly early latencies, within the first 100 ms of sensory processing. The anatomical localization of this early effect however was still uncertain. In this study, we estimated the sources of the early effect in magnetoencephalographic (MEG) recordings, and analyzed intracranial electroencephalographic (iEEG) signal from seven epileptic patients in the modified version of the contextual cueing paradigm we recently developed. In spite of a lack of behavioral effect in the patient population, the striking agreement between the two electrophysiological datasets suggests that memory for spatial relations leads to differential responses in the anterior temporal lobe before 100 ms. The intracranial data further revealed orbitofrontal and more posterior temporal memory related activities around 100 ms. Altogether, the data point toward an early interaction between contextual memories and perceptual processing. The anterior temporal cortex, in particular appears to play a critical role in merging sensory processing with unconscious memory as soon as it gets activated.

1. Introduction

Visual context, defined as semantic and spatial relationships between objects in scenes (Biederman, 1981), is a helpful cue when trying to localize and identify an object. Learned unconsciously and within a few minutes, spatial (Chun and Jiang, 1998) or semantic (Goujon, Didierjean, and Marmèche, in press) context can be used to guide perception and attention

* *Corresponding author*. Laboratoire de Neurosciences Cognitives et Imagerie Cérébrale, LENA CNRS UPR640, 47 Bd de l'Hôpital, 75651 Paris Cedex 13, France.
E-mail address: maximilien.chaumon@gmail.com (M. Chaumon).

0006-8993/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2009.05.087

(Bar, 2004; Chun, 2000; Oliva and Torralba, 2007). However, the level at which contextual knowledge interacts with object processing is still a matter of debate (Auckland, et al., 2007; Henderson and Hollingworth, 1999). Does the context directly bias sensory analysis, guiding even the earliest steps of perceptual processing? Or does it interfere with brain processing only at later stages to help perceptual decision making or response selection?

Pioneer electrophysiological studies on the effects of context on neural responses in humans (Ganis and Kutas, 2003) and monkeys (Miyashita, et al., 1996) found late effects (above 300 ms) suggestive of post-perceptual effects. More recently, contextual effects on sensory processing have been shown but at a relatively late stage (around 170 ms Bar et al., 2006), compatible with an effect of contextual memory on perceptual decision rather than on the sensory processing itself. However, we recently described how unconsciously learned spatial relationships modified stimulus-driven MEG responses at their very beginning, between 50 and 100 ms (Chaumon, et al., 2008). This result was surprising in several respects: first, as just mentioned, the effect was earlier than expected based on previous studies, indicating that contextual memory may have an effect on early sensory processing, biasing even its earliest steps. Second, the effect peaked at occipital sensors, consistent with an origin in the underlying sensory cortices. This was surprising because several recent studies have suggested an implication of more anterior regions in contextual memory (Aminoff, Gronau, and Bar, 2007; Bar and Aminoff, 2003; Chun and Phelps, 1999; Greene, et al., 2007). Furthermore, the anterior temporal lobes are known to be a key place of interaction between perception and memory (Miyashita, 1993). However, some unconscious memories may be stored in and retrieved from sensory cortices (Badgaiyan, 2005; Slotnick and Schacter, 2006) and the topography of the MEG effect was also suggestive of an involvement of more anterior regions (Chaumon et al., 2008). As a consequence, the present study aimed at determining whether or not temporal regions are implicated in the early effects of contextual memory on sensory processing.

We had the opportunity to directly assess the involvement of the human temporal lobe in contextual memory retrieval, because this structure is thoroughly explored with intracranial electrodes in epileptic patients undergoing presurgical seizure focus localization. The task used is based on the contextual cueing paradigm (Chun and Jiang, 1998). Subjects searched for a 'T' shaped target among 'L' shaped distractors (Fig. 1) for hundreds of trials. Unknown to them, all distractor layouts were presented several times along the experiment. There were only 24 different distractor layouts repeated 12 times. Half of these distractor layouts were associated with a constant target position along the experiment and constituted the Predictive (P) condition. Each given distractor layout in this condition predicted specifically where the target would be found. On the contrary, the other half of the distractor layouts were associated with a changing target position along the experiment and constituted the non-Predictive (nP) condition. In this condition, given a certain layout of distractors, it was thus impossible to predict where the target would be found.

We recorded intracranial EEG activity in 7 epileptic patients and compared the results with the estimated sources of MEG data recorded from 16 normal subjects in an earlier experiment (Chaumon et al., 2008). We determine here whether temporal regions are involved in the quick retrieval of unconscious contextual memories by measuring specifically the differences in the early evoked electrophysiological data at the end of the experiment at 167 recorded sites.

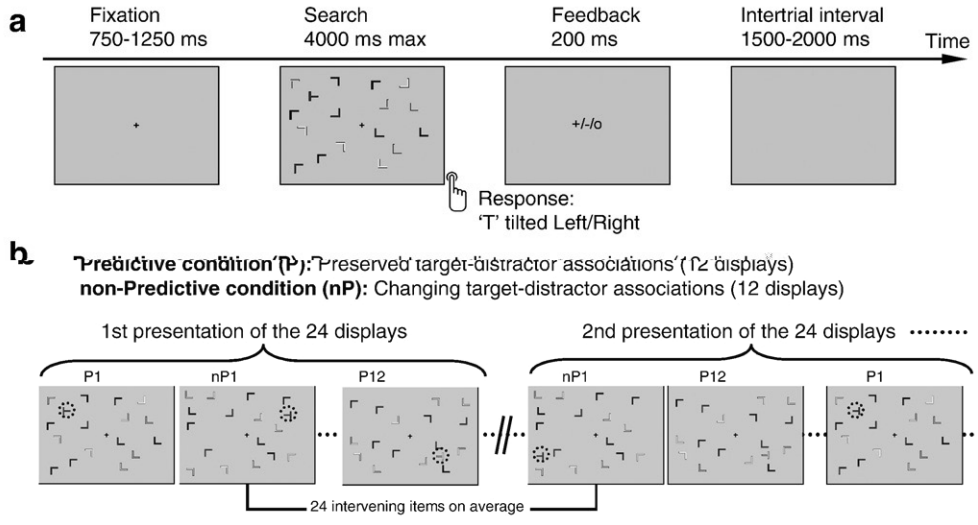

Fig. 1 – Paradigm. (a) Subjects searched for the "T" and reported its orientation (tilted left or right). The subject's response (around 1400 ms on average) interrupted the visual display and triggered a feedback screen ('+' or '–' for good and bad response respectively). An absence of response after 4 s was followed by an 'o' feedback. (b) Experimental sequence. In the Predictive (P) configurations, a given array of Ls was associated with the same target position throughout the experiment (for instance array P1 is associated here with a T in the upper left quadrant). In the non-Predictive configurations, the target location changed on each presentation of a given configuration (for instance array nP1 here).

2. Results

2.1. Behavior

In normal subjects, we have previously reported (Chaumon et al., 2008) a clear behavioral effect of learning contextual regularities. Correct reaction times above 300 ms within the average reaction time ± 2 standard deviations were analyzed. Subjects were 79 ± 16 ms faster at finding the target in the P condition than in the nP condition at the end of the experiment ($t(15) = 4.87$, $p < 0.001$). Behavioral data in patients were thoroughly analyzed but none of our measures could detect an effect of contextual cueing in reaction times. We report the results from the repeated measures ANOVA with two factors (condition and presentation numbers), as classically used in contextual cueing experiments. None of the factors, nor their interaction reached significance (all $F < 1$). A standard *t*-test approach, as used previously (Chaumon et al., 2008) did not show any significant difference neither at the subject level, nor at the group level (all $T < 1$). Reaction times for each subject in each condition are summarized in Table 1. On average, the patients' reaction times were 540 ms longer than the normal subjects' reaction times. Patients also made more errors (12%) than normal subjects did (3%) but there was no difference between P and nP conditions in either case.

After the experiment, patients were asked explicitly to report anything they may have noticed about the images in the experiment. None ever mentioned a repetition of any kind. They were then told that images were repeated. None reported having noticed this. This suggests that patients were not conscious of the spatial relationships between target and context. Normal subjects were more thoroughly tested and did not show any sign of explicit knowledge, as reported previously (Chaumon et al., 2008).

2.2. MEG source localization

Normal subjects showed a strong behavioral effect. Where in the brain do we observe the first electrophysiological counterparts of this effect? To answer this question, we reanalyzed MEG data recorded previously and estimated the cortical sources of the unconscious memory effect.

The minimum norm estimate of the origin of the differential MEG activity in the two conditions during presentations 9 to 12 at the peak of the effect (90–100 ms; Chaumon et al., 2008) was calculated for each subject and submitted to parametric tests (two tailed paired *t*-tests). The map on Fig. 2a shows the statistical map of differential activity thresholded at $|T(15)| > 2.94$, corresponding to a $p < 0.01$ (uncorrected two tailed *t*-test). The differentially activated sources were found essentially in the left anterior temporal lobe. The most significant cluster was close to the anterior portion of the hippocampal formation (surrounded in blue on Fig. 2a and blue trace on Fig. 2b), and the second most significant cluster was found in the inferior portion of the left anterior temporal lobe (surrounded in green on Fig. 2a and green trace on Fig. 2b). The time course of these two regions is shown on Fig. 2b. The effect peaked at 90 ms at both sites, in perfect agreement with differences observed at the scalp level (Chaumon et al., 2008).

2.3. iEEG evoked potentials

Do we find differential activity in the same structures in the implanted patients? To identify the cortical structures that could distinguish between P and nP displays after learning, we systematically tested the difference in the signal evoked by P and nP displays using a randomization procedure (see Experimental procedures). Only contacts reaching $p < 0.01$ for 10 ms at least between 30 and 120 ms were considered. Nine bipolar contacts were isolated in this manner. These contacts dissociated the two conditions early after stimulus onset on presentations 9 to 12, at the end of the experiment. Noteworthy, none of these contacts showed any significant difference during presentations 1 to 4. As a consequence, although some of the contacts reported below are close to the region of epileptic focus (Table 1), we are confident that the difference in response depends on learning of contextual relations rather than in epileptic activity (which in any case was discarded from all analysis when visible).

These contacts are grouped here by anatomical localization and this grouping is also reflected in the latency of the effects. The anterior temporal group (Fig. 3) is made of five contacts in the medial (Figs. 3a and b), inferior (Fig. 3c) and lateral (Figs. 3d and e) parts of the anterior temporal cortex. This anterior temporal group is also characterized by the earliest differentiation between Predictive and non-Predictive displays, with differences peaking between 55 and 105 ms. A more posterior group (Fig. 4) is made of 2 contacts in the lateral temporal lobe, with differences between predictive and non predictive

Table 1 – Individual average reaction times (ms) per patient included in the analysis.

	Presentations 1 to 4			Presentations 9 to 12		
	Predictive	Non-Predictive	Difference	Predictive	Non-Predictive	Difference
Patient01	2375 ± 19	2324 ± 18	51	2088 ± 17	2105 ± 15	−16
Patient03	2427 ± 20	2743 ± 24	−316	2042 ± 17	2018 ± 20	24
Patient05	1135 ± 11	1109 ± 9	26	842 ± 7	829 ± 4	13
Patient06	2003 ± 18	2177 ± 17	−174	1888 ± 19	1899 ± 13	−11
Patient07	2137 ± 16	1688 ± 12	449	2119 ± 15	2064 ± 19	55

For each patient, reaction times outside mean ± 2 standard deviations were discarded.
The "Difference" column shows the contextual cueing effect (P — nP reaction times). Negative values in this column show shortenings of reaction times in the P relative to nP condition.

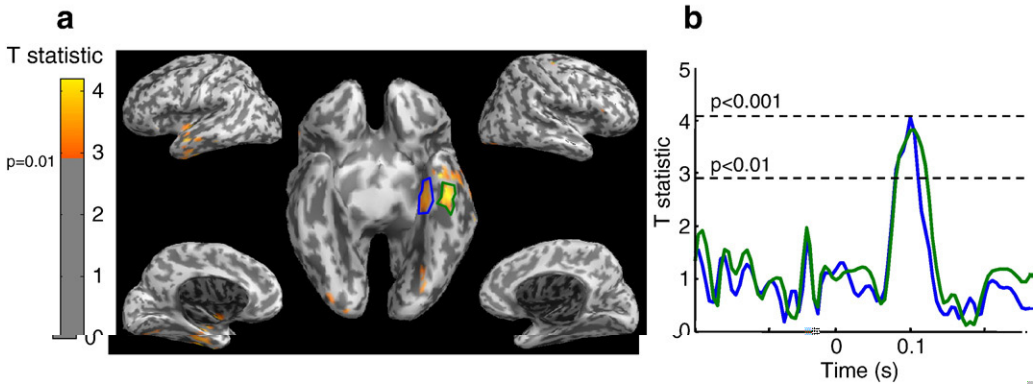

Fig. 2 – Differentially activated sources in the MEG experiment during presentations 9 to 12. (a) Statistical maps of the difference in estimated sources activity between P and nP responses at the end of the experiment (presentations 9 to 12) at the peak of significance in the evoked MEG data (90–100 ms). Colored sources have a $|T|>2.94$ ($p<0.01$ two tailed paired t-tests uncorrected for multiple comparisons). Lateral and medial views are shown on the top and bottom rows respectively. The central map is a ventral view with the anterior part pointing upwards. This latter view shows several clusters of activity in the left medial anterior temporal lobe. (b) Time course of the absolute value of the T statistic on the anterior sources surrounded in blue and green on the central map in a. Thresholds on the y axis are for two tailed paired t-tests.

conditions starting at 100 ms. Last, two recording sites in the orbitofrontal cortex (Fig. 5) differentiate P and nP displays in the same latency range. We use these three regions (anterior temporal, posterior lateral temporal and orbitofrontal) to describe the results in the following paragraphs.

2.4. *Anterior temporal contacts*

Five contacts that differentiate P and nP displays at the end of the experiment were found in the anterior temporal lobes bilaterally in three different patients. Their Talaraich coordinates and anatomical localization in the horizontal plane are shown in Fig. 3 (left column). All these contacts (Fig. 3) are located in Brodman area (BA) 21 or at the border between BA 20 and BA 21. Although they obviously record neural activity from the anterior temporal lobe, it is difficult to be more accurate on their position, in particular along the medial/lateral axis: because we used bipolar montages, the intrinsic resolution is constrained by inter-contact spacing, in the order of 1 cm.

All these contacts showed early, visually-driven responses that were affected by our experimental conditions (Fig. 3, middle and right column). The first peak of the response was observed before 105 ms at all sites, and it was significantly affected by the type of display presented. Importantly, it appeared that this first response was of opposite polarity in the P and nP conditions, suggesting that the neural populations responding to these two types of displays could be different.

Crucially, the difference between the responses to P and nP displays was present only at the end of the experiment (Fig. 3 right column). At the beginning of the experiment, when the predictive nature of the P displays had not yet been registered, these anterior regions did not respond or responded weakly to the search displays, and considered all displays equivalent.

It is worth noting that contact patient06 TeBL3-4 (Fig. 3d) was situated at the border of a dysplasic lesion present in patient06. This contact is nevertheless included in the analysis because it showed a response to the presentation of the images, as shown on the time courses in the middle of Fig. 3, fourth row. It is also comparable in position and latency with the effect at contact patient01 Amyg1-2 (Fig. 3e) and thus seems to reflect a response that can be observed without any lesion to this part of the brain.

2.5. *Posterior lateral temporal contacts*

The second group of contacts was found more laterally and more posterior in the temporal lobe, in the middle temporal gyrus (BA 21).

Two contacts from two patients responded around 100 ms in this region. As shown on the curves and the bar plot of Fig. 4a, contact patient06 HiMo4-3 dissociated P and nP conditions at 100 ms during presentations 9 to 12 only. The bar plot of Fig. 4a suggests that the dissociation between conditions came from a raise of potential selective to the Predictive condition on the average of presentations 9 to 12. As shown on Fig. 4b, contact patient05 TmBi6-5, the dissociation peaked at 115 ms on the average of presentations 9 to 12, resulting both from a raise of potential in the Predictive condition and a decrease in potential in the non-Predictive condition.

2.6. *Orbitofrontal contacts*

Finally, two contacts dissociated P and nP displays in the orbitofrontal cortex (BA 11, Fig. 5).

As shown on Fig. 5a, contact patient05 OFrP2-3 was situated in the right hemisphere and dissociated Predictive and non-Predictive conditions at 102 ms, only at the end of the experiment. The second contact (patient07 OrAg2-1, Fig. 5b) was situated in the left hemisphere and dissociated the two conditions only at the end of the experiment. The dissociation originated mostly from the appearance of a response specific to the Predictive condition at this contact.

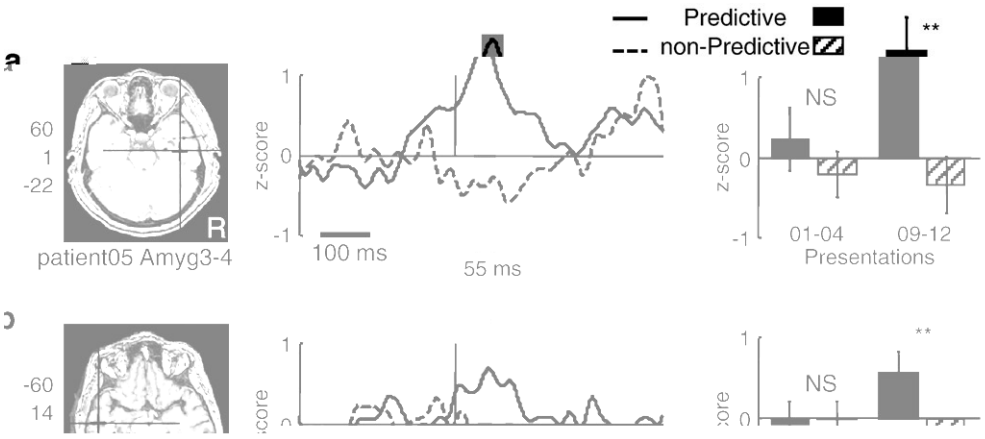

Fig. 3 – Contacts in the anterior temporal cortex dissociate predictive and non predictive arrays from 55 to 105 ms. Five bipolar contacts in three different patients show significantly different responses to Predictive (P) and non-Predictive (nP) displays during the exploiting phase (presentations 9 to 12) but not during the learning phase (presentations 1 to 4). Reference to each of the contacts is made in the main text using letters a to e. For each contact, coordinates in the Talairach space are shown on the left of the horizontal view. The cross on these views shows the exact location of the middle between the two adjacent contacts used for each bipolar montage. The curves in the middle show the time course of the evoked potentials in z units relative to the baseline (–300 to 0 ms before scene onset). Statistical tests were computed from –300 to 400 ms and were significant ($p < 0.01$ for more than 10 ms) only during the shaded time windows on presentations 9 to 12. No significant effect was seen on presentations 1 to 4 on these contacts. The latency of the peak of significance is indicated below each time course. Bar plots show the average amplitude in z units during the significant time windows shaded in grey in the P and nP conditions separately, at the beginning (presentations 1 to 4) and at the end (presentations 9 to 12) of the experiment. (*$p < .05$; **$p < .01$; NS: non significant).

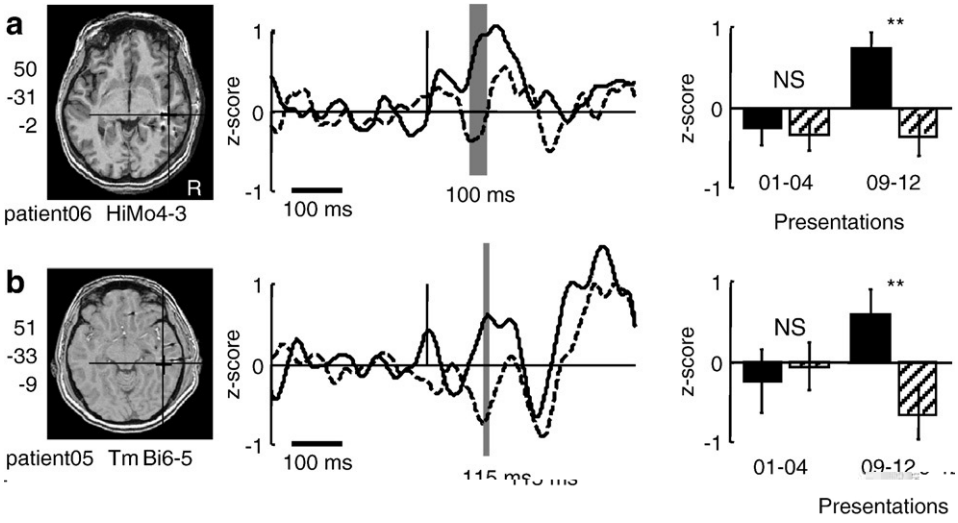

Fig. 4 – Contacts in the posterior lateral temporal cortex dissociate predictive and non predictive arrays after 100 ms. Two bipolar contacts in two different patients show significantly different responses to Predictive (P) and non-Predictive (nP) displays during the exploiting phase (presentations 9 to 12) but not during the learning phase (presentations 1 to 4). Reference to each of the contacts is made in the main text using letters a and b. For each contact, coordinates in the Talairach space are shown on the left of a horizontal view. The cross on these views shows the exact location of the middle between the two adjacent contacts used for each bipolar montage. The curves in the middle show the time course of the evoked potentials in z units relative to the baseline (−300 to 0 ms before scene onset). Statistical tests were computed from −300 to 400 ms and were significant ($p<0.01$ for more than 10 ms) only during the shaded time windows on presentations 9 to 12. No significant effect was seen on presentations 1 to 4 on these contacts. The latency of the peak of significance is indicated below each time course. Bar plots show the average amplitude in z units during the significant time windows shaded in grey in the P and nP conditions separately, at the beginning (presentations 1 to 4) and at the end (presentations 9 to 12) of the experiment. (*$p<.05$; **$p<.01$; NS: non significant).

Interestingly, both contacts responded to the displays with a biphasic response specific to the Predictive condition, peaking around 100 ms and later at around 350 ms. The second response however appeared not significantly different between the two conditions.

3. Discussion

In this study, we used whole head MEG in normal subjects and intracranial EEG in epileptic patients to localize the brain regions dissociating regular from irregular spatial contextual relations in visual search. One striking feature of the present study is the agreement in localization of spatial contextual effects between normal subjects and patients. In two independent sets of subjects, we were able to show early effects of contextual regularities emerging in brain responses in anterior temporal lobe before 100 ms. The source reconstruction technique used on the MEG data showed an effect of spatial regularities mainly located in the anterior temporal lobe. This effect was confirmed in four patients whose brain dissociated regular from irregular contextual relations from 55 to 128 ms at several anterior temporal electrodes. Significant differences appeared in both datasets in brain responses between scenes with steady distractor-target spatial relations (P condition) and scenes with variable distractor-target spatial relations (nP condition). This unconscious memory for spatial contextual relations leads to differential responses in the anterior portion of the temporal lobe (BA 20, 21) and the amygdala, which is consistent with the estimated MEG sources obtained in normal subjects in the same paradigm. Additionally, we observed differential responses in more posterior regions of the temporal lobe (posterior BA 21), as well as in the orbitofrontal cortex (BA 11). Altogether, our results show a very early involvement of the temporal lobe in the interaction between unconscious contextual memory and visual processing.

The behavioral contextual cueing effect could only be obtained in the experiment with normal subjects (Chaumon et al., 2008). Patients did not show a behavioral advantage in the P condition. Although this lack of behavioral effect may be seen as a pitfall in our data, the agreement between the intracranial and MEG data – both at the anatomical and temporal level – is striking and a strong argument that we are actually looking at the same neural mechanism. Furthermore, three other reasons lead us to think that both measures documented here reflect the same brain mechanisms: first, around 15 subjects are usually required in order to get a reliable behavioral effect, while only 5 patients are included in the behavioral analysis here. Second, as mentioned earlier, the agreement between the two datasets, both at the anatomical level and in the latency domain is striking. Finally, modifications of neural activity in sensory cortices following repetition are usually not correlated with behavioral facilitation in priming experiments (Schacter, et al., 2007), and better neural discrimination does not always translate in a behavioral effect (Mruczek and Sheinberg, 2007). Rather, the difference between

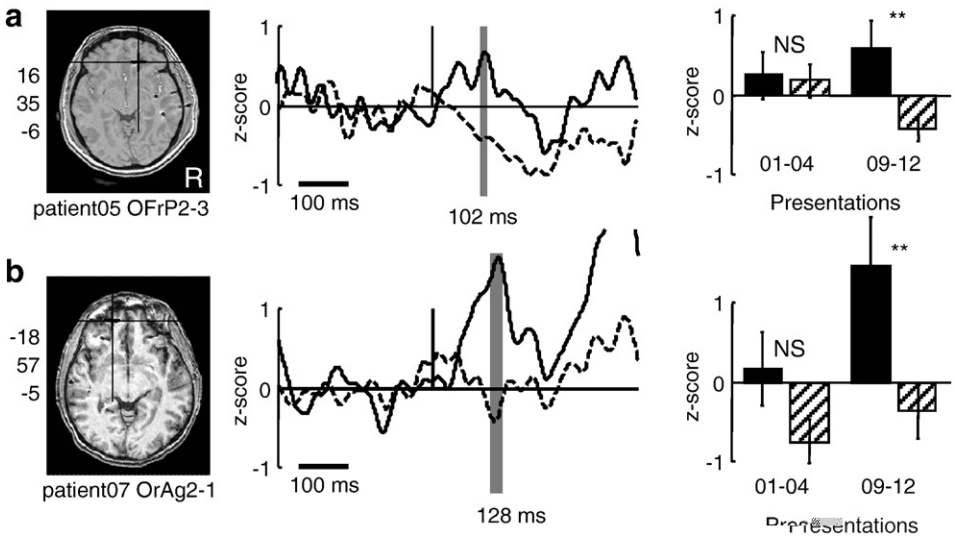

Fig. 5 – Contacts in the orbitofrontal cortex dissociate predictive and non predictive arrays after 100 ms. Two bipolar contacts in two different patients show significantly different responses to Predictive (P) and non-Predictive (nP) displays during the exploiting phase (presentations 9 to 12) but not during the learning phase (presentations 1 to 4). Reference to each of the contacts is made in the main text using letters a and b. For each contact, coordinates in the Talairach space are shown on the left of a horizontal view. The cross on these views shows the exact location of the middle between the two adjacent contacts used for each bipolar montage. The curves in the middle show the time course of the evoked potentials in z units relative to the baseline (−300 to 0 ms before scene onset). Statistical tests were computed from −300 to 400 ms and were significant ($p<0.01$ for more than 10 ms) only during the shaded time windows on presentations 9 to 12. No significant effect was seen on presentations 1 to 4 on these contacts. The latency of the peak of significance is indicated below each time course. Bar plots show the average amplitude in z units during the significant time windows shaded in grey in the P and nP conditions separately, at the beginning (presentations 1 to 4) and at the end (presentations 9 to 12) of the experiment. ($p<.01$; NS: non significant).**

P and nP displays at the end of the experiment attests that learning occurred in patients as well as in normal subjects, although in patients this modification of the early neural processing does not seem to have major repercussions on reaction times 1 to 2 s later. The convergence between 2 distinct sets of data is all the more important that neither alone is completely convincing: source reconstruction of MEG signals is notoriously imprecise, in particular in deep structures such as the anterior temporal lobe, and there is always a doubt that signals from these regions in epileptic patients are altered by their pathological condition. Here two distinct and independent data sets point toward an early involvement of the anterior temporal cortex, therefore giving much weight to the result.

Visual responses in the anterior temporal cortex are known to support visual memory for objects and associations of objects both in humans and animals (Kourtzi and DiCarlo, 2006; Miyashita and Hayashi, 2000). In this region, learning rapidly shapes the sensory system to enhance selectivity in the anterior temporal lobe (Baker, et al., 2002; Freedman, et al., 2006; Mruczek and Sheinberg, 2007). Still, such a rapid and highly specific dissociation between displays is surprising. Other studies that reported such latencies with single unit recordings in humans (from 52 ms Kreiman, et al., 2000) and with scalp event related potentials (from 75 ms VanRullen and Thorpe, 2001), but in these studies the early differential activities were attributable to low level differences in the presented stimuli. Such differences were absent in the present experiment: the low level features of the visual images were strictly identical. The only difference between P and nP images was related to experience accumulated during the experiment. The differences reported here are thus the consequence of a very rapid and specific learning occurring in less than 25 min. Indeed, the differential responses appear only during the last presentations (Figs. 2–4, compare presentations 1 to 4 and 9 to 12 on the bar graphs to the right). The question of the mechanisms of this learning is out of the scope of this paper and is addressed elsewhere (Chaumon, et al., in press). Briefly, this paper corroborates the view that high frequency oscillations participate in learning. These oscillations may be a mean of artificially rehearsing neural activation patterns in order to forge a more efficient neural representation of contextual regularities subsequently activated very rapidly.

Contrary to others in implicit (Greene et al., 2007) and explicit (Burgess, et al., 2001; Ross and Slotnick, 2008) tasks, we did not find a direct hippocampal activation in response to contextual learning in our task. However, it should be noted that our task differed from classical contextual cueing experiments because in our experiment contexts were equally repeated in the two conditions, thereby minimizing the old/new differences that are known to activate the hippocampus (Ranganath and Rainer, 2003). Furthermore, it has been suggested that non predictive nature of a display is learned (Jungé, et al., 2007). In our experiment, the hippocampus may

thus have been recruited equally in both P and nP conditions and hence not show up in the P vs. nP comparison. Similarly, Olson et al. (2001) used a classical contextual cueing paradigm and found no effect directly in the hippocampus.

We also observed differential activation of more posterior temporal regions, as well as in the orbitofrontal cortex, in the 100 ms range. The orbitofrontal cortex is well known for its high level of plasticity. It is at the confluent of all sensory processing streams and is thought to integrate sensory cues and attribute a value to the sensory landscape in a highly flexible manner (Rolls and Grabenhorst., 2008). Activity in the orbitofrontal cortex has also been suggested to signal the formation of an initial guess regarding the identity of objects to be identified from coarse information transmitted directly from early sensory cortices (Bar et al., 2006). In the present experiment, the orbitofrontal activity may reflect value encoded in P contexts and signal the formation of an initial guess of the target location. The model proposed by Bar et al. (2006) suggests that activity from the orbitofrontal cortex influences directly the response in the temporal areas. Our data supports recent evidence of a parallel activation of temporal and frontal regions (Kveraga et al. 2007) and corroborate the idea of a feedback effect of memory on early visual areas. In this view, the effect shown here may represent the source of memory feedback on visual areas suggested by Olson et al. (2001).

Finally, one should keep in mind that implicit memories may be stored in early visual areas (Badgaiyan, 2005; Slotnick and Schacter, 2006). If it is the case here, then the effects we see in the anterior temporal lobe could be the downstream consequence of a modified early perceptual processing. Because early visual areas are not sampled by the intracranial electrodes, we cannot take advantage of the experiment in patients to disentangle this issue. The MEG on the other hand covers the whole head and should in principle show sources in occipital areas if these were activated differentially by contextual regularities (as was suggested by the occipital topography of the difference in Chaumon et al., 2008, Fig. 5). However, the source reconstruction method we used (minimum norm estimate of cortically constrained sources on an anatomical template common to all subjects) may not be well suited to detect sources in the early visual cortices, that are known to be anatomically highly variable across subjects. Thus, we do not make any claim regarding the contribution of other areas in contextual memory retrieval. In any case, however, recurrent processing is unlikely before 100 ms in the temporal lobe (Bullier, 2001). The neural sensory architecture must thus have been modified during learning to enable the subsequent detection of the contextual regularities in a feed forward manner.

In conclusion, we confirm by the present report that unconscious contextual memory dissociates images with and without steady context–target relations within 50–100 ms. We further demonstrate that the anterior temporal cortex plays a key role in integrating visual processing and uconscious contextual memories, as surprisingly early latencies. The anterior temporal cortex reveals an amazing plasticity, effective in less than half an hour, similar in that respect to what is known of the orbitofrontal cortex (Thorpe et al. 1983).

4. Experimental procedures

4.1. *Stimuli*

Stimuli and paradigm were fully described previously (Chaumon et al., 2008). In patients, the only difference was a reduced number of trials. Briefly, each display consisted of a unique configuration of 16 L distractors tilted randomly at 0, 90, 180, or 270° and a T target on a grey background. Items (red, green, blue, or yellow, 0.4×0.4 deg) were randomly placed on an invisible 12×10 grid subtending 12.5×7.5° (3–5 items per quadrant), with a maximal jitter of 0.5° kept constant throughout the experiment. Target positions were constrained to 12 possible locations arranged symmetrically with respect to the center of the screen. An L could never appear at any of these 12 locations. A new set of stimuli was generated for each subject.

4.2. *Paradigm*

A fixation cross (750–1250 ms) was followed by the search array (Fig. 1a). Subjects had to find the T and report its orientation (left or right) by a button press. The subject's response (on average around 1900 ms) interrupted the search display presentation, triggered a feedback screen (+ or – for good or bad response) and initiated the next trial. Failure to respond within 4000 ms triggered a time-out sign (o), and the next trial was initiated (inter-trial interval 1500–2000 ms). Unknown to the subjects, images consisted of two randomly intermingled categories of displays. All configurations were presented the same number of times (Fig. 1b). In each Predictive configuration, all items in the display were identical across repetitions. In the non-Predictive configurations, the T position changed from one presentation of the same distractor configuration to the other. The 12 possible target locations were used the same number of times across repetitions in the Predictive and non-Predictive configurations and the orientation of the target was chosen randomly at each presentation.

The two configuration types (Predictive/non-Predictive) were randomly intermixed. The number of intervening items between two successive occurrences of the same image was set to be similar in the two conditions (mean and standard deviation differing by <5% for each subject).

4.3. *Procedure*

Images were back-projected on a translucent screen placed at 110 cm from the subject's eyes using a computer data projector (60 Hz). Twelve Predictive and 12 non-Predictive configurations were randomly generated for each subject and each configuration was presented 12 times. The experiment comprised 3 runs of 96 trials each. After the 3 runs, subjects were asked whether they noticed anything during the experiment and informed about the existence of Predictive and non-Predictive configurations. No subject ever reported noticing the repetition of any image spontaneously during this debriefing nor when asked explicitly.

In the MEG experiment, this procedure was repeated twice in a row with different stimuli (subjects saw 24 configuration

of each condition) to increase the number of trials per condition and enhance signal to noise ratio. In other respects, the procedure was identical in the two experiments.

4.4. Patients

Seven epileptic patients (mean age: 34+/−9, 5 males, 6 right handed) gave their written informed consent to participate to the experiment. All had normal or corrected to normal vision. The project was approved by the Local Ethical Committee.

Patients, suffering from severe and pharmacoresistant partial epilepsies were chronically recorded in video-EEG unit with depth electrodes (Ad-TechMedical Instruments, Racine, WI). Electrodes were composed of 4–10 contacts 2.3 mm long, 10 mm apart, mounted on a 1 mm wide flexible plastic probe and referenced to the nose. On total, signal was recorded from 345 contacts. The structures to be explored were defined according to the localization hypotheses resulting from the non-invasive data including electro-clinical and neuro-imaging (MRI, PET, SPECT) evaluations (Adam et al., 1997).

Each patient was explored with 6 to 11 electrodes which corresponded to an average of 49+/−5 contacts per patient. Temporal and extra-temporal lobe electrodes were inserted with a Leksell frame, in the direction suited to the different targeted structures (horizontal or oblique, and lateral-to-medial or posterior-to-anterior or vice versa). In the temporal lobe, the electrodes explored the amygdala, the hippocampus at three (anterior, middle and posterior) levels, the temporal pole and the different temporal neocortical areas (Adam et al., 1996).

One patient (patient06) had a dysplasic lesion in the left anterior medial temporal lobe which however seemed to show a visual response and was thus included in the analysis. Two patients were excluded from the analysis because they presented too many interictal epileptic discharges during the whole recording session. Data from five patients and 167 contacts was thus analyzed.

Epileptogenic zone was localized in each patient and is presented in Table 2, along with the number of contacts implanted, age and laterality of each patient.

4.5. Signal analysis

4.5.1. iEEG recordings and analysis

Continuous data were collected at the MEG-EEG Centre, Hôpital Pitié-Salpêtrière (Paris, France). Electrocardiogram (ECG) and vertical and horizontal electro-oculograms (EOG) were also recorded. The local field potential (LFP) was digitized at 400 Hz and resampled at 1250 Hz by interpolation. Epochs were extracted (from −400 ms to +400 ms from image onset). To reduce the influence of distant sources by volume conduction, bipolar differences were computed between neighboring contacts (1 cm spacing). Contacts with continuous epileptic activity or large variations were rejected from the analysis, leading to a total of 167 contacts analyzed out of the 249 contacts recorded in the patients included in the analysis. All trials were visually inspected, and trials with epileptic activity were rejected. On average, 25.8±13 trials were included in each condition per patient. Trials were then low-pass filtered (30 Hz). To minimize the influence of noisy trials, a Zscore of each trial was computed ($Z_t = \frac{x_t - \overline{BL}}{\sigma_{BL}}$, where Z_t is the Zscore value at time t, x_t is the raw data value at time t, $\overline{BL}$ is the average baseline value from −300 to 0 ms and σ_{BL} is the standard deviation of the baseline along time). Evoked potentials were computed by averaging Zscore data (time courses on Figs. 2–4). Statistical comparisons were computed between the two conditions separately for the beginning (presentations 1 to 4) and end (presentations 9 to 12) of the experiment. We used a randomization technique as follows to assess the statistical significance of the differences observed between conditions for each subject at each contact. The difference between the evoked potentials in the two conditions was compared to an estimate of the expected difference distribution under the null hypothesis. This expected null distribution of the data was estimated using a randomization procedure repeated 2000 times: trials were randomly assigned to one of two groups of the same size as the actual conditions, yielding to a permuted difference. *p* values were computed at each time point as the number of permuted differences reaching a higher level than the difference actually observed between conditions divided by the number of permutations.

In order to compare our results with our previous study (Chaumon et al., 2008), we focused our analysis on early activity in the late part of the experiment (presentations 9 to 12). We considered only those contacts whose *p* value was below 0.01 for at least 10 ms (12 time samples). Because we wanted to include any differential response occurring in a time window compatible with early sensory processing, the time window of interest was enlarged by 20 ms on both sides compared to the one used in the MEG experiment. We thus report all contacts passing the threshold in the 30–120 ms time window. For each of these contacts, standard *t*-tests were also performed on the same time windows at the beginning of the

Table 2 – Epileptogenic zone localization, number of contacts implanted, age and laterality for each recorded patient.

	Epileptogenic zone	Number of contacts implanted	Age	Laterality
Patient01	Left anterior amygdalo-hippocampal	60	27	R
Patient02	Right anterior hippocampus	36	34	L
Patient03	Right basal neocortical temporal	48	40	R
Patient04	Left medial posterior orbitofrontal	60	50	R
Patient05	Right anterior hippocampus and temporo-polar	44	22	R
Patient06	Left anterior hippocampus	50	27	R
Patient07	Right orbitofrontal cortex	47	36	R

The two shaded lines correspond to the patients that were excluded from the analysis because of too many interictal epileptic discharges.

experiment (presentations 1 to 4) to ensure that the differential response in the two conditions resulted from experience with the displays. Data thresholded at different more or less conservative thresholds kept the same general topography. We report only the data using the above mentioned threshold in the results section.

4.5.2. *Source localization of the MEG signal*

MEG data preprocessing has been described in detail elsewhere (Chaumon et al., 2008). Cortical current density mapping was obtained using a distributed model consisting of 10,000 current dipoles in each subject and in each condition. Dipole locations and orientations were constrained to the cortical mantle of a generic brain model built from the standard brain of the Montreal Neurological Institute using the BrainSuite software package (http://brainsuite.usc.edu/). This head model was then warped to the standard geometry of the MEG sensor cap. The warping procedure and all subsequent source analysis and surface visualization were processed with the BrainStorm software package (http://neuroimage.usc.edu/brainstorm). Cortical current maps were computed from the MEG time series using a linear inverse estimator (weighted minimum norm current estimate).

Data averaged in the time window 90–100 ms was compared between the two conditions in the last part of the experiment, when the behavioral effect was well established (presentations 9 to 12) as in the previous paper (Fig. 5 in Chaumon et al., 2008). The time course of source activity was also computed using a sliding average window of 10 ms from −200 to +250 ms. Statistical comparison was performed using standard Student *t*-statistics mapping.

Acknowledgments

We thank Antoine Ducorps and Florence Bouchet for help with electrophysiological recordings, and Denis Schwartz for help with data computation. This experiment is supported by a grant from French ministry of research (ACI Neurosciences Intégratives et computationnelles) and the Agence Nationale de la Recherche (projet 1st impression) to CTB. MC is supported by a grant from the Fondation pour la Recherche médicale (FRM).

REFERENCES

Adam, C., Clemenceau, S., Semah, F., Hasboun, D., Samson, S., Aboujaoude, N., et al., 1996. Variability of presentation in medial temporal lobe epilepsy: a study of 30 operated cases. Acta Neurol. Scand. 94 (1), 1–11.

Adam, C., Clemenceau, S., Semah, F., Hasboun, D., Samson, S., Dormont, D., et al., 1997. Stratégie d'évaluation et résultats chirurgicaux dans l'épilepsie de la face médiale du lobe temporal. Rev. Neurol. 153 (11), 641–651.

Aminoff, E., Gronau, N., Bar, M., 2007. The parahippocampal cortex mediates spatial and nonspatial associations. Cereb. Cortex 17 (7), 1493–1503.

Auckland, M.E., Cave, K.R., Donnelly, N., 2007. Nontarget objects can influence perceptual processes during object recognition. Psychon. Bull. Rev. 14, 332–337.

Badgaiyan, R.D., 2005. Conscious awareness of retrieval: an exploration of the cortical connectivity. Int. J. Psychophysiol. 55 (2), 257–262.

Baker, C.I., Behrmann, M., Olson, C.R., 2002. Impact of learning on representation of parts and wholes in monkey inferotemporal cortex. Nat. Neurosci. 5 (11), 1210–1216.

Bar, M., 2004. Visual objects in context. Nat. Rev., Neurosci. 5 (8), 617–629.

Bar, M., Aminoff, E., 2003. Cortical analysis of visual context. Neuron 38 (2), 347–358.

Bar, M., Kassam, K.S., Ghuman, A.S., Boshyan, J., Schmidt, A.M., Dale, A.M., et al., 2006. Top-down facilitation of visual recognition. Proc. Natl. Acad. Sci. U. S. A. 103 (2), 449–454.

Biederman, I., 1981. On the semantics of a glance at a scene. In: Pomerantz, M.K.J.R. (Ed.), Perceptual Organization. Lawrence Erlbaum, Hlilsdale, New Jersey, pp. 213–263.

Bullier, J., 2001. Integrated model of visual processing. Brain Res. Rev. 36 (2–3), 96–107.

Burgess, N., Maguire, E.A., Spiers, H.J., O'Keefe, J., 2001. A temporoparietal and prefrontal network for retrieving the spatial context of lifelike events. NeuroImage 14 (2), 439–453.

Chaumon, M., Drouet, V., Tallon-Baudry, C., 2008. Unconscious associative memory affects visual processing before 100 ms. J. Vision 8 (3), 1–10.

Chaumon, M., Schwartz, D., Tallon-Baudry, C. (in press). Unconscious learning versus visual perception: dissociable roles for gamma oscillations revealed in MEG. J. Cogn. Neurosci. 0 (0), 1–13. doi:10.1162/jocn.2008.21155.

Chun, M.M., 2000. Contextual cueing of visual attention. Trends Cogn. Sci. 4 (5), 170–178.

Chun, M.M., Jiang, Y., 1998. Contextual cueing: implicit learning and memory of visual context guides spatial attention. Cognit. Psychol 36 (1), 28–71.

Chun, M., Phelps, E., 1999. Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage. Nat. Neurosci. 2 (9), 844–847.

Freedman, D.J., Riesenhuber, M., Poggio, T., Miller, E.K., 2006. Experience-dependent sharpening of visual shape selectivity in inferior temporal cortex. Cereb. Cortex 16 (11), 1631–1644.

Ganis, G., Kutas, M., 2003. An electrophysiological study of scene effects on object identification. Brain Res. Cogn. Brain Res. 16 (2), 123–144.

Goujon, A., Didierjean, A., Marmèche, E., 2009. Semantic contextual cueing and visual attention. J. Exp. Psychol. Hum. Percept. Perform. 35 (1), 50–71.

Greene, A.J., Gross, W.L., Elsinger, C.L., Rao, S.M., 2007. Hippocampal differentiation without recognition: an fMRI analysis of the contextual cueing task. Learn. Mem. 14 (8), 548–553.

Henderson, J.M., Hollingworth, A., 1999. High-level scene perception. Annu. Rev. Psychol. 50, 243–271.

Jungé, J.A., Scholl, B.J., Chun, M.M., 2007. How is spatial context learning integrated over signal versus noise? A primacy effect in contextual cueing. Vis. Cogn. 15 (1), 1–11.

Kourtzi, Z., DiCarlo, J.J., 2006. Learning and neural plasticity in visual object recognition. Curr. Opin. Neurobiol. 16 (2), 152–158.

Kreiman, G., Koch, C., Fried, I., 2000. Category-specific visual responses of single neurons in the human medial temporal lobe. Nat. Neurosci. 3 (9), 946–953.

Kveraga, K., Boshyan, J., Bar, M., 2007. Magnocellular projections as the trigger of top-down facilitation in recognition. J. Neurosci. 27 (48), 13232–13240.

Miyashita, Y., 1993. Inferior temporal cortex — where visual–perception meets memory. Annu. Rev. Neurosci. 16, 245–263.

Miyashita, Y., Hayashi, T., 2000. Neural representation of visual objects: encoding and top-down activation. Curr. Opin. Neurobiol. 10 (2), 187–194.
Miyashita, Y., Okuno, H., Tokuyama, W., Ihara, T., Nakajima, K., 1996. Feedback signal from medial temporal lobe mediates visual associative mnemonic codes of inferotemporal neurons. Brain Res. Cogn. Brain Res. 5 (1–2), 81–86.
Mruczek, R.E.B., Sheinberg, D.L., 2007. Context familiarity enhances target processing by inferior temporal cortex neurons. J. Neurosci. 27 (32), 8533–8545.
Oliva, A., Torralba, A., 2007. The role of context in object recognition. Trends Cogn. Sci. 11 (12), 520–527.
Olson, I.R., Chun, M.M., Allison, T., 2001. Contextual guidance of attention: human intracranial event-related potential evidence for feedback modulation in anatomically early temporally late stages of visual processing. Brain 124 (Pt. 7), 1417–1425.
Ranganath, C., Rainer, G., 2003. Neural mechanisms for detecting and remembering novel events. Nat. Rev., Neurosci. 4 (3), 193–202.
Rolls, E.T., Grabenhorst, F., 2008. The orbitofrontal cortex and beyond: from affect to decision-making. Prog. Neurobiol. 86 (3), 216–244.
Ross, R.S., Slotnick, S.D., 2008. The hippocampus is preferentially associated with memory for spatial context. J. Cogn. Neurosci. 20 (3), 432–446.
Schacter, D.L., Wig, G.S., Stevens, W.D., 2007. Reductions in cortical activity during priming. Curr. Opin. Neurobiol. 17 (2), 171–176.
Slotnick, S.D., Schacter, D.L., 2006. The nature of memory related activity in early visual areas. Neuropsychologia 44 (14), 2874–2886.
Thorpe, S.J., Rolls, E.T., Maddison, S., 1983. The orbitofrontal cortex: neuronal activity in the behaving monkey. Exp. Brain Res. 49 (1), 93–115, doi:10.1007/BF00235545.
VanRullen, R., Thorpe, S.J., 2001. The time course of visual processing: from early perception to decision-making. J. Cogn. Neurosci. 13 (4), 454–461.