Rules Rule! Brain Activity Dissociates the Representations of Stimulus Contingencies with Varying Levels of Complexity

Chun-Yu Tse[1,2], Kathy A. Low[1], Monica Fabiani[1], and Gabriele Gratton[1]

Abstract

■ The significance of stimuli is linked not only to their nature but also to the sequential structure in which they are embedded, which gives rise to contingency rules. Humans have an extraordinary ability to extract and exploit these rules, as exemplified by the role of grammar and syntax in language. To study the brain representations of contingency rules, we recorded ERPs and event-related optical signal (EROS; which uses near-infrared light to measure the optical changes associated with neuronal responses). We used sequences of high- and low-frequency tones varying according to three contingency rules, which were orthogonally manipulated and differed in processing requirements: A Single Repetition rule required only template matching, a Local Probability rule required relating a stimulus to its context, and a Global Probability rule could be derived through template matching or with reference to the global sequence context. ERP activity at 200–300 msec was related to the Single Repetition and Global Probability rules (reflecting access to representations based on template matching), whereas longer-latency activity (300-450 msec) was related to the Local Probability and Global Probability rules (reflecting access to representations incorporating contextual information). EROS responses with corresponding latencies indicated that the earlier activity involved the superior temporal gyrus, whereas later responses involved a fronto-parietal network. This suggests that the brain can simultaneously hold different models of stimulus contingencies at different levels of the information processing system according to their processing requirements, as indicated by the latency and location of the corresponding brain activity. ■

INTRODUCTION

Extracting regularities in the temporal order of stimuli (i.e., their sequential structure) is important for predicting the identity of the next stimulus, improving processing efficiency (e.g., Koch & Hoffmann, 2000) and informing various psychological functions including conditioning (e.g., Clark & Squire, 1998), language (e.g., Opitz & Friederici, 2004), and sequence learning (e.g., Bischoff-Grethe, Goedert, Willingham, & Grafton, 2004; Grafton, Hazeltine, & Ivry, 1995). Models have been proposed to account for the ability to integrate temporal structures across time (Hawkins, George, & Niemasik, 2009; Cleeremans & McClelland, 1991).

Cognitive neuroscientists have recognized the importance of sequential structures and studied them extensively. In particular, ERPs have shown to be a very useful tool to demonstrate brain responses that are associated with the violation of expectations about sequential structures (for reviews, see Fabiani, Gratton, & Federmeir, 2007; Fabiani, 2006; see also Polich, 2007; Donchin & Coles, 1988; Donchin, 1981; Näätänen & Michie, 1979). The presence of these brain responses demonstrates that our brain continuously makes predictions about the nature of upcoming events based on the sequence of stimuli to which it has recently been exposed. Interestingly, different ERP components are associated with the violations of different sequential rules. Some of these responses, such as the N1 (Picton, Alain, Otten, Ritter, & Achim, 2000; Näätänen & Picton, 1987) or the MMN (Näätänen, Paavilainen, Rinne, & Alho, 2007; Näätänen & Michie, 1979), appear to be mostly related to the violation of relatively simple regularity rules based on physical characteristics of the stimuli (such as stimulus duration, intensity, pitch, or timing; Rinne, Degerman, & Alho, 2005; Sable, Low, Maclin, Fabiani, & Gratton, 2004; Jacobsen & Schröger, 2001; Sabri & Campbell, 2001; Budd, Barry, Gordon, Rennie, & Michie, 1998; Yabe, Tervaniemi, Reinikainen, & Näätänen, 1997), whereas others, such as the P300 or P3b (Polich, 2007; Donchin, 1981; Duncan-Johnson & Donchin, 1977), may reflect more complex or abstract rules, such as higher-order relationships between stimuli (Brumback Peltz, Gratton, & Fabiani, 2011; Brumback, Low, Gratton, & Fabiani, 2005; Squires, Petuchowski, Wickens, & Donchin, 1977) or properties that allow for their categorization (e.g., Kutas, McCarthy, & Donchin, 1977), although they may also respond to the violation of simpler rules, such as overall stimulus probability (Duncan-Johnson & Donchin, 1977). These data indicate that our brains may use different predictive

[1]University of Illinois at Urbana-Champaign, [2]National University of Singapore

rules at the same time. Typically, the brain responses related to the violation of more complex rules have longer latencies, suggesting that stimulus processing occurs through an orderly series of abstraction levels (e.g., Shin, Fabiani, & Gratton, 2006).

The examination of brain activities evolving over time requires methods of analysis with high temporal resolution, such as ERPs. However, scalp-recorded ERPs provide limited information about the brain structures involved in their generation. Furthermore, this limited spatial resolution makes it sometimes difficult to separate the various activities that are involved in identifying the violation of particular sequential rules. Nevertheless, by combining ERP source analysis and fMRI recordings and by examining corresponding data obtained with magneto-encephalography, investigators have identified a network of structures involved in change detection in simple tasks such as the oddball paradigm. For example Opitz and colleagues (Opitz, Rinne, Mecklinger, von Cramon, & Schröger, 2002; Opitz, Mecklinger, von Cramon, & Kruggel, 1999) found that both superior temporal and inferior frontal regions were activated in the same conditions in which MMN and P300 were elicited. These structures, as well as parietal regions, were also reported in other studies (e.g., Linden, 2005; Kiehl, Laurens, Duty, Forster, & Liddle, 2001; Clark, Fannon, Lai, Benson, & Bauer, 2000; Linden et al., 1999; Alho et al., 1998; McCarthy, Luby, Gore, & Goldman-Rakic, 1997; Giard, Perrin, Pernier, & Bouchet, 1990).

Over the last several years, we have developed a noninvasive methodology, the event-related optical signal (EROS), which, although maintaining the temporal resolution characteristic of ERPs, provides information about the time course of activity in localized cortical structures (Gratton & Fabiani, 2007, 2010; Gratton, Corballis, Cho, Fabiani, & Hood, 1995). EROS is based on the measurement of near-infrared light scattering changes by tissue, associated with neuronal depolarization and hyperpolarization (e.g., Rector, Carter, Volegov, & George, 2005; Rector, Poe, Kristensen, & Harper, 1997), and provides (at least in principle) a combination of subcentimeter spatial resolution and microsecond-level temporal resolution. When the cortex is active, the associated cell swelling and conformational changes in the neuronal membranes lead to a decrease in light scattering (e.g., Foust & Rector, 2007). As a result, near-infrared light gets into a deeper layer of the gray matter before it is scattered back to the detector (Gratton et al., 1995; Fishkin & Gratton, 1993). By measuring the increase in the length of the light path, active brain regions can be identified. The main limitation of EROS is its reduced penetration, capable of monitoring activity only for structures less than 3–4 cm from the surface of the head.

Several studies have shown that EROS can be used to investigate the violation of sequential expectancies (e.g., Tse & Penney, 2007, 2008; Sable et al., 2007; Fabiani, Low, Wee, Sable, & Gratton, 2006; Low, Leaver, Kramer, Fabiani, & Gratton, 2006; Tse, Tien, & Penney, 2006; Rinne et al., 1999). However, until recently, EROS recordings were limited to small cortical regions, covering at most one lobe of the brain at a time. In this study, instrumentation and recording advances have allowed us to record from an extended optical montage capable of monitoring practically all of the brain regions less than 3–4 cm from the surface of the scalp. This is the first study reporting data based on this methodology.

This extended recording montage allows us to focus on several different brain regions within the same study. As such, we can concurrently investigate the temporal properties of the brain responses of structures sensitive to sequential deviances related to different levels of abstraction. For this, we used a paradigm in which the stimulus sequence was generated on the basis of different contingency rules. We use the label "contingency rules" to indicate the temporal contingencies embedded in a stimulus sequence. We expect these rules to vary in their processing requirements, as different mechanisms may be involved in tuning the corresponding mental representations. Borrowing terminology from computer science, we conceptualize that contingency rules may require the formulation of static or dynamic internal representations, or both. A static internal representation is a template established by the most common stimulus pattern. Subsequent stimuli that fit the template elicit automatic processing with improved efficiency. A dynamic representation, instead, involves a running update of a model to bias the prediction of future events. We assume that static representations are based on sensory memory whereas dynamic representations require working memory.

This conceptualization leads to predict that early, preattentive ERP components such as the MMN should manifest the tuning of static representations (e.g., Näätänen et al., 2007; Näätänen & Michie, 1979) whereas longer-latency components requiring the engagement of attention, such as the P300, would index the tuning of dynamic representations (e.g., Polich, 2007; Donchin, 1981). This view is consistent with the regularity violation account of the MMN (Schröger, 2007; Winkler, 2007) and with the context-updating hypothesis for P300 (Donchin & Coles, 1988; Donchin, 1981), as well as with its most recent formulation proposed by Polich (2007).

On the basis of a hierarchical view of brain organization (e.g., Badre, 2008; Badre & D'Esposito, 2007; Fuster, 2001, 2004, 2006), we hypothesized that contingency rules requiring only the application of static templates could be represented at cortical levels that are proximal to sensory input (i.e., secondary sensory cortices). Previous research has linked these structures to sensory memory (Calhoun, Adali, Pearlson, & Kiehl, 2006; Näätänen & Winkler, 1999; Romanski et al., 1999). Instead, rules requiring dynamic representations, in which information is maintained over a longer stimulus sequence, could be represented at more distal cortical levels in regions related to attention control and goal-oriented processing (i.e., along a fronto-parietal network; Corbetta & Shulman, 2002). These structures

have been linked to working memory and attention control (Mantini, Corbetta, Perrucci, Romani, & Del Gratta, 2009; Benar et al., 2007; Calhoun et al., 2006; Bledowski et al., 2004; Hopfinger, Buonocore, & Mangun, 2000; Halgren, Marinkovic, & Chauvel, 1998).

We tested these hypotheses by contrasting the brain activity associated with the representations of contingency rules with different processing requirements in the context of an auditory oddball paradigm, in which the stimulus sequence was manipulated. We concurrently recorded brain activity with ERPs and EROS to reveal the spatio-temporal dynamics of the brain in representing sequential contingency rules and to cross-validate these two high temporal resolution methods.

To date, many of the brain imaging studies using the oddball paradigm to investigate the representation of temporal contingencies have focused on studying deviance detection (i.e., rule violation; Horvath, Czigler, Sussman, & Winkler, 2001; but see Bendixen, Roeber, & Schröger, 2007, for an example of sequence based on alternations). However, it is equally important to understand the representation of regularity among a sequence of standard, recurring, stimuli. The current study employed an orthogonal contrast approach, different from the one commonly used in MMN and P300 studies, to investigate regularity representation in the human brain. Instead of comparing deviant against standard stimuli in an oddball paradigm, we explored the neural substrates of contingency rules by comparing the brain responses to the stimuli governed by multiple rules simultaneously. In other words, we also investigated the brain responses to the standard stimuli whose occurrence was governed by different contingency rules.

To achieve varying levels of sequential complexity, we modified a standard auditory oddball paradigm, in which a high tone and a low tone alternated regularly on most trials within the sequence by introducing three underlying contingency rules. The three rules were a statistical (Global Probability) rule, a relational (Single Repetition) rule, and a more complex, context-related (Local Probability) rule. The Global Probability rule dictated that 75% of the tones within the sequence were alternations (e.g., high, low, high, low) whereas 25% were repetitions (e.g., high, low, high, *high*), thus creating a differential overall probability between two conditions (alternation vs. repetition), which is typical of oddball paradigms. The Single Repetition rule dictated that a tone following a repetition must be an alternation (e.g., high, low, *high*, *high*, *low*). The Local Probability rule dictated that a repetition could only occur on odd trials. If one kept track of the tones as pairs, the first tone of the pair had a 50% chance of being an alternation or a repetition, whereas the second tone was always an alternation.[1] On the basis of these contingency rules, the tones were categorized into four types. Because of their statistical properties, three statistically orthogonal contrasts corresponding to the three contingency rules were constructed to describe the relationships between the four tone types for testing the presence of each contingency rule in the behavioral ERP and EROS data.

In summary, our hypotheses were the following:

(1) Extracting information related to the simplest rule (Single Repetition), stating that three equal stimuli can never occur in a row and thus only requiring memory for last two stimuli (sensory memory), would result in the elicitation of an MMN/N2 ERP response and EROS activity at the same latency in temporal cortex.
(2) Extracting information related to the most complex rule (Local Probability), stating that the second stimulus in a pair must be an alternation and thus requiring to keep track of the positions of pairs within the sequence (working memory), would result in the elicitation of a P300 ERP response and EROS activity at the same latency within the fronto-parietal network.
(3) Extracting information related to the intermediate rule (Global Probability), stating that alternations are overall more likely than repetitions, can be based on both sensory and working memory representations and therefore elicit a mixture of the two types of brain activities described above.

METHODS

Participants

Sixteen participants (age range = 19–27 years) who were naive to the contingency rules at the beginning of the experiment entered the study after giving informed consent. All procedures were approved by the institutional review board of the University of Illinois at Urbana-Champaign. According to self-reports, all participants had normal hearing, were not taking any psychoactive medications, and had no history of neurological disorders or head trauma. Scores on the Edinburgh Handedness Inventory (Oldfield, 1971) showed that all of the participants were right-handed.

Stimuli and Procedures

A choice RT task was used in this study. Participants were presented with sequences of auditory tones (70 dB sound pressure level) of 500 Hz (high-frequency tone) and 350 Hz (low-frequency tone) and were required to indicate whether each tone was high or low by pressing the left/right buttons on a response box with their left/right thumbs. The mapping of high/low tones to response hands was counterbalanced across participants. Throughout the experiment, participants were asked to fixate on a cross at the center of the computer screen. The duration of all tones was 400 msec, and the ISI was 1600 msec (tone offset to tone onset). The interval allocated for responding lasted until 1200 msec after tone offset.

In each experimental block, 50% of the tones were high frequency and the other 50% were low frequency. However, among successive tones, 75% followed an alternating pattern

(i.e., high–low or low–high) and 25% followed a repetition pattern (i.e., high–high or low–low). We define this ratio of alternation versus repetition as the Global Probability (or "statistical") rule (Koch & Hoffmann, 2000). In addition, the sequences were set up such that when a repetition occurred, the tone that followed would always be an alternation (i.e., there were never three identical tones in a row). We define this condition as the Single Repetition (or "relational") rule (Koch & Hoffmann, 2000). Finally, the tones could also be thought of as occurring in pairs, with odd trials having a 50:50 chance of being high or low, and even trials always occurring as an alternation and therefore being 100% predictable given the preceding tone (see Figure 1). To exploit this predictive information, a representation of the odd–even pairing must be available. Note that the tone pairing was not explicit, because the tones had a constant ISI, and participants were not informed of this aspect of the contingency. This rule required keeping track of the context in which stimuli were presented. Predictability based on tone pairs was defined as the Local Probability (or "context-related") rule. The first two tones of each block were omitted from all analyses, because not enough contextual information was available at that moment. However, it should be noted that the first two tones of each block were always different from each other and thus provided a clue to the participants that pairing may be important in the sequence.

These rules differ along two dimensions—template mismatch and requirement for contextual or working memory updating. We conceptualized that, to apply the Global Probability and the Single Repetition rules to facilitate the processing of the current tone, a template of the most probable upcoming tone was needed. An alternation template was necessary to implement the Global Probability rule, because 75% of the tones were alternations. However, for the other 25% of tones that were repetitions, the alternation template was violated and, therefore, carried high information value. These violations, in turn, set the stage for the Single Repetition rule. Most of the tones in the sequence followed the Global Probability rule, and therefore, their identity could not be known with certainty until after they were presented. The tone immediately following a repetition, however, could be predicted with 100% certainty. Under the Single Repetition rule, the sequence never contained more than two identical tones in a row (i.e., the sequence *yxx***X** could not occur). Thus, a tone following a repetition must be an alternation and therefore contained low information value (i.e., the tone would always match the template).

For the memory-updating dimension of the rules, we conceptualized that both the Global Probability and the Local Probability rules required integrating the properties of the current tone into a memory template needed for subsequent tone processing. For the Global Probability rule, the alternating/repeating nature of the current tone was integrated into memory to help keep track of the relative frequencies of alternations and repetitions. We expected that repetitions, because they were rarer and because they set up expectations about the upcoming stimulus, would provide more information than alternations and therefore require more processing. Under the Local Probability rule, the ordinal position of the current tone within a pair (odd vs. even) was integrated into memory to inform the ordinal position of the next tone. Because repetitions could only occur on odd trials whereas even trials must be alternations, knowing the ordinal position of a tone could reduce processing workload. In contrast, for the Single Repetition rule, no memory updating extending beyond the last two items was required, because the sequence started afresh after a repetition.

On the basis of these contingency rules, the tones were categorized into four types: Tone 1 of an alternation pair (AP-T1), Tone 2 of an alternation pair (AP-T2), Tone 1 of a repetition pair (RP-T1), and Tone 2 of a repetition pair (RP-T2), independent of the pitch of the tones (i.e., high or low; see Figure 1 and Table 1).

The behavioral, ERP, and EROS data were recorded in four separate sessions: a practice session, to test the hypothesis that learning of the different rules had occurred (because the contingency rules were not explicitly explained to the participants); and three sessions during which data were recorded. Given the limitations of our

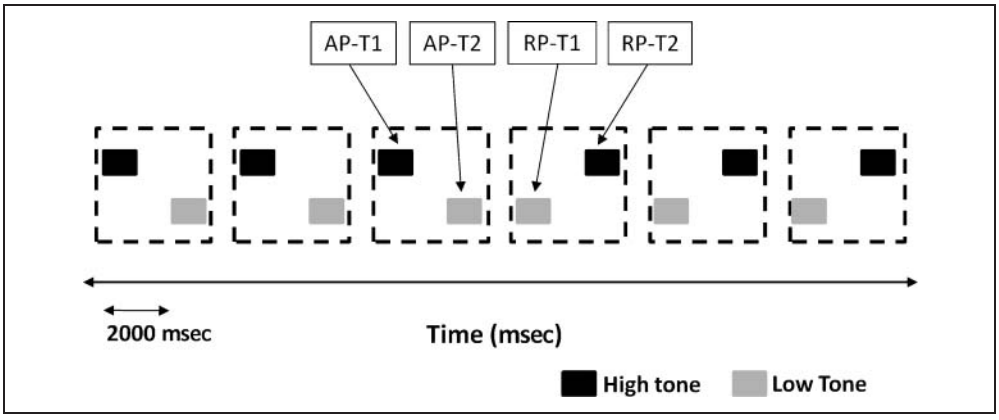

Figure 1. Schematic example of a stimulus sequence and tone classification.

Table 1. Summary of Rules and Analysis Contrasts

Rule Name	*Rule*	*Processes Required*	*Rationale*	*Contrast*	*Stimulus Label*	*Information Value*	*Contrast Weight*
A. Global Probability	Alternations are *more frequent* than repetitions	Keeping track of short sequences or use context	Compare repetitions with alternations	Repetitions vs. alternations	AP-T1	Low	−0.33
					AP-T2	Low	−0.33
					RP-T1	High	+1
					RP-T2	Low	−0.33
B. Single Repetition	After a repetition *always* an alternation	Keeping track of short sequences	Compare alternations occurring after alternations or repetitions	*alt*-ALT vs. *rep*-ALT[a]	AP-T1	High	+0.5
					AP-T2	High	+0.5
					RP-T1	–	0
					RP-T2	Low	−1
C. Local Probability	Odd trials can be repetitions; even trials are *always* alternations	Keeping track of position within a series (context)	Compare the first and second stimulus of a pair. Series beginning with repetitions may create special conditions (see rule A)	First vs. second stimulus in pair[b]	AP-T1	High	+1
					AP-T2	Low	−1
					RP-T1	–	0
					RP-T2	–	0

[a]Only focused on alternations; repetitions are covered by Rule A.

[b]Only focused on pairs beginning with alternations, as those starting with a repetition are covered by Rules A and B. Typical sequences for stimuli (current stimulus in bold capital letters): AP-T1: *xy***X-**; AP-T2: *yx***yX**; RP-T1: *yx***X-**; RP-T2: *xy***yX**.

recording system, EROS recording required two sessions; the third experimental session was used for ERP recording. The optical and electrophysiological recording sessions were interleaved. In the practice and ERP sessions, 98 tones (50% high and 50% low) were presented in each experimental block, with a total of 490 tones across five blocks. In the EROS sessions, 30 tones (50% high and 50% low) were presented in each of 10 experimental blocks, for each of four optical recording montages (i.e., light source/detector configurations). Across the two EROS sessions, a total of 2400 tones were presented. Both Montages A and B covered frontal and parietal regions, whereas Montages C and D covered central (between frontal and parietal) and occipital regions. Montages A and B were identical except for the fact that the source/detector configurations were shifted by one column on the helmet from left to right. The same was done for Montages C and D. This allowed us to increase the density of spatial sampling.

ERP Recording and Preprocessing

The EEG was recorded with Ag–AgCl electrodes at 21 scalp locations based on the standard 10–20 system. All active electrodes were referenced on-line to an electrode placed on the left mastoid. An average mastoid reference was computed off-line, subtracted from all scalp channels, and used for the analysis. Four additional electrodes, one above and one below the right eye and two at the outer canthi of each eye, were used for bipolar vertical and horizontal EOG recordings. The EEG and EOG were filtered on-line using a 0.01–30 Hz band pass and sampled at 100 Hz. Electrode impedance was kept below 10 kΩ. The EEG data were divided into epochs around each tone with 200-msec prestimulus baseline and 1000-msec poststimulus recording. Ocular artifacts were corrected (Gratton, Coles, & Donchin, 1983), and trials with voltage changes greater than 200 μV across the 1200-msec recording window were rejected. This resulted in the rejection of ~15% of the trials. The electrophysiological data were signal-averaged for each subject, channel, and tone type with time-locking to the onset of the tones. On the basis of research on regularity detection and rule learning (Fabiani et al., 2007; Näätänen et al., 2007; Donchin, 1981; Näätänen & Michie, 1979), time windows were set up to calculate the mean amplitude of the N2 effect (between 200 and 300 msec poststimulus)[2] and P300 effects (between 300 and 450 msec poststimulus) in the following analyses.

EROS Recording and Preprocessing

Optical data were recorded using a frequency domain oxymeter (Imagent, ISS Inc., Champaign, IL). Frequency-modulated near-infrared light (830 nm, modulated at 110 MHz) emitted from laser diodes was channeled to the participant's head surface via individual optic fibers (diameter = 400 μm). Light that scattered through the head was collected by fiber bundles (diameter = 3 mm) connected to photo-multiplier tubes. Photo-multiplier tubes were modulated at 110.00625 MHz, generating a 6250 Hz heterodyning (i.e., cross-correlation) frequency.

The source and detector fibers were held on the participant's head using a rigid helmet. In each EROS session, optical data were collected from four montages comprising 768 channels (i.e., 16 detectors, each receiving light from 12 time-multiplexed light sources per montage).[3] Consistent with our previous work (for a review, see Gratton & Fabiani, 2010), only phase data are presented in this study. The final sampling rate was 19.2 msec per channel (corresponding to a sampling frequency of 52.0833 Hz).

To record optical data simultaneously from a large number of locations covering the entire scalp without creating cross-talk between channels, special montages of the sources and detectors were used; these montages were designed so that it was never the case that more than 12 sources were less than 6 cm away from a particular detector (at this distance practically no light emitted by a source reaches the detector). The spatial position of each montage was such that, when combined, they provided coverage for most of the cortical surface (see Figure 2). Montage order was counterbalanced across participants. Channels with source–detector distances of less than 15 mm or greater than 55 mm were excluded from further analysis, because they were too short to reach the cortical surface or too long to have sufficient light (Gratton et al., 2006). This corresponded to approximately 1/4 of the channels.

The locations of sources and detectors, as well as the nasion and pre-auricular points of each participant, were digitized with a Polhemus Fastrak 3Space 3D digitizer (Colchester, VT). Volumetric T-1 weighted MRIs were also obtained for each participant using a Siemens Magnetom Allegra 3-T scanner. Within the scanner, the nasion and pre-auricular points were marked with Beekley Spots (Beekley Corporation, Bristol, CT) for coregistration of the functional optical data with the structural MRI (Whalen, Maclin, Fabiani, & Gratton, 2008). The individually coregistered data were then Talairach-transformed to permit registration across participants (Talairach & Tournoux, 1988).

The optical data were corrected off-line for phase wrapping, normalized to a mean of zero, pulse corrected (Gratton & Corballis, 1995), and filtered with a 1–10 Hz band-pass filter. The data were then divided into epochs around each tone with a 200-msec prestimulus baseline and 800-msec poststimulus recording. Finally, these epochs were averaged for each subject, channel, time point, and tone type. The influence of any remaining noisy channels was reduced by eliminating from the analysis any channels that had phase standard deviations of greater than 160 psec.

The averaged data were analyzed using in-house software (Opt-3D; Gratton, 2000). The optical signal for a given voxel was defined by averaging channels whose mean diffusion paths (modeled as a curved ellipsoid) intersected a given brain volume voxel (Wolf et al., 2000). An 8-mm Gaussian filter (based on a 2-cm kernel) was used

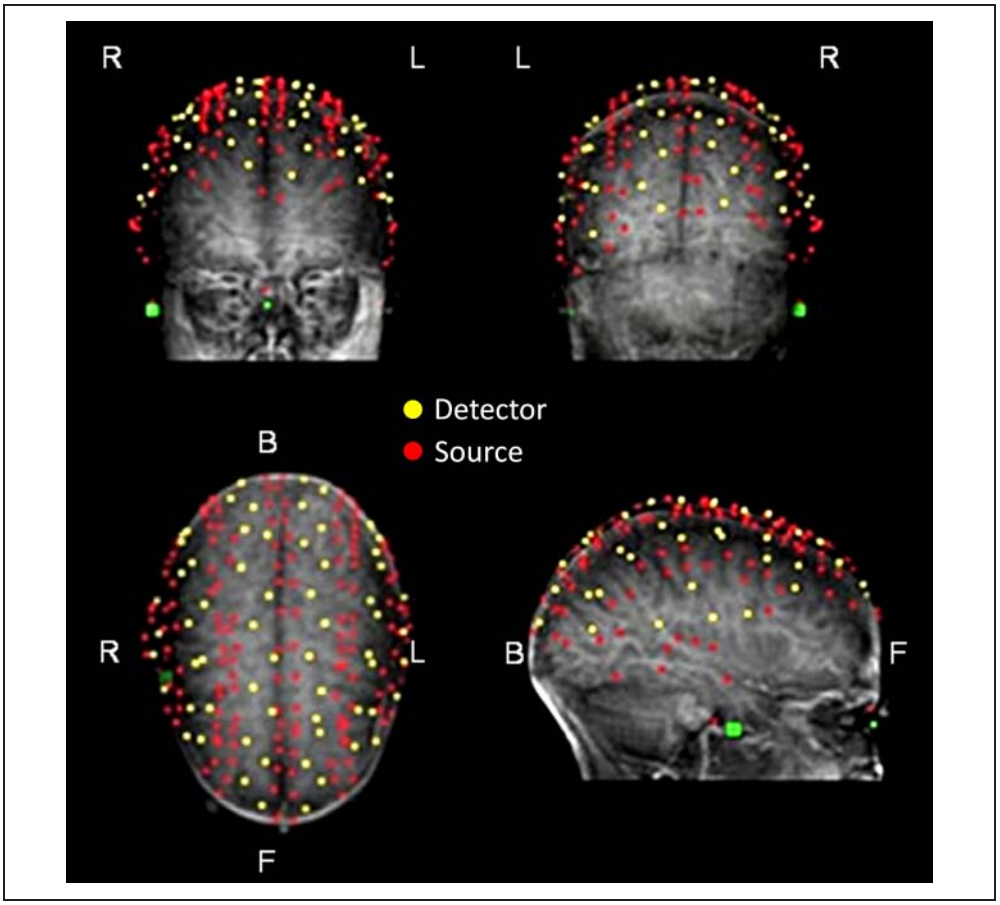

Figure 2. Anterior coronal (top left), posterior coronal (top right), superior axial (bottom left), and right lateral (bottom right) views of the EROS recording montages. The positions of the light source fibers (red dots), detector fibers (yellow dots), and nasion and pre-auricular points (green dots) were coregistered on the structural MRI of each participant. F = front; B = back; L = left; R = right.

to spatially filter the data. The group-level *t* statistics were calculated using an error term pooled across time. These *t* values were then converted to *Z* scores and orthogonally projected onto images of the superior (comprising *x*, left–right, and *y*, anterior–posterior, values of Talairach coordinates only) and sagittal (comprising *y*, anterior–posterior, and *z*, dorsal–ventral, values of Talairach coordinates only) surfaces of a brain in Talairach space.[4]

EROS analysis was based on a combined ROI and interval of interest (IOI) approach (hypothesis-driven ROI and IOI analyses). The bilateral ROIs and the IOIs were selected on the basis of previous published research. Specifically, a 1.5 × 1.5 cm temporal ROI was selected (Tse & Penney, 2007; Tse et al., 2006; Rinne et al., 2005; Doeller et al., 2003; Opitz et al., 1999, 2002) for the N2 time window, whereas a 2.5 × 2.5 cm frontal ROI covering the superior and middle frontal cortices (Casey et al., 2001; Kiehl et al., 2001; Linden et al., 1999) and a 2.5 × 2.5 cm parietal ROI (Mantini et al., 2009; Benar et al., 2007; Calhoun et al., 2006; Bledowski et al., 2004) were selected for the P300 time window. Within each ROI, corrections for multiple comparisons were carried out using the methods described in Friston and colleagues (1994). It should be noted that this procedure is different from some fMRI ROI analyses in which all voxels within the ROI are averaged and analyzed as a single unit. Instead, we performed a voxel-by-voxel analysis but used the ROIs as a principled method for restricting the number of "a priori" comparisons. In addition, we also performed exploratory whole-brain analyses (excluding activations within the ROIs) to examine whether other areas not predicted a priori showed consistent patterns of activation.

Contrast Analyses

All statistical analyses (for behavior, ERP, and EROS data) presented in this study are based on the use of planned orthogonal contrasts testing the independent sensitivity to each of the three rules (see Table 1). The experimental design allowed for three orthogonal contrasts, one for each rule. One-sample *t* tests (one-tailed) were used to test for the significance of individual contrasts, demonstrating the sensitivity of each dependent variable to each rule (directional tests were used because, for each dependent variable, specific hypotheses about the direction of the effects were made). Different weights were assigned to the four trial types according to the contingency rules (see Table 1) with the constraint that the sum of the cross products of the contrasts was equal to zero (i.e., orthogonal contrasts). As long as the assignment of the contrast weights satisfies this constraint, statistical orthogonality of the contrasts is achieved, although some of the trial types are involved in more than one contrast. The weights

assigned can be interpreted as the relative effort needed for processing the tones and are related to the amount of information they provide. It was expected that tones with positive weights would be associated with longer response times and stronger brain responses compared with tones with negative weights for a particular contrast. Zero weights were assigned to tones that were not involved in the calculation of the contrast.

Under the Global Probability rule, the weight assigned to RP-T1 was positive, because a rare repetition occurred, whereas the other three stimuli (RP-T2, AP-T1, and AP-T2), all of which were alternations, were given equal and negative weights (see Figure 1 and Table 1). It was predicted that the rare repetition tone would lead to longer response times and stronger brain responses.

Under the Single Repetition rule, we assigned a negative weight to the RP-T2 stimulus, since the presence of an alternation there was entirely predictable, because a stimulus repetition was always followed by an alternation. We contrasted this to those conditions in which an alternation occurred but could not be predicted by this rule, and therefore, the stimuli provided some information (AP-T1 and AP-T2). For this contrast, we ignored (i.e., gave a weight of 0) to the RP-T1 condition, because a different situation (a repetition) occurred then, and thus, the stimuli were not comparable. Note that this contrast, therefore, is entirely based on alternation trials but compared conditions in which the alternation could be predicted from conditions in which it could not. Thus, we predicted that the processing of RP-T2 (when the alternation could be predicted) would be easier and faster than that of the other alternation tones (i.e., AP-T1 and AP-T2).

Under the Local Probability rule, we contrasted the two stimuli in the alternating pair. This was the most complex rule, which required keeping track of the position of the stimulus within the sequence (i.e., first or second stimulus in a pair). If the participants were actually able to do this, then they would know that the second stimulus of a pair was always an alternation and therefore entirely predictable whereas the first was not (and thus, it provided information). The repetition tone pair stimuli (RP-T1 and RP-T2) were excluded from this contrast because clear predictions could be made about both stimuli in this pair based on the previous two rules (for RP-T1, the stimulus is a rare repetition; for RP-T2, the stimulus is predictable because a repetition is always followed by an alternation). For this contrast, we predicted that the reaction to AP-T1 would be slower and its processing more effortful as this stimulus provides more information than the AP-T2 stimulus.

RESULTS

Behavioral Results

Mean RTs across participants and standard errors of the means for the four trial types in the experimental sessions are shown in Figure 3A. Differences across trial types are apparent in both experimental sessions, indicating learning of the contingency rules. To better understand which specific rule was learned, we used the orthogonal contrasts presented in the Methods section. Figure 3B shows the mean values and standard errors of the means for the contrast-weighted analysis of RTs for each of the three rules (see Table 1).[5] Table 2 summarizes the statistical results for the contrast analyses on RTs. Contrasts corresponding to all three rules were statistically significant for both the ERP and EROS sessions.

To ensure that participants acquired the contingency rules by the end of the practice session and before the beginning of the experimental sessions, three planned repeated-measures ANOVAs (Subsession × Trial Types) were conducted to examine the sequential change in RTs of the four trial types across subsessions (first 15% of the trials vs. last 15% of the trials in the practice session, last 15% of the trials in the practice session vs. first 15% of trials in the ERP session,[6] first 15% vs. last 15% of trials in the ERP session). Mean RTs for the first and last 15% of the trials in the practice and ERP sessions for the four trial types are shown in Figure 4.

The first ANOVA (contrasting the beginning and end of the training session) revealed a main effect of Subsession, $F(1, 15) = 5.79, p < .05$, and an interaction between Subsession and Trial Types, $F(3, 45) = 3.07, p < .05$; however, the main effect of Trial Type was not statistically significant, $F(3, 45) = 2.13$.

The second ANOVA (contrasting the end of the training session with the beginning of the first ERP session) revealed a significant main effect of Subsession, $F(1, 15) = 6.37, p < .05$, and Trial Type, $F(3, 45) = 12.10, p < .05$; however, in this case, the interaction between Subsession and Trial Type was not statistically significant ($F(3, 45) < 1$). Similar results were found in the third ANOVA, contrasting the beginning of the first ERP session with the end of the last ERP session. This analysis revealed significant main effects of Subsession, $F(1, 15) = 5.09, p < .05$, and Trial Type, $F(3, 45) = 13.15, p < .05$, but no significant interaction between subsession and trial type $F(3, 45) = 2.12$. These results imply that the contingency rules were learned during the practice session, with no subsequent significant differential effect between trial types. A practice effect was visible throughout the experimental sessions, but it only affected the overall behavioral performance, independent of trial types.

In summary, the behavioral data indicate that, after learning the rules during the practice session, the rules were utilized to process the tones in the remainder of the sessions in which brain activity recordings were obtained.

ERP Results

Grand-averaged ERP waveforms for each trial type are shown in Figure 5A at the midline electrodes. Responses differentiating the trial types are evident in the 200–300 msec

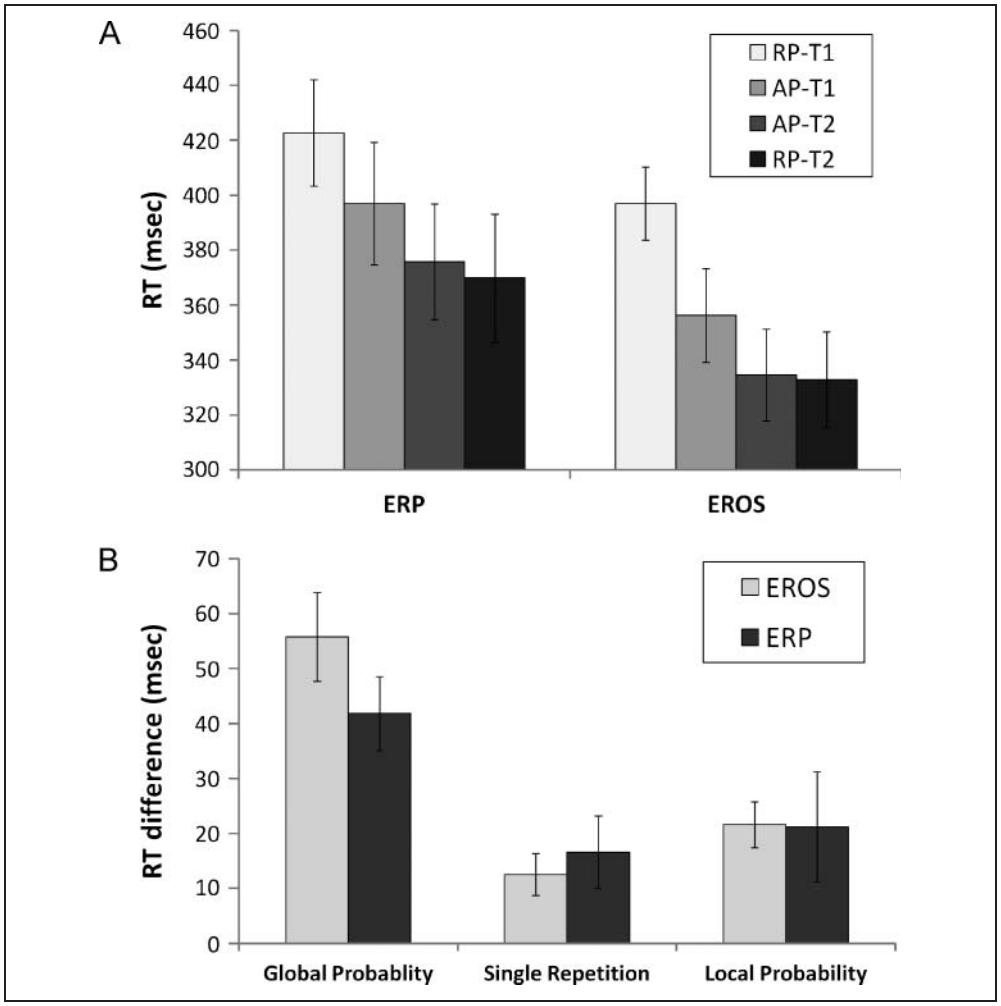

Figure 3. (A) Average RTs for each of the four trial types for the ERP and combined EROS sessions. (B) Contrast analysis of RT for each contingency rule for the ERP and combined EROS sessions.

window (corresponding to the N2 component, which is analogous to the MMN in active tasks) and in the 300-450 msec window (corresponding to the P300 component). Repeated-measures ANOVA showed a significant Time Window (N2 vs. P300) × Trial Type interaction, $F(3, 45) = 50.60$, $p < .001$, epsilon with Greenhouse–Geisser correction = .50, and a main effect of Trial Type, $F(3, 45) = 6.54$, $p < .01$. The main effect of Measurement Interval (N2–P300) was not statistically significant, $F(1, 45) = 4.06$. Follow-up one-way repeated-measures ANOVAs showed a significant difference in the N2 and P300 amplitudes among the four trial types, Fs(3, 45) = 3.72 and 40.52, respectively, ps < .05. Further analyses with t tests (Table 3) demonstrated dissociations between the N2 and P300 amplitudes. The N2 was larger for AP-T2 than RP-T2, with no difference between AP-T1 and AP-T2. In contrast, P300 was larger for AP-T1 than AP-T2, whereas there was no difference between AP-T2 and RP-T2.

Contrast weights were applied to reconstruct the waveforms corresponding to the application of contingency

Table 2. Contrast Analysis of RTs for Each Experimental Session

	Global Probability		*Single Repetition*		*Local Probability*	
Sessions	*WM (SD)*	*t*	*WM (SD)*	*t*	*WM (SD)*	*t*
ERP	41.82 (26.18)	6.39*	16.57 (25.46)	2.60*	21.22 (38.62)	2.29*
EROS	55.73 (31.30)	7.12*	12.51 (14.88)	3.36*	21.60 (6.04)	5.39*

The means are weighted (WM) according to the contrast.

*$p < .05$ (one-tailed), $df = 15$.

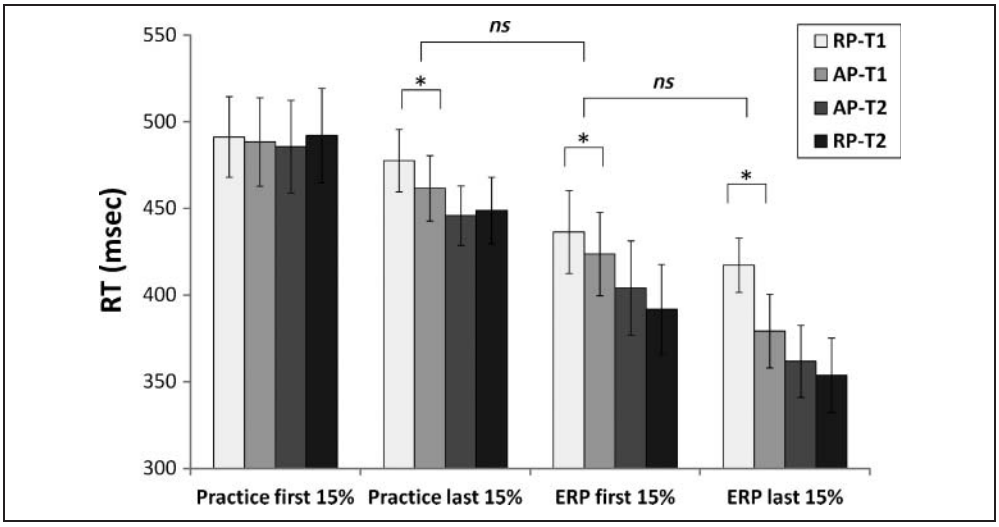

Figure 4. Average RTs for the first and last 15% of the trials in the practice and ERP sessions, for each of the four trial types.

rules (Figure 5B). The contrast analyses showed significant responses in the N2 time window for the Global Probability and Single Repetition rules, but not the Local Probability rule, and significant responses in the P300 time window for the Global Probability and Local Probability rules, but not the Single Repetition rule (see Table 4). In other words, ERP signatures corresponding to all three rules were found at different latencies. Processing related to

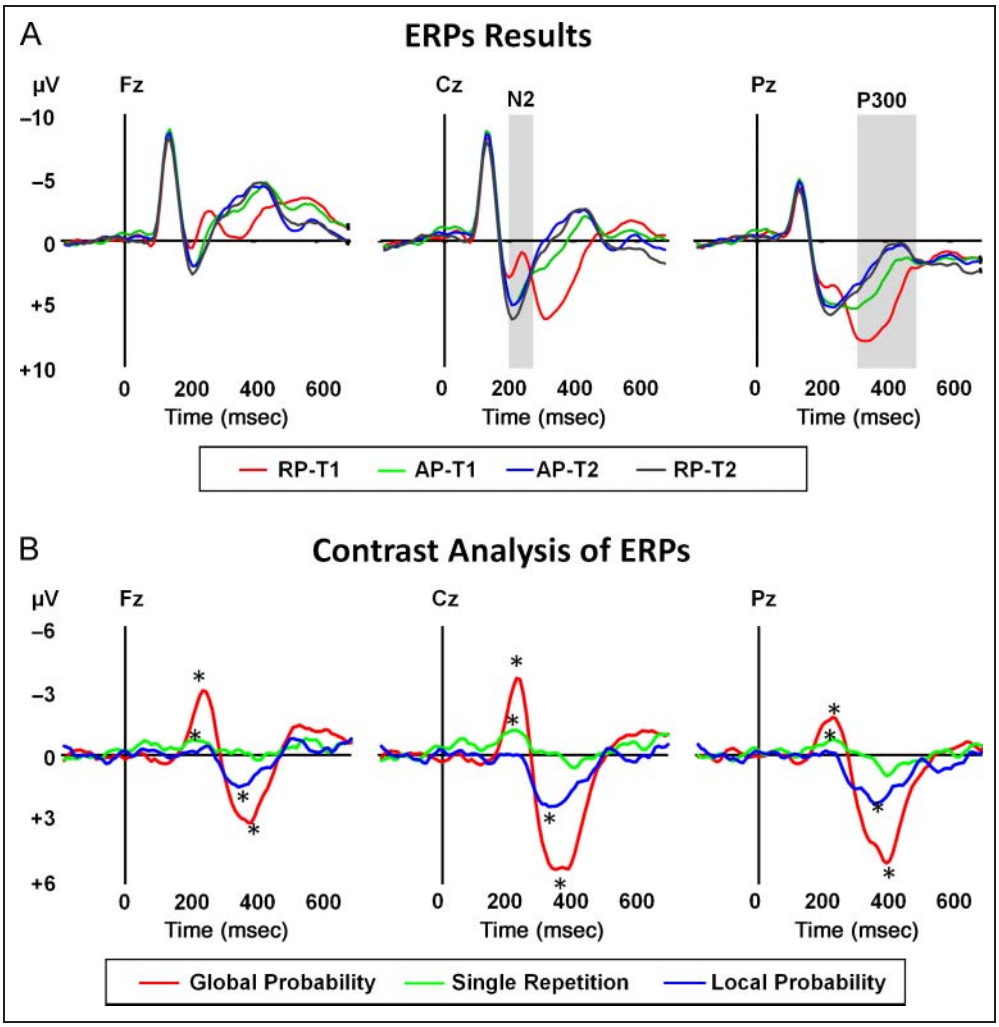

Figure 5. (A) Grand-averaged ERPs waveforms at midline electrodes for each trial type. The measurement windows are highlighted in light gray. (B) Contrast analysis of ERP waveforms for each contingency rule. *$p < .05$, significant contrast.

Table 3. *t* tests for the 200–300 msec (N2, Electrode Cz) and the 300–450 msec (P300, Electrode Pz) Time Windows

	RP-T1 vs. AP-T1		*AP-T1 vs. AP-T2*		*AP-T2 vs. RP-T2*	
Time Windows	*Mean (SD)*	*t*	*Mean (SD)*	*t*	*Mean (SD)*	*t*
N2 (Cz)	−1.33 (2.14)	−2.49*	0.60 (1.77)	1.36	−1.06 (1.23)	−3.45*
P300 (Pz)	2.79 (1.66)	6.72*	1.77 (1.53)	4.62*	−0.52 (1.70)	−1.21

*$p < .05$ (two-tailed), $df = 15$.

the Global Probability rule started around 200 msec and was sustained through 450 msec. ERP evidence of the processing of the Single Repetition rule occurred earlier than that of the Local Probability rule.

EROS Results

Statistical maps of EROS data based on the same contrast approach presented above are shown in Figure 6. Note that different maps can be obtained for different latencies. We used here the same time windows used for the ERP analyses but adapted to the EROS sampling rate (19.2 msec). Thus, the first IOI was between 211 and 287 msec and the second IOI was between 307 and 460 msec. In the first interval (at the latency of the N2 ERP effects), the EROS results showed significant left temporal activation at 268 msec sensitive to the Global Probability and Single Repetition rules, but not to the Local Probability rule. In the second interval (at the latency of the P300 effects), the EROS results showed significant frontal and parietal activities sensitive to the Global Probability rule at 441 msec and the Local Probability rule at 345 msec, but not to the Single Repetition rule. The peak *Z* scores, critical *Z*, and locations of the peak optical responses in Talairach coordinates are reported in Table 5. Consistent with our predictions, these results showed that the rules associated with static internal representations (i.e., Global Probability and Single Repetition) were processed in temporal regions at earlier time intervals, whereas the earliest evidence for the utilization of dynamic internal representations (Global Probability and Local Probability) occurred within a fronto-parietal network at later time intervals. These results also demonstrated the activation of ROIs and IOIs specific to each rule by showing a double dissociation pattern: frontal-parietal activations during the P300 time window were found for the Local Probability rule, but not for the Single Repetition rule, whereas a temporal cortex activation during the N2 time window was found for the Single Repetition rule, but not for the Local Probability rule. Similar double dissociation patterns were observed for the ERP N2 and P300 intervals.

To determine the degree of overlap in the activated pixels for both the superior temporal gyrus (STG) activation in the Single Repetition and Global Probability contrasts and the superior frontal gyrus (SFG) activation in the Global and Local Probability contrasts, we conducted a conjunction analysis, which is also presented in Figure 6. In this figure, conjunction areas are shown in red. Importantly, in all cases, there was some overlap between the areas activated as a function of the various contrasts within the ROIs.

In addition to the hypothesis-driven ROI analysis presented above, we also conducted a whole-brain analysis using a Gaussian-field approach to correct for multiple comparisons. As this analysis was not planned, it should be considered exploratory. The results of this analysis are

Table 4. Contrast Analyses for the 200–300 msec (N2) and the 300–450 msec (P300) Time Windows for the Fz, Cz, and Pz Electrodes

		Global Probability		*Single Repetition*		*Local Probability*	
Component (Time Window)	*Electrode*	*WM (SD)*	*t*	*WM (SD)*	*t*	*WM (SD)*	*t*
N2 (200–300 msec)	Fz	−1.79 (2.33)	−3.08*	−0.49 (1.05)	−1.87*	−0.08 (1.30)	−0.25
	Cz	−1.29 (2.63)	−1.95*	−0.76 (1.22)	−2.49*	0.60 (1.77)	1.36
	Pz	−0.78 (1.79)	−1.73*	−0.48 (1.02)	−1.89*	0.47 (1.62)	1.15
P300 (300–450 msec)	Fz	2.19 (1.60)	5.47*	−0.07 (1.38)	−0.21	1.03 (1.33)	3.11*
	Cz	4.40 (1.59)	11.07*	0.13 (1.80)	0.29	1.90 (1.77)	4.27*
	Pz	3.80 (1.67)	9.08*	0.37 (1.58)	0.93	1.77 (1.53)	4.62*

The means are weighted (WM, in μV) according to the contrast.

*$p < .05$ (one-tailed), $df = 15$.

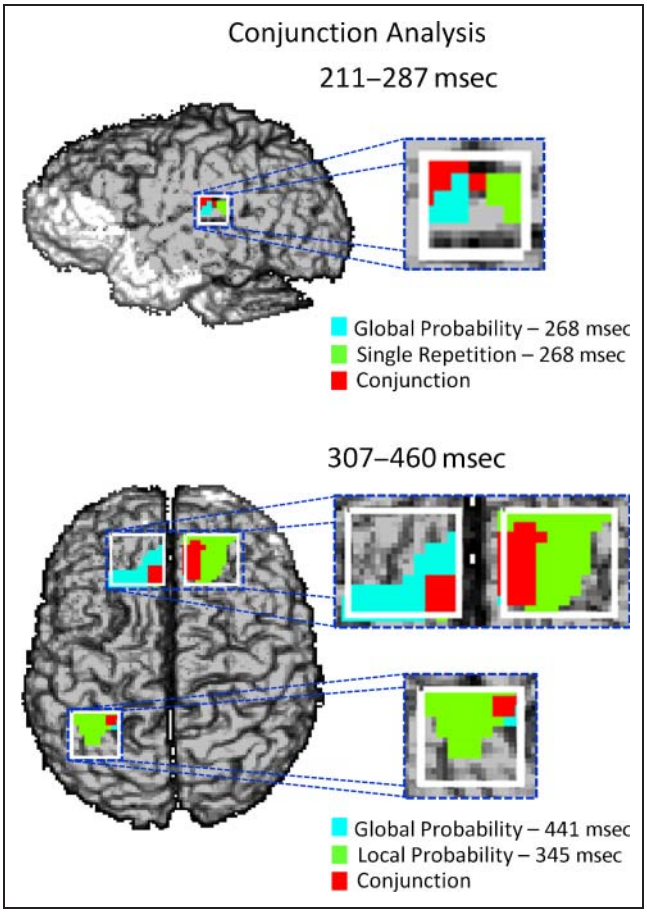

Figure 6. Statistical maps of EROS data based on the contrasts for the three contingency rules (hypothesis-driven ROI and IOI analyses). The white boxes indicate the ROIs, and the IOIs are indicated by the time ranges displayed on top of each map. The dark gray shading shows the areas of cortex interrogated by the recording montages. Top: Left STG ROI during the MMN–N2 interval (211–287 msec latency). Blue indicates voxels with a significant effect for the Global Probability contrast only, green indicates voxels with a significant effect for the Single Repetition contrast only, and red indicates voxels with significant effects for both contrasts (all effects adjusted for multiple comparisons). A blow-up of the ROI is displayed to the right of the map. Bottom: SFG and parietal ROIs during the P300 interval (307–460 msec latency). Blue indicates voxels with significant effect for the Global Probability contrast only, green indicates voxels with significant effect for the Local Probability contrast only, and red indicates voxels with significant effects for both contrasts (all effects adjusted for multiple comparisons). Blow-up insets of the ROIs are displayed to the right of the map.

presented in Table 6. Statistically significant activations inside the ROIs (as shown in Figure 6 or listed in Table 5) are excluded in this whole-brain analysis. Although none of the activations outside the ROIs (which are masked in Figure 6) passed the alpha $< .05$ whole-brain criterion, a few of them came close (alpha $< .10$). Specifically, the largest of these activations were at 211 msec in the right inferior temporal gyrus for the single repetition contrast and at 364 msec in the right inferior frontal gyrus for the local probability contrast. Activations in both of these areas have been reported in oddball paradigms in previous fMRI and EROS studies (e.g., Tse & Penney, 2008; Tse et al., 2006; Waberski et al., 2001).

DISCUSSION

The current study provides evidence that the brain is simultaneously sensitive to multiple contingency rules, which can be differentiated from each other spatio-temporally along a static versus dynamic dimension. Specifically, a novel procedure was employed to explore the brain responses to stimuli governed by multiple temporal rules. Orthogonal contrasts were used to investigate brain representations of sequential regularities embedded within a 50:50 choice RT task. Different from traditional oddball MMN or P300 studies, which investigated the brain responses to deviance or rule violation by comparing the deviant against the standard stimuli, the current study also highlighted the brain responses representing the regularity between standard stimuli.

The ERP results showed that the rules were processed at different latencies. Evidence for stimulus differentiation based on the Global Probability rule emerged between 200 and 450 msec poststimulus, for the Single Repetition rule between 200 and 300 msec, and for the Local Probability rule between 300 and 450 msec. In addition to confirming the latency differences shown by the ERPs, the EROS results further suggested that the brain areas involved in processing varied for different rules. For the Global Probability rule, differentiation was evident first in the superior temporal cortex, followed by the prefrontal and parietal cortices. For the Single Repetition rule, differentiation was evident early on in temporal regions, and for the Local Probability rule, the first evidence of differentiation occurred in frontal and parietal regions. This supports the hypothesis that there are both temporal and spatial differentiations in the processing of the contingency rules.

The ERP and EROS results are consistent with the use of a static (template-mismatch) to dynamic (contextual/working memory updating) dimension to classify the representations used to implement contingency rules. The different levels of this dimension also correspond well to the framework used to interpret the N2 and P300 ERP components, respectively. It has been suggested that the N2 is related to mismatch processing when incoming stimuli are not consistent with the expectancy derived from a memory template (Folstein & VanPetten, 2008). Furthermore, the amplitude of the N2 increases with decreases in the probability of stimuli (Bruin & Wijers, 2002). The N2 appears closely linked to the MMN, another well-studied ERP component, with the main difference between them being that the N2 is observed when stimuli require attention whereas this is not necessary for the MMN. Consistent with this view, Horvath and colleagues (2001) also showed that variations in the MMN indicate that multiple representations of contingency rules can be simultaneously maintained even in the absence of attention. This may suggest that

Table 5. Peak EROS Responses for the Global Probability, Single Repetition, and Local Probability Rules (Hypothesis-driven ROIs and IOIs Analyses)

Left Temporal ROI (211–287 msec)

Rule[a]	*ROI–time (msec)*	*Peak Z (Z Critical)*	*y, z*[b]	*Location*[c]	*BA*[d]
GP	Left temporal–268 msec	2.83 (1.75)	−26, 17	STG	42
SR	Left temporal–268 msec	2.52 (2.07)	−38, 12	STG	22
LP	Left temporal–268 msec	0.14 (1.90)	*ns*	*ns*	*ns*

Frontal and Parietal ROIs (307–460 msec)

Rule[a]	*ROI–time (msec)*	*Peak Z (Z Critical)*	*x, y*[b]	*Location*[c]	*BA*[d]
GP	Right frontal–441	2.84 (2.35)	4, 32	SFG	6, 8
GP	Left frontal–441	2.86 (2.40)	−6, 32	SFG	6, 8
GP	Left parietal–441	2.23 (2.21)	−28, −48	SPL	7
SR	Frontal–345	1.84 (2.32)	*ns*	*ns*	*ns*
SR	Left parietal–345	0.16 (2.04)	*ns*	*ns*	*ns*
SR	Frontal–441	−2.39 (2.46)	*ns*	*ns*	*ns*
SR	Left parietal–441	1.03 (2.22)	*ns*	*ns*	*ns*
LP	Right frontal–345	3.60 (2.39)	12, 32	SFG	6
LP	Left frontal–345	3.20 (2.51)	−8, 19	SFG	6
LP	Left parietal–345	2.98 (2.33)	−38, −48	SPL, IPL	7, 40

[a]GP = Global Probability; SR = Single Repetition; LP = Local Probability.

[b]*x*, *y*, and *z* are Talairach coordinates; *ns* = nonsignificant.

[c]BA = Brodmann's area; STG = superior temporal gyrus; SFG = superior frontal gyrus; SPL = superior parietal lobe; IPL = inferior parietal lobe.

[d]Brodmann's areas and corresponding brain regions were obtained from the Talairach Daemon Atlas.

the implementation of simple static rules may not require attention.

The P300 component, instead, is only elicited in paradigms requiring attention (see Fabiani et al., 2007; Polich, 2007, for reviews). An influential view of this component proposes that it is a manifestation of context updating of working memory templates to prepare the brain for future tasks and that it is therefore predictive of subsequent responses (Donchin & Coles, 1988; Donchin, 1981; see also Fabiani, 2006). Furthermore, P300 amplitude reflects local probability changes in the stimulus sequence (Brumback Peltz et al., 2011; Brumback et al., 2005; Squires et al., 1977). Although a recent review by Polich (2007) highlights the different functional significance of the P3a and P3b subcomponents of the P300 (as well as their differential anatomical and biochemical substrates), the current study was not designed to distinguish between them. Thus, we can expect that both subcomponents will be activated concurrently.

For the Global Probability rule, it is not surprising that a template was formed for the alternating pattern, as 75% of the trials were alternations. Violations of the alternating pattern (i.e., repetitions) produced a template mismatch as indicated by the N2 effect and reflected by the early temporal lobe activity. In addition, the Global Probability rule also required a running memory update of the alternation/repetition frequency, so that appropriate responses could be made to future stimuli. The enhanced P300 elicited by this rule may be an index of this updating process. Lesion (Knight, Scabini, Woods, & Clayworth, 1989; Knight, 1984), fMRI (Polich, 2007; Linden, 2005; Kirino, Belger, Goldman-Rakic, & McCarthy, 2000), and multimodal brain imaging studies combining ERP and fMRI (Mantini et al., 2009; Benar et al., 2007; Calhoun et al., 2006; Bledowski et al., 2004) link the P300 to a fronto-parietal network. Our results are consistent with these studies.

Note that most fMRI studies also show temporal activity in the oddball paradigm (e.g., Clark et al., 2000). However, the current study suggests that the temporal activation may be functionally separated from the fronto-parietal activation. Furthermore, the spatiotemporal properties of the observed frontal activity were similar to those found in a previous EROS study that used auditory active and passive oddball paradigms (Low et al., 2006). The data reported

Table 6. Whole-brain Exploratory Analyses of EROS Responses

Rule[a]	*Time (msec)–View*	*Peak Z*[b]	*y(x), z(y)*[c]	*Location*[d]	*BA*
211–287 msec					
GP	249–R lateral	3.05	−61, −1	R MTG	37
GP	268–L lateral	3.12	−3, −18	L MTG	21
SR	211–Axial	3.36	49, 29	R MFG	9
SR	211–R lateral	**3.89**	−16, −16	R ITG	21
SR	211–L lateral	3.38	29, 17	L IFG	46
SR	230–L lateral	3.01	−91, 9	L MOG	19
SR	268–R lateral	3.70	−78, −1	R MOG	19
LP	268–Axial	3.23	−8, −43	L paracentral	5
307–460 msec					
GP	345–L lateral	3.12	−86, 4	L MOG	18
GP	383–R lateral	3.22	−39, −13	R MTG	21
GP	403–L lateral	3.29	−91, 22	L cuneus	19
SR	345–L lateral	3.13	34, 27	L MFG	9
SR	345-R lateral	3.15	−38, 52	R IPL	40
SR	383–Axial	3.43	59, −43	R SMG	40
LP	364–Axial	3.42	49, 14	R MFG	8
LP	364–R lateral	**3.88**	9, 24	R IFG	9
LP	383–L lateral	3.50	−33, −16	L ITG	20

[a]GP = Global Probability; SR = Single Repetition; LP = Local Probability.

[b]For reference, without correction for multiple comparison, Z score > 3.09, $p < .001$, one-tailed; with correction for multiple comparison, Z score > 3.45, $p < .2$; Z score > 3.70, $p < .1$; and Z score > 3.90, $p < .05$.

[c]For lateral views coordinates are y and z, for axial views coordinates are x and y.

[d]It should be noted that activations within the ROIs or part of the same extended clusters were excluded from the whole-brain analyses. L = left; R = right; MTG = middle temporal gyrus; MFG = middle frontal gyrus; ITG = inferior temporal gyrus; IFG = inferior frontal gyrus; MOG = middle occipital gyrus; IPL = inferior parietal lobule; SMG = supramarginal gyrus.

Bold font indicates values below the .10 level of significance with correction for multiple comparisons.

here are consistent with the notion that the frontal cortex integrates information across time and may be critical for dynamic representations (Fuster, 2001, 2004, 2006).

The Single Repetition rule did not require participants to maintain information for more than two consecutive stimuli and could then be implemented by using (static) sensory memory mechanisms, which can be supported by secondary auditory areas (as the stimuli were auditory). This contrasted with the Local Probability rule, which required participants to dynamically keep track of the ordinal position of each tone within a pair. The running memory-updating process required by the Local Probability rule was associated with the observed P300 effect and EROS fronto-parietal activity. Note, however, that an N2 as well as superior temporal cortex activity were not observed in association with this rule. This may reflect the greater representational demands underlying this contingency rule, which requires integrating ongoing information with contextual information (related to the ordinal position of the stimulus within the sequence). This type of representation may not be attainable at early (proximal to sensory input) cortical levels and may only be achieved at more distal representational levels (see Badre, 2008; Badre & D'Esposito, 2007; Fuster, 2001, 2004, 2006, for a hierarchical view of processing within the brain). The data of the current study suggest that the frontal cortex may be very important for holding representations that include contextual information and/or need to be kept active over extended periods (i.e., for representations related to working memory; see Kirino et al., 2000).

The conjunction analysis revealed that, for both the temporal and frontal ROIs, there was overlap between the areas activated by different contrasts (simple repetition and global probability for the temporal ROI and global

probability and local probability for the frontal ROIs). However, the whole-brain analyses suggested that, for each condition, there might also be additional activations during the same intervals (although no other response actually passed the whole brain .05 criterion). Specifically, during the MMN–N2 interval, the whole-brain analysis suggests that the single repetition rule might be associated with activation of the inferior temporal gyrus (bilaterally, but more prominent to the right) and middle occipital gyrus (bilaterally), whereas the global probability rule showed subthreshold activation of the middle temporal gyrus (also bilaterally).

Similarly, the fronto-parietal network activities observed in the Global Probability and Local Probability contrasts partially overlapped (Figure 6, bottom) but also showed some differences in their spatial distribution. The frontal activity for the Global Probability rule was more left-lateralized and extended to posterior frontal regions. Conversely, the frontal activity associated with the Local Probability rule was more right-lateralized and extended anteriorly. As the Global Probability rule involves the "oddball" stimuli whereas the Local Probability rule involves the nonrepeating "standards," the difference in the distribution of their respective frontal activities may reflect slightly different mechanisms in dynamic memory updating. Differences in the spatial distribution of temporal cortex activities were also observed between the Global Probability and Single Repetition contrasts. Further research is needed to better understand these differences. These data can also be interpreted within the framework of a connectionist model proposed by Cleeremans and McClelland (1991). In this model, the ability to integrate temporal structures across time requires continuous tuning of an internal representation or processor for optimal performance. Current input interacts with an existing context unit, formulated based on previous input, to produce a response. This model has been applied to syntax extraction from letter sequence in words or word sequence in sentences (Elman, 1990) and procedural memory mechanisms that support repetition priming and skill learning (Gupta & Cohen, 2002). Template matching and memory updating can be conceived as manifestations of the operation of the context unit in the model. In addition, the current study suggests that there are different types of context units involved, depending on the processing requirements of the rules. This idea is analogous to Gupta and Cohen's (2002) proposal that different representations or processors are being tuned for optimal performance in repetition priming and skill learning.

The acquisition of sequential rules, including various forms of stimulus repetitions and alternations, has been the target of a large number of electrophysiological investigations. For instance Bendixen et al. (2007) showed that an MMN–P3a complex can reveal the rapid learning of rules about the sequencing of background, irrelevant stimuli. The authors proposed that these rules are governed by a "predictability" principle: The brain response is the largest for stimuli for which predictability, based on the previous sequence, is the smallest. Our behavioral results can in fact be explained by this more parsimonious account (i.e., RP-T1 > AP-T1 > AP-T2 = RP-T2), in agreement with the Bendixen et al. (2007) study. However, our ERP and EROS data also indicate that different predictions are made at different levels within the brain. For instance, the EROS data suggest that some regions of the brain (such as the STG) use a rule for which the most predictable stimulus is RP-T2, followed by AP-T2, AP-T1, and RP-T1. However, for another region (SFG), RP-T2 was not different from AP-T2: According to the predictability principle (for which the amplitude of the brain response is inversely related to stimulus predictability), these two regions (STG and SFG) must use different representational rules. Similarly, such an account cannot fully explain the dissociation between the N2 (AP-T1 = AP-T2 > RP-T2) and P300 (AP-T1 > AP-T2 = RP-T2) ERP responses to the nonrepeating trials. This dissociation suggests that the MMN–N2–P3 complex is not a single entity and that different types of sequential rule processes may be associated with the elicitation of the N2 and P300 components. Thus, although the contingency rule hypothesis proposed in this study may be less parsimonious than the probability or predictability hypothesis proposed by Bendixen et al. (2007), it does provide a more comprehensive account of the behavioral and brain imaging results presented here.

There are striking similarities in the temporal aspects of the EROS and ERP results. The EROS temporal and frontal cortex activities were observed in time windows consistent with the N2 and P300 responses. More interestingly, a comparison between the P300 components elicited by the Local Probability and Global Probability rules showed that the P300 effect for the Global Probability rule occurred later than that for the Local Probability rule. This small temporal difference was also reflected in the frontal cortex activity observed with EROS for the Global Probability rule, which occurred later than that for the Local Probability rule. Similar to previous studies with simultaneous EROS and ERP recordings (e.g., Tse & Penney, 2008; Tse et al., 2007; Low et al., 2006; Rinne et al., 1999), several of which also showed specific correlations between EROS and ERP time courses, the current study suggests a close temporal correspondence between ERP and EROS effects.

This study investigated the brain activity related to the representation of sequential rules differing in their level of abstraction. Similar problems are also investigated in artificial grammar studies, which have examined brain activities associated with the application of artificial grammar rules. For example, our results are consistent with an intracranial recording study by Sahin, Pinker, Cash, Schomer, and Halgren (2009), showing that inferior frontal cortex is involved in processing grammar rules. Brain imaging studies have also shown that relevant areas include temporal cortex (e.g., Lieberman, Chang, Chiao, Bookheimer, & Knowlton, 2004), frontal regions (e.g., Makuuchi, Bahlmann, Anwander, & Friederici, 2009; Bahlmann, Schubotz, &

Friederici, 2008; Forkstam, Hagoort, Fernandez, Ingvar, & Petersson, 2006; Fletcher, Büchel, Josephs, Friston, & Dolan, 1999), and parietal cortex (e.g., Skosnik et al., 2002), all regions that were found to be activated in the current experiment. In addition, some of these studies also pointed at a possible role of deep structures, such as the caudate (Lieberman et al., 2004), which cannot be measured with EROS and ERPs. Thus, despite differences between the sequential auditory paradigm used in the current study and those used in these artificial grammar studies, it is possible that some underlying relationships may exist between the brain mechanisms used to instantiate higher-level rules. Note that temporal cortex was activated in the current study as well as in the artificial grammar summarized above. Here we interpreted the temporal cortex activation as a reflection of the engagement of sensory memory. However, temporal cortex structures may also be involved in multimodal processing related to language and syntax processing (Tse et al., 2007; Bulkin & Groh, 2006; Calvert et al., 1997).

The paradigm we adopted in the current study differs from some of the traditional oddball paradigms used to research the MMN–N2 and P300 components of the ERP, in that the use of a complex set of contingency rules allowed us to examine in detail processing for all items in the stimulus sequence. Specifically, these rules allowed us to dissociate the N2 and P300 responses and to link them to particular optical phenomena. This link does not imply that the areas where the optical effects were observed are directly responsible for the scalp electrical measures. This statement would require application of forward models and more sophisticated tests than those carried out here. However, the activation observed here are consistent with current thinking about possible sources of the MMN–N2 and P300 (e.g., Polich, 2007; Opitz et al., 2002).

Furthermore, whereas the data demonstrate that different brain regions may all be involved in the processing of events according to sequential structures, they also show that different sequential expectancies may be reflected by their activation patterns. The results, however, do not imply that participants are aware of these sequential rules. In fact, recent evidence suggests that participants may adopt different processing strategies based on contingency rules without being aware of them (e.g., Ghinescu, Stadler, Schachtman, Gratton, & Fabiani, 2010). In our study, the behavioral and brain measures do not directly address the issue of consciousness. Nevertheless, they demonstrate that our brains are particularly well adapted to pick up regularities in our environment, even some as abstract and processing-demanding as the Local Probability rule and that they may do so although there are no explicit instructions about these rules.

An essential element of this study is the use of orthogonal contrasts to characterize the responses of the brain according to particular rules. Orthogonality here is intended merely in statistical terms. Basically, the contrasts we used are orthogonal, in the same sense in which a stratified sample study achieves orthogonality. In other words, statistically uncorrelated information was used to compute the various effects. This approach, per se, does not imply that the brain considers these different pieces of information as unrelated and that the brain (or behavioral) responses can be dissociated. In fact, our data indicate an imperfect dissociation: Whereas the Single Repetition and Local Probability rules are associated with different brain responses (both in the ERP and EROS data), the Global Probability rule shows effects that are partly overlapping with both of the other two rules. In other words, we took this approach to test the brain implementation of (and its possible discrimination between) rules, but we never predicted a one-to-one mapping between rules and brain responses. Although some brain responses appear to incorporate information from multiple rules, different brain regions show sensitivity to different (and dissociable) rules that are used to generate expectations for upcoming stimuli. In this sense, the Global Probability rule appears to generate expectations that affect brain activity at multiple levels (perhaps reflecting its greater generality and fundamental importance), whereas the other two rules appear more specific in their effects, only influencing the representations at one level of the brain processing stream.

It is also important to consider that we have used a very specific set of orthogonal contrasts, reflecting certain particular sequential rules, but that in fact there are a number of other orthogonal contrasts we could have set up, if we had followed a different organizational principle. The advantage of our set was that (a) it was theoretically justified, (b) it was established a priori, and (c) it was found out to have a clear explanatory value, indicating that different rules are used at different levels of processing within the brain.

In summary, the current study takes advantage of EROS measures covering the entire cortical surface for the first time and compares them to ERPs recorded in the same participants to provide useful insights into the mechanisms underlying sequential rule representations. The data indicate that different forms of rules, involving static or dynamic representations, may be supported by different cortical activities related to perceptual and working memory processing, respectively.

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Reprint requests should be sent to Gabriele Gratton, Beckman Institute, 405 N. Mathews Ave., Urbana, IL 61801-2325, or via e-mail: grattong@illinois.edu.

Notes

1. In other words, the Local Probability rule states that p(alternation | first tone of the pair) = .5 and p(alternation |

second tone of the pair) = 1. This expands on the Global Probability rule, where p(alternation) = .75 for all trials, without having to keep track of the tones in the pair.

2. Because this is an active task, we refer to an N2 effect instead of an MMN effect.

3. The current coming from each PMT (i.e., detector) was sampled at 50 kHz. However, the light sources were time-multiplexed, each staying on for a period of 1.6 msec and off for a period of 17.6 msec. Therefore the PMTs received light form each source only for a period corresponding to 10 cycles of the cross-correlation frequency. To avoid cross talk, the first and last cycles were discarded and the intermediate eight cycles (corresponding to 64 data points) were entered into a fast Fourier transform to compute light intensity and phase delay at the cross-correlation frequency for a particular channel at a particular time point.

4. For additional information about the steps involved in the analysis of optical data, see Figure 1 in Tse, Gordon, Fabiani, and Gratton (2010) and Gratton and Fabiani (2009).

5. A repeated-measures ANOVA was conducted to verify that the two EROS sessions did not differ from each other in behavior. As expected, the Session × Contrast interaction was not significant ($F(2, 14) = 2.28$). Therefore the two EROS sessions were collapsed in all analyses to increase statistical power.

6. As the ERP session was identical to the practice session, the RTs of the practice session were compared against the ERP session to investigate learning effects.

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