

# Implicit Learning of Sequential Regularities and Spatial Contexts in Corticobasal Syndrome

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The present study investigated two forms of implicit learning in patients with corticobasal syndrome (CBS): contextual cueing and sequence learning. The former primarily implicates the medial temporal lobe system, and the latter, fronto-striatal-cerebellar circuits. Results revealed relatively preserved contextual cueing in patients with CBS. By contrast, sequence learning showed impairments, which seemed to reflect inability to execute correct responses in the presence of intact learning of the sequence. These findings provide the first characterization of implicit learning systems in CBS, and show that the two systems are differentially affected in patients with CBS.

**Keywords:** Implicit learning, corticobasal syndrome, spatial contexts, sequence learning, dementia

## Introduction

The corticobasal syndrome (CBS) refers to a constellation of signs and symptoms including asymmetric rigidity and apraxia, alien limb phenomenon, cortical sensory loss, myoclonus and dystonia (Gibb, Luthert, & Marsden, 1989; Kertesz, 1997; Lang, 2000; Rebeiz, Kolodony, & Richardson, 1967). It is a rare, progressive disorder characterized by asymmetric cortical atrophy, typically in the frontoparietal regions, and also basal ganglia and nigral degenerations (Boeve, Lang, & Litvan, 2003; Josephs et al., 2002; Litvan et al., 1997). It is difficult to clinically distinguish CBS from other parkinsonian syndromes (Boeve et al., 2003). Neuropsychological testing in patients with CBS indicates impairment in cognitive domains subserved by frontal/frontostriatal and parietal networks, including attention, executive functions, verbal fluency, language, and visuospatial functioning; tests of memory, on the other hand, show very little impairment, particularly early in the disease course (Massman, Kreiter, Jankovic,

& Doody, 1996; Pillon et al., 1995). Very little is known, however, with regards to performance on tests that are targeted at specific components of cognitive processes. Such targeted tests have advantages over global assessment of cognition because they are aimed at specific component processes whose brain mediation and innervation are relatively well understood (Greenwood, Lambert, Sunderland, & Parasuraman, 2005).

The present study was designed to investigate implicit learning systems in CBS. Implicit learning generally refers to a situation where a person learns about the structure of a stimulus environment without conscious effort to learn and without ability to describe what has been learned (Reber, 1993). It is fundamentally different from explicit learning, in which people are aware of what they have learned and are able to describe it (Frensch, 1998). Implicit learning has several forms, which involve different neural substrates (Forkstam & Petersson, 2005; Frensch & Ruenger, 2003), and are differentially affected in clinical populations (Doyon et al., 1997; Gomez-Beldarrain et al., 1998; Helmuth, Mayr, & Daum, 2000; Howard, Howard,

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Japikse, & Eden, 2005; Knopman & Nissen, 1991; Siegert, Taylor, Weatherall, & Abernethy, 2006) and in healthy aging (Howard et al., 2004b). Recent evidence suggests that different forms of implicit learning are also modulated differently by genotype (Keri et al., 2005; Negash et al., 2006).

We investigated two forms of implicit learning in CBS patients – sequence learning and contextual cueing. This comparison is of particular interest because the two learning tasks call primarily upon different neural substrates that are known to be differentially affected in CBS, thereby aiding in the understanding of the differential neuroanatomical and cognitive changes associated with CBS.

To investigate sequence learning, we used an alternating serial reaction time (ASRT) task (Howard & Howard, 1997). In this task, alternate stimuli follow a predetermined pattern while the remaining stimuli are selected randomly. For example, a person assigned the pattern 132 (where 1 stands for the left-most position and 3 for the right most) would encounter the following series, where “r” stands for a randomly chosen one of the three positions: 1r3r2r1r3r2, and so on. Thus, predictable pattern events are embedded in random, unpredictable ones. The ASRT task taps learning of higher-order regularities in that the lowest level of regularity to be learned is second-order (i.e., which triplets are more likely to occur); pattern and random trials do not differ either in 0th order information (i.e., relative frequency of individual events) or in 1st order information (i.e., relative frequency of pairs of events). Further, trial-by-trial analyses of response times and accuracy in previous ASRT studies (Howard et al., 2004a; Howard & Howard, 1997) indicate that what people learn in this task is second-order information, such that their performance becomes increasingly sensitive to the frequency with which triplets of items occur. The ASRT task also yields relatively pure implicit learning in that people find it difficult to either describe what they have learned (Howard & Howard, 1997) or discriminate between pattern and random sequences (Japikse, Howard, & Howard, 2001; Negash, Howard, Japikse, & Howard, 2003).

Clinical and neuroimaging studies indicate that implicit learning of sequences is mediated primarily by the fronto-striatal-cerebellar system (Curran, 1998; Gomez Beldarrain et al., 1999; Honda et al., 1998; Willingham, Salidis, & Gabrieli, 2002). For example, studies of Parkinson’s and Huntington’s disease patients with damage to the basal ganglia, as well as cerebellar patients have shown sequence-specific learning deficits on the SRT task, indicating the involvement of the striatal dopaminergic system and cerebellum in sequence learning (Doyon et al., 1997; Gomez-Beldarrain et al., 1998; Helmuth et al., 2000; Knopman & Nissen, 1991). Neuroimaging studies have also shown the involvement of fronto-striatal regions during sequence learning (Fletcher et al., 2004; Seidler et al., 2005; Willingham et al., 2002). Further, studies of healthy aging, which is characterized by structural and functional losses in prefrontal cortex, have shown implicit learning deficits in older adults, particularly in learning sequences that contained higher-order regularities (Curran, 1997a; Howard et al., 2004a; Howard & Howard, 1997).

The contextual cueing paradigm, on the other hand, is a visual search task developed by Chun and Jiang (1998) to study how spatial context is learned. In this task, people are asked to search for a target (e.g., a horizontal T) in an array of distractors (rotated L’s). Unbeknownst to participants, some displays contain repeated configurations that provide a spatial context that cues the location of the target, while novel displays are generated randomly. Results reveal that with practice, people respond faster to repeated than to new configurations (Chun, 2000; Olson & Chun, 2002). Furthermore, such learning has been shown to occur implicitly in that people do not develop explicit knowledge of the relationship between the spatial context and the target location. Clinical studies indicate that such contextual learning depends on the medial temporal lobe system, particularly entorhinal and parahippocampal regions, in that amnesic patients with damage to these regions show contextual cueing deficits (Chun & Phelps, 1999; Manns & Squire, 2001). Further, previous research has shown a dissociation in healthy aging such that contextual cueing, which depends on these medial temporal regions, was preserved in healthy older adults, whereas sequence learning, which relies on the fronto-striatal system, showed impairment (Howard et al., 2004b), consistent with recent evidence of differential vulnerability of medial temporal and prefrontal regions in healthy aging (Buckner, 2004; Head, Snyder, Girton, Morris, & Buckner, 2005).

We administered both of the above paradigms to CBS patients and healthy elderly controls, to test the hypothesis that sequence learning, which relies on the integrity of the fronto-striatal system, is impaired in CBS patients compared to controls, while contextual cueing, which depends on the medial temporal lobe system, remains relatively spared. Research using these two tasks in patients diagnosed with amnesic mild cognitive impairment (MCI) (Petersen et al., 1999) has shown the reverse pattern such that MCI patients with medial temporal lobe atrophy revealed contextual cueing deficits compared to healthy controls, whereas their sequence learning was relatively preserved (Negash et al., 2006).

## Methods

### Participants

Participants were recruited through the Mayo Alzheimer’s Disease Research Center (ADRC) or Alzheimer’s Disease Patient Registry (ADPR) at the Mayo Clinic, Rochester, MN. Individuals participating in the ADRC/ADPR are evaluated by a behavioral neurologist who obtains a medical history from an informant, completes a short test mental status examination (Kokmen, Naessens, & Offord, 1987), the Hachinski Ischemic Scale (Rosen, Terry, Fuld, Katzman, & Peck, 1980), and performs a neurologic examination. Laboratory tests include CBC count, thyroid function tests, Vitamin B-12, folic acid levels, sensitive thyroid stimulating hormone level, and syphilis serology. Participants undergo brain imaging (computed tomography or

magnetic resonance imaging) and an extensive neuropsychological battery. Diagnoses are established via a consensus meeting of behavioral neurologists, neuropsychologists, geriatricians, neuropsychiatrists, and nurses. The study was approved by the Mayo Institutional Review Board.

Five (four female/one male) patients with corticobasal syndrome (CBS) were compared to five (four female/one male) healthy controls. The mean age and education for the patients were 67.2 ( $SD = 3.3$ ) and 13.6 ( $SD = 2.3$ ), respectively, and for the controls they were 67.2 ( $SD = 4.5$ ) and 13.6 ( $SD = 1.3$ ), respectively. The groups did not differ significantly in their scores on the Mini-Mental State Exam; 27.2 ( $SD = 2.5$ ) for the patients and 29.2 ( $SD = 0.4$ ) for the controls ( $p > .05$ ).

The diagnosis of CBS was made in accordance with the criteria established in Boeve et al. (2003). Controls were individuals who: (1) are independently functioning community dwellers, (2) do not have active neurological or psychiatric conditions, (3) have no cognitive complaints, (4) have a normal neurological exam, and (5) are not taking any psychoactive medications in doses that would impact cognition (Ivnik et al., 1992). Figure 1 displays the magnetic resonance images (MRI) for the CBS patients.

### Apparatus and behavioral paradigms

#### Contextual cueing task

In this task, participants were asked to locate and identify a target item among 11 distractors. These 12 items were shown as white characters on a gray background. The target was a horizontal T with the tail pointing either left or right, and the distractors were Ls randomly rotated by  $0^\circ$ ,  $90^\circ$ ,  $180^\circ$ , or  $270^\circ$ , as

used in Chun and Phelps (1999). Each element subtended approximately  $1.1^\circ$  of visual angle at a viewing distance of 56 cm. Arrays were generated by randomly placing the 12 items into cells of an invisible  $6 \times 8$  (rows  $\times$  columns) grid. Across arrays, target location was balanced for eccentricity with respect to the center of the screen as well as for left and right screen half. Targets never appeared in the four center cells or at the extreme corners of the display grid. Every element was randomly repositioned within its cell by  $\pm 2$  pixels along each axis to avoid colinearity with other elements. A set of 12 arrays was constructed for repeated presentation (details are given below).

#### ASRT task

Participants were seated in front of a Macintosh G4 computer with a 15-inch monitor (Apple Computer, Inc., Cupertino, CA). Three open circles ( $.5^\circ$  each) were presented horizontally on the computer screen, where on each trial, one of the circles filled in with a black color. Participants were asked to place the three middle fingers of their dominant hand on the "j", "k", and "l" keys (marked with blue stickers) and respond to the location of the filled in circle by pressing the corresponding key as quickly as possible. The left-most position corresponded to the "j" key, while the right-most position corresponded to the "l" key. The circle remained filled in until participants pressed the correct key, and then another target appeared after a delay of 120 ms.

#### Procedure

Each participant completed both the contextual cueing and the ASRT tasks, with the ASRT being followed by contextual cueing. The contextual cueing task began with a 24-trial practice

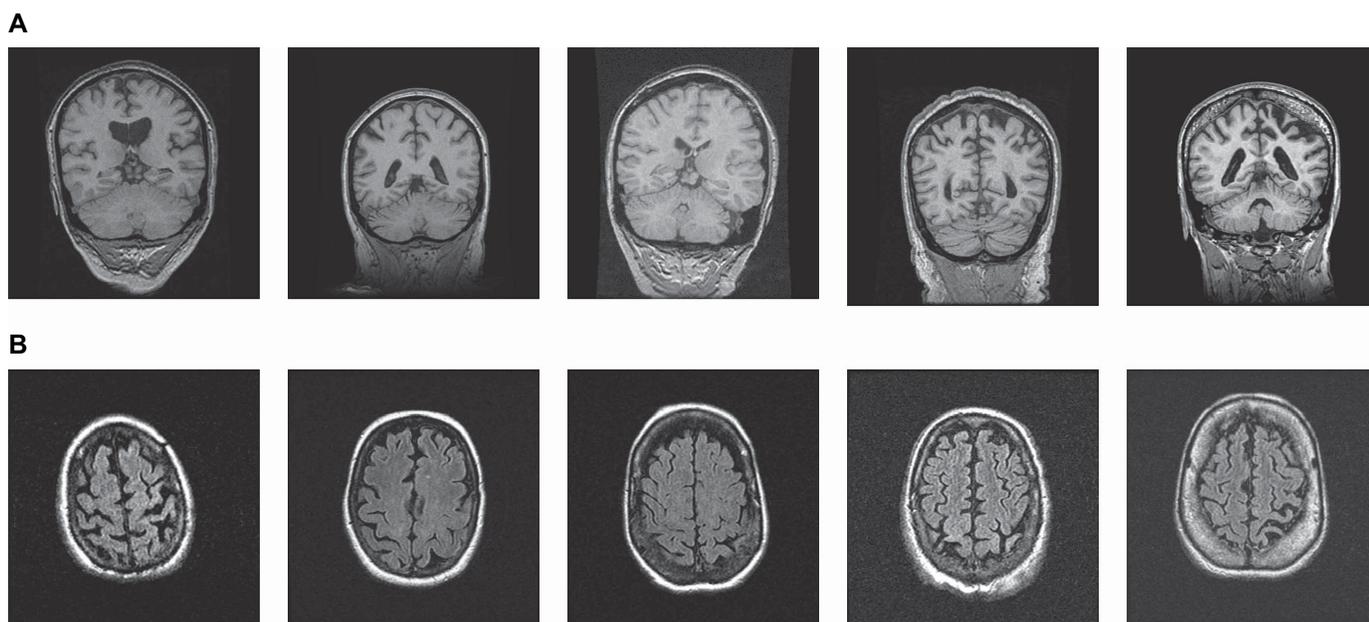


Fig. 1. Coronal T1-weighted (A) and axial FLAIR (B) MR images for each of the five patients with the corticobasal syndrome (CBS).

block. On each trial, participants were shown the target “T” among a background of “L”s. Their task was to locate the “T” on the screen, determine which way it is facing, and press the key that corresponds to that direction as QUICKLY and as ACCURATELY as possible. Each trial began with a white fixation dot approximately  $0.5^\circ$  centered on the screen. After 1 s the dot was replaced by a search array and the participant was to press a key indicating the target orientation. They were informed that “an occasional error is acceptable (e.g., one error per block of 24 trials).” Auditory feedback was provided after every response (a beep or tone to signal correct or error responses, respectively). A different search array was presented on each trial in the practice block. Following the practice block, participants completed 10 learning blocks of 24 trials each. Learning blocks were similar to practice except that only 12 of the search arrays were new in each learning block (new configurations). The remaining 12 arrays (repeated configurations) were repeated across blocks, appearing once in each block. The repeated configurations predicted the location of the target element, but not its orientation. Presentation order was randomized within blocks, and people were encouraged to take a short break between blocks.

After the final learning block, there was a post-experimental interview in which people were asked a series of questions to obtain insights into their strategy and their declarative knowledge of the task. The first three questions were open-ended: (a) “Do you have anything to report regarding the task?” (b) “Did you notice anything special about the task or the material?” (c) “Did you notice anything special about the way in which the stimuli were presented? If so, please explain.” The last three questions asked specifically about repetitions: (d) “Did you notice whether certain configurations (spatial layout or locations of the items) were being repeated from block to block?” (e) “If so, when did you begin to notice this repetition?” (f) “Did you explicitly try to memorize any of the configurations?”

For the ASRT task, they were seated in front of the computer and were given the following instructions: “In this study, we are trying to learn more about how practice affects motor performance. We want to find out just how much people are able to speed their responses when they are given extended practice on a simple reaction time task.” They were not given any information about the regularity that was embedded in this task.

Participants completed 20 blocks of the ASRT task, each block consisting of 10 random warm-up trials followed by 60 experimental trials. These 60 trials consisted of a 6-item sequence, in which pattern trials alternated with random trials (e.g., 1r2r3r) and this 6-item sequence repeated 10 times in a block. Thus, altogether, participants responded to 1,400 trials, or 200 repetitions of the pattern. One CBS patient was unable to perform the ASRT task due to a severe limb apraxia, thus four patients were matched with four healthy controls for the ASRT analyses. One of the following two sequences was given to half of the participants in each group: 1r2r3r and 3r2r1r.

At the end of each of the 20 blocks, the computer displayed an end-of-block feedback. This feedback gave participants their speed information on the most recent block and the immediately preceding block. In order to minimize fatigue, participants were asked to rest their eyes for at least thirty seconds in between blocks, and to take additional breaks as needed.

At the end, a post-experimental interview assessed whether participants had gained any verbalizable pattern knowledge. The experimenter read aloud the following questions one at a time and recorded participants’ responses. (1) “Did you notice anything to report regarding the task?” (2) “Did you notice anything special about the task or the materials?” (3) “Did you notice any regularity in the way the stimulus was moving on the screen?” If subjects answered, “yes” to question 3, they were asked (4) “Did you attempt to take advantage of any regularities you noticed in order to anticipate subsequent targets? If so, did this help?” (5) “In fact, there was some regularity to the sequences you observed. What do you think it was? That is, try to describe any regularity you think might have been there.”

Participants in this study were not given additional tests of explicit knowledge so as to avoid fatigue, especially in the CBS patients. Nonetheless, earlier research using both of these tasks has shown that other measures, such as recognition, recall, and generation tasks, also demonstrate that learning is implicit even among college students (Howard et al., 2004b; Howard, Howard, Japikse, & Eden, 2006). The whole procedure lasted approximately 2 h.

#### *Data reduction and statistical analysis*

For the contextual cueing task, the 10 blocks were grouped into five epochs, each containing two blocks. For each participant, a mean response time (RT) was determined separately for correct responses to new and repeated configurations on each block. The mean RTs were then averaged across blocks to obtain a mean RT for each individual and configuration type (new or repeated) on each epoch. Learning on this task was reflected in the difference in performance between repeated and new configurations, and it was measured by calculating learning scores, i.e., overall RT on new configurations minus that on repeated configurations.

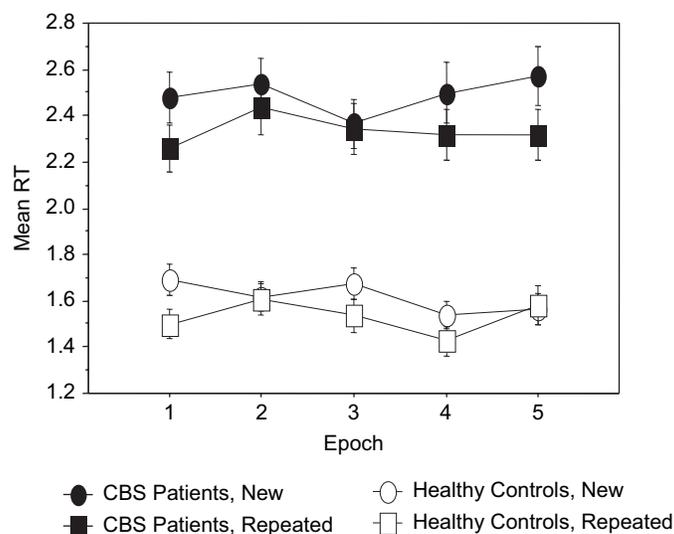
For the ASRT task, the 20 blocks were grouped into four epochs, each containing five blocks. The data from the first 10 random trials of each block were not analyzed. For the remaining 60 trials, each person’s sequence was parsed into a series of overlapping triplets using a sliding three-trial window. The final trial in this window was then assigned to one of four triplet categories: Consistent, Inconsistent, Trill, and Repetition. Consistent triplets are those that are consistent with the sequence a person was given during the ASRT session. For example, if a person was given the following sequence: 1-r-2-r-3-r, where “r” denotes a random selection of one of the three positions, then triplets 122, 213, and 331

represent Consistent triplets which occur often. Inconsistent triplets, on the other hand, are encountered less often during the ASRT session because they can end only on random trials (e.g., 231, 312). Trills are those triplets that begin and end with the same element, with a different element in the middle (e.g., 121), and Runs are those triplets that contain repetitions of a single element (e.g., 222). Trials completing a Run or Trill triplet were removed from the analyses because these were not counterbalanced across participants and differences between them could reflect pre-existing response bias as shown in previous findings (see Howard et al., 2004a). For the remaining categories, the median response time for correct trials was calculated separately for Consistent and Inconsistent triplets for each block. Then, the means of these block medians were calculated for each epoch to yield the mean response time for each triplet type for each participant. Learning on this task was the difference in performance between Consistent and Inconsistent triplets, and it was measured by calculating the learning scores for RT (overall RT on Inconsistent triplets minus Consistent triplets) and accuracy (overall accuracy on Consistent triplets minus Inconsistent triplets) measures.

Similar data reduction procedures were used for accuracy. For the contextual cueing task, the overall accuracy for the CBS group was 97% and that for the control group was 99%. On the ASRT task, the overall accuracy for the CBS group was 90% and that for the control group was 94%. The accuracy data on the contextual cueing did not reveal group differences, probably due to ceiling effects.

The main form of analysis was mixed design ANOVAs, with simple effects analyses and *post-hoc* comparisons carried out as appropriate. An alpha level of .05 was used throughout, with results meeting the .10 level being reported as marginal. Significance tests were always two-tailed.

For each task, we first show the mean response times (and accuracy for the ASRT task) as a function of epoch and trial type (Inconsistent vs. Consistent for the ASRT and Novel vs. Repeated for Contextual Cueing) in figures 2 and 4. This makes it possible to see any overall differences in response time between groups as well as the general shape of the learning functions. However, as the figures show, the data are very variable when broken down to this extent, due to the small *n* and the large between-subjects variability in overall RT. Therefore, for the rest of the analyses, in order to account for differences among subjects in overall speed and variability (Christ, 2001), the mean RTs were transformed into *z*-scores using each subject's mean and standard deviation across all correct trials to compute that subject's *z*-scores. These were then collapsed across epochs to give a measure of learning of the regularity (trial type effect) for each subject. These overall trial type effects can be unambiguously attributed to learning of the regularity, because as described above, the specific stimuli in each trial type are counterbalanced across subjects. Thus, any significant trial type effects must be due to learning, rather than to differences among the stimuli themselves. The use of the *z*-scores and the overall learning measures



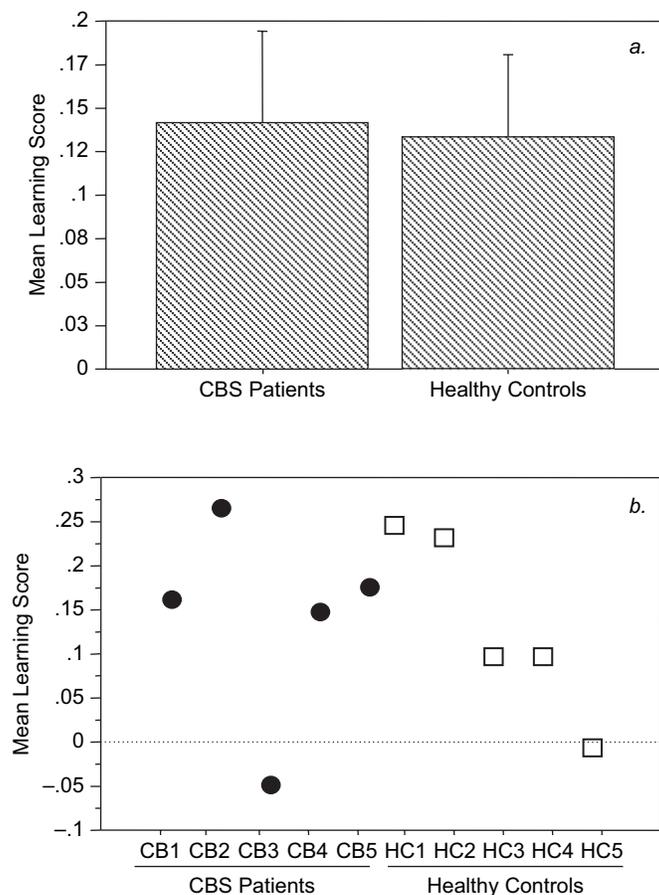
**Fig. 2.** Performance on contextual cueing task on RT measure across epochs on New (circles) and Repeated (squares) configurations for CBS patients (filled-in symbols) and healthy controls (open symbols). Error bars represent one standard error.

increased our ability to detect group differences in overall sensitivity to the regularity, which is our main focus.

## Results

### Contextual cueing

Figure 2 shows the mean response times across epochs on new and repeated configurations for CBS and control groups. First, looking at overall performance, CBS patients were slower overall compared to controls. The main effect of Group,  $F(1, 8) = 5.57$ ,  $MS_E = 3.43$ ,  $p = .04$  was significant. Contextual cueing in this task was measured by calculating each participant's learning score, i.e., overall RT on new configurations minus that on repeated configurations, collapsed across epochs. Figure 3a shows the mean learning scores for CBS and control groups. These positive learning scores indicate that both groups were faster on repeated than new configurations, and that the groups showed similar amounts of contextual cueing. Figure 3b shows the learning scores for each individual in each group, and indicates that four of the five subjects in each group showed contextual cueing in that they were faster on repeated than new configurations. In keeping with these observations, the Group (CBS Patients vs. Controls)  $\times$  Configuration (New vs. Repeated) ANOVA on learning scores revealed a main effect of Configuration,  $F(1, 8) = 15.43$ ,  $MS_E = 0.006$ ,  $p = .004$ , indicating that people performed better on repeated than new configurations. Further, separate ANOVAs on each group showed a significant main effect of Configuration for controls,  $F(1, 4) = 8.24$ ,  $MS_E = 0.005$ ,  $p = .04$  and a marginal effect for the patients,  $F(1, 4) = 7.32$ ,  $MS_E = 0.007$ ,  $p = .05$ . The Group  $\times$  Configuration

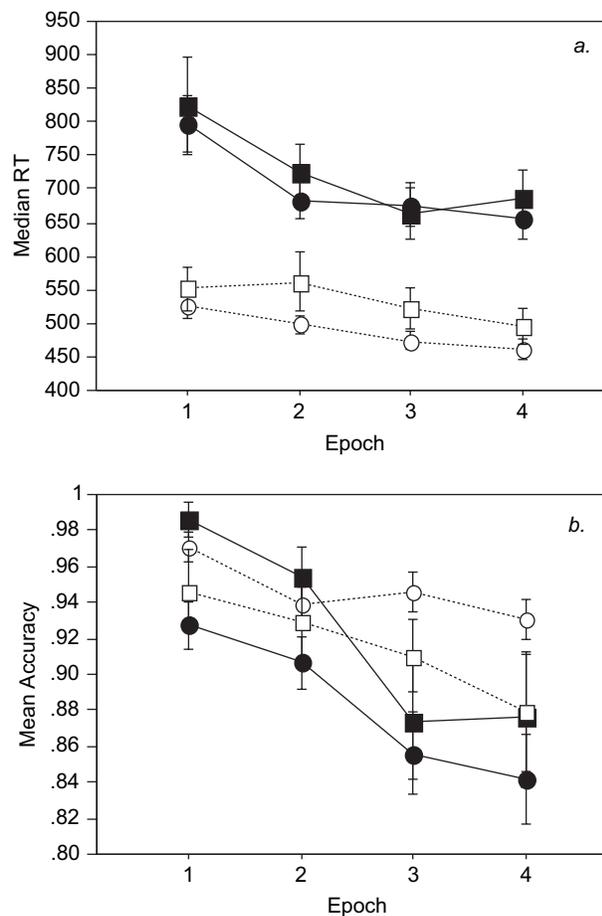


**Fig. 3.** Learning scores on contextual cueing task for CBS and control groups (a) and for each individual in each group (b). Error bars represent one standard error.

interaction, on the other hand, did not reach significance,  $F(1, 4) = 0.014$ ,  $MS_E = 0.006$ ,  $p = .91$ , suggesting that the groups did not differ in their contextual cueing.

#### ASRT learning

Figure 4a shows the mean response times across epochs on Consistent and Inconsistent triplets for CBS and control groups; figure 4b shows the mean accuracy. Both groups showed general skill learning in that their response times decreased across epochs; the main effect of Epoch was significant,  $F(3, 18) = 11.06$ ,  $MS_E = 1455.65$ ,  $p = .0002$ . Overall accuracy decreased across epochs,  $F(3, 18) = 5.84$ ,  $MS_E = 0.001$ ,  $p = .005$ . This decrease is apparent in all our ASRT studies (Feeney, Howard, & Howard, 2002; Howard et al., 2004a; Howard & Howard, 1997) and in research from other laboratories using other kinds of probabilistic regularities (Curran, 1997a; Schvaneveldt & Gomez, 1998). People usually report that they feel as though their fingers take over with practice on the task, leading them to make more and more “oops” errors. Of course, as the analyses below indicate, these errors occur more often on inconsistent trials than on



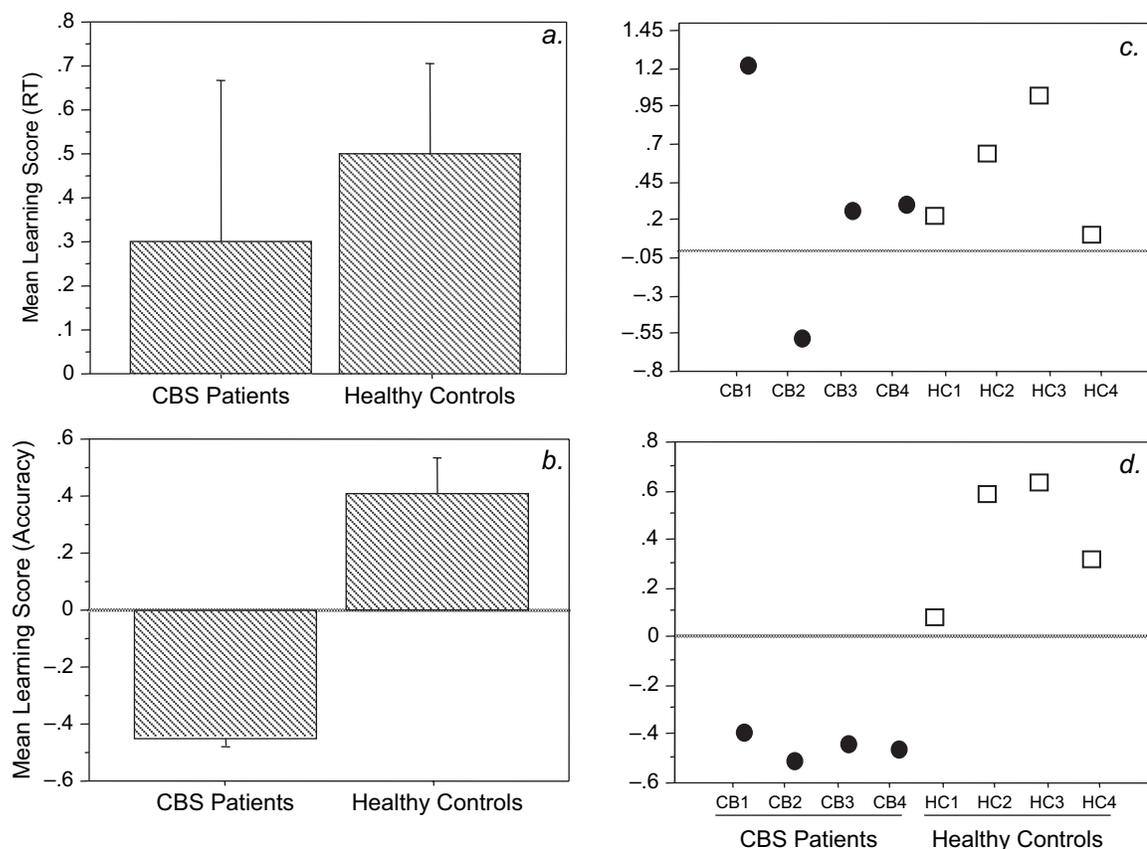
**Fig. 4.** Performance on ASRT task on RT (a) and accuracy (b) measures across epochs on Consistent (circles) and Inconsistent (squares) triplets for CBS patients (filled-in symbols) and healthy controls (open symbols; dotted lines). Error bars represent one standard error.

**Fig. 4.** Performance on ASRT task on RT (a) and accuracy (b) measures across epochs on Consistent (circles) and Inconsistent (squares) triplets for CBS patients (filled-in symbols) and healthy controls (open symbols; dotted lines). Error bars represent one standard error.

consistent ones, and hence reflect learning of the regularity. The CBS group appeared to be slower and less accurate than controls, but the main effects of Group did not reach significance,  $F(1, 6) = 3.05$ ,  $MS_E = 111702.72$ ,  $p = .13$  and  $F(1, 6) = 0.71$ ,  $MS_E = 0.02$ ,  $p = .43$ , for response times and accuracy measures, respectively.

As was done for contextual cueing, learning scores collapsed across epochs were calculated on  $z$ -transformed values for RT (overall RT on Inconsistent triplets minus Consistent triplets) and accuracy (overall accuracy on Consistent triplets minus Inconsistent triplets) measures.

Figure 5a,b shows the mean learning scores for CBS and control groups on the response time and accuracy measures, respectively; figure 5c,d shows the learning scores for each individual in each group. The control group showed triplet learning on both measures, where a positive learning score



**Fig. 5.** Learning scores on the ASRT task on the RT measure for CBS and control groups (a) and for each individual in each group (c), and on the accuracy measure for CBS and control groups (b) and for each individual in each group (d). Error bars represent one standard error.

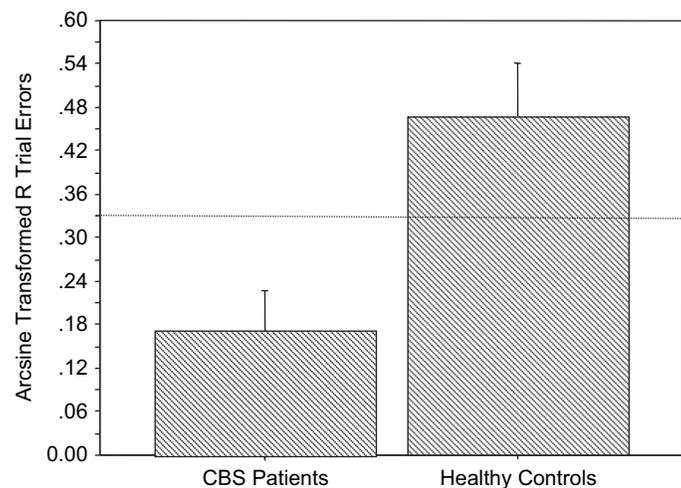
indicated that they were faster and more accurate on Consistent than Inconsistent triplets. The CBS group, on the other hand, revealed the reverse pattern on the accuracy measure, where they were more accurate on Inconsistent than Consistent triplets. This was also the case on individual subjects level, where each CBS patient showed the reverse pattern on the accuracy measure (figure 5d).

In keeping with these observations, the Group (CBS Patients vs. Controls)  $\times$  Triplet Type (Consistent vs. Inconsistent) ANOVA on accuracy revealed a significant Group  $\times$  Triplet Type interaction,  $F(1, 6) = 42.97$ ,  $MS_E = 0.017$ ,  $p = .0006$ , indicating group differences in ASRT learning scores. The RT measure did not reveal a significant interaction  $F(1, 6) = 0.217$ ,  $MS_E = 0.176$ ,  $p = .66$ . Further, separate ANOVAs on each group on the RT measure revealed a marginal Triplet Type effect for the controls,  $F(1, 3) = 5.64$ ,  $MS_E = 0.088$ ,  $p = .09$ , but none for the patients  $F(1, 3) = 0.689$ ,  $MS_E = 0.265$ ,  $p = .47$ . On the other hand, on the accuracy measure, separate ANOVAs revealed a main effect of Triplet Type for the control group favoring Consistent over Inconsistent triplets,  $F(1, 3) = 10.22$ ,  $MS_E = 0.033$ ,  $p = .0494$ , whereas the CBS group revealed a main effect in the reverse direction, favoring Inconsistent over Consistent triplets,  $F(1, 3) = 255.64$ ,  $MS_E = 0.002$ ,  $p = .0005$ .

To determine whether this reverse pattern on accuracy is not just a group effect but can also be seen on individual subjects data, we conducted separate Triplet Type  $\times$  Epoch ANOVAs for each person, using blocks within each epoch to determine error variance. As figure 5d indicates and ANOVAs confirm, the main effect of Triplet Type (Consistent vs. Inconsistent) was significant,  $F(1, 52)$ ,  $p < .05$ , favoring Inconsistent triplets for three of the four patients and, though in this same direction, did not reach significance for the remaining patient. For the controls, the main effect was significant favoring Consistent triplets for two out of the four participants and in this same direction though not significant for the remaining two. Thus, the reverse pattern on accuracy was seen even at the level of individual subjects for the CBS patients but not for controls.

#### Expectancy-based errors

To determine what proportion of errors on random trials were expectancy-based and reflected sensitivity to the structure of the sequence, errors on random trials were classified into two categories. Those that resulted in a triplet that was consistent with the sequence regularity were called structure-consistent,



**Fig. 6.** Mean arcsine transformed structure-consistent errors produced on random trials on the ASRT task for CBS patients and healthy controls. The dashed line represents chance level<sup>1</sup>. Error bars represent one standard error.

whereas those that resulted in a triplet that was inconsistent with the regularity were called structure-inconsistent. For example, if a participant whose sequence was 1r2r3r encountered a triplet 211, then incorrectly responding to the last item in the triplet with a 3 would be considered a structure-consistent error, whereas incorrectly responding with a 2 would be considered a structure-inconsistent error. For each participant, then, the proportion of all errors on random trials that were structure-consistent was determined. Figure 6 shows the mean proportion of structure-consistent errors for CBS patients and healthy controls, collapsed across the epochs.

As the figure shows, controls made a larger proportion of structure consistent errors than CBS patients; the main effect of Group,  $F(1, 6) = 10.04$ ,  $MS_E = 0.011$ ,  $p = .02$ , was significant, suggesting that the groups differed in their expectancy-based errors. Two-tailed  $t$ -tests were also performed to compare the observed proportions for each group with what would be expected by chance, which was .33.<sup>1</sup> The

<sup>1</sup>We determined chance by counting the number of possible ways to make a structure-consistent error and dividing by the total number of errors that can occur. To calculate the denominator we note that there are three possible responses to each of the 27 event triplets, two of which produce an error. Hence, there are 54 possible errors (27 triplets  $\times$  2 errors). For the numerator, we determine the number of errors that will be structure-consistent. Of the 27 possible triplets, 9 are structure-consistent ( $3 \times 3 \times 1$ ) and 18 are structure-inconsistent ( $3 \times 3 \times 2$ ). Errors occurring for the 9 structure consistent event triplets are structure-inconsistent by definition. For the 18 possible inconsistent event triplets only one of the two error responses will be structure-consistent, making a total of 18 structure-consistent errors. Therefore, chance responding will produce one of the 18 structure-consistent errors with probability .33 (i.e., 18/54).

proportion of structure-consistent errors for the control group was in the direction of being greater than what would be expected by chance, but it did not reach significance,  $t(3) = 1.8$ ,  $p = .16$ , presumably due to low power. For the patients, on the other hand, there was a marginally significant difference from chance,  $t(3) = 11.39$ ,  $p = .06$ , but, as the figure shows, indicating CBS patients made fewer structure-consistent errors than what would be expected by chance.

#### Verbal reports

Finally, in order to determine whether learning in these tasks was indeed implicit and had occurred without explicit knowledge, post-experimental interviews at the end of each were assessed. These reports revealed that participants did not gain awareness about the regularities embedded in either of the tasks. When asked if they noticed any regularity, the responses from most of the participants were "I don't know". Participants reported that they primarily focused on responding to targets as quickly as they could, and as such, they were unable to describe the regularities embedded in the tasks.

#### Discussion

The present study examined sequence learning and contextual cueing in CBS patients compared to healthy controls matched on age, gender and education. Several findings emerged. First, verbal reports in both tasks indicated that learning had occurred implicitly such that participants in each group were unable to notice or describe the regularities embedded in either of the tasks. Secondly, and importantly, contextual cueing was found to be relatively preserved in CBS patients, whereas sequence learning revealed impairments. It was not, however, that the patients failed to learn the sequential regularity in the ASRT task. Such a failure of learning would have been revealed by a lack of differences between Consistent and Inconsistent trials. But, in fact, on the response time measure, the patients and controls showed equivalent learning in that for both groups Consistent trials were faster than Inconsistent. In contrast, on the accuracy learning measure, patients with CBS revealed the reverse pattern from controls in that the patients were more accurate on Inconsistent than on Consistent triplets. This reverse pattern was also seen at the level of individual subjects for the CBS patients, whereas the typical Consistent more accurate than Inconsistent pattern was shown for the controls. In addition, the expectancy-based errors, which reflected pattern sensitivity, were significantly lower for CBS patients compared to healthy controls. But again it was not that these expectancy-based errors failed to reveal sequence learning in the patients (which would be seen in chance performance), but rather that the patients showed fewer such errors than would be expected by chance. To our knowledge, this is the first report comparing two different implicit learning tasks in corticobasal

syndrome, and showing that these two tasks, which have different neural substrates, are differentially affected in CBS patients.

The specific nature of the implicit learning deficit shown in the CBS patients is particularly striking and unique. It seems clear that their deficit lies in their ability to respond accurately, not in the learning itself. That is, CBS patients were able to internalize the sequence structure in that they differentiated between Consistent and Inconsistent triplets as reliably as controls did. The CBS patients, like the controls, responded more quickly to Consistent than Inconsistent events, revealing that they had learned the regularity. However, for the patients, but not the controls, this faster responding on the Consistent trials was accompanied by significantly more errors on Consistent than Inconsistent trials. Further, it is not only the patients' fast responding on the Consistent trials that led to more errors, as might be expected if the patients were showing a simple speed/accuracy tradeoff. That is, when the patients did make errors on unpredictable trials, these errors were not random, tending instead to be inconsistent with the pattern regularity. Again this is in contrast to controls that tended to make pattern-consistent errors.

Although the mechanism underlying the patients' atypical pattern of results is unclear, it is known that CBS patients have ideomotor apraxia, in which they essentially know what to do but are unable to do it (Boeve et al., 2003; Litvan et al., 2003; Zadikoff & Lang, 2005). CBS patients also show yes/no reversals, where they verbalize or gesture "yes" when meaning no, or vice versa, and this phenomenon is likely due to frontosubcortical dysfunction, in which mental flexibility and inhibitory control are impaired (Fratelli, Duffy, Litvan, Patsalides, & Grafman, 2003). This is consistent with several neuroimaging and neuropsychological studies showing frontostriatal involvement in cognitive control, including response inhibition and task-set switching (Aron, Robbins, & Poldrack, 2004; Cincotta & Seger, 2007; MacDonald, Cohen, Stenger, & Carter, 2000). It is also consistent with studies showing that patients with ideomotor apraxia are impaired in motor performance, but not in the learning per se (Motomura, Redbrake, Hartje, & Willmes, 1995; Pistarini, Guarnaschelli, Arrigo, Bazzini, & Zonca, 1990). As such, it is possible that clinical features in CBS, such as ideomotor apraxia and yes/no reversals, contributed to the atypical expression of knowledge in the patients, leading them to make more inconsistent responses on both predictable and unpredictable trials. Further, this conflict occurred in the realm of implicit learning, where patients knew what to do only *implicitly* but still were unable to execute the correct motor response. Additional work is needed to directly examine the relationship between clinical manifestations and implicit sequence learning in CBS patients.

This study also provides further insights into the dissociations between the two learning systems that underlie these tasks. Research comparing these two tasks in healthy aging

has shown a dissociation such that sequence learning, which primarily depended on the age-susceptible fronto-striatal system, was impaired in healthy older adults compared to young people, whereas contextual cueing, which relied on the relatively preserved medial temporal system, remained intact (Howard et al., 2004b). On the other hand, MCI patients have been shown to reveal contextual cueing deficits compared to healthy controls, whereas their sequence learning was relatively preserved (Negash et al., 2006). Studies that separately examined one of these tasks in brain injured patients have also shown the medial temporal lobe involvement for contextual cueing (Chun & Phelps, 1999; Manns & Squire, 2001). Although there is some evidence that the medial temporal lobe may also be involved when higher-order sequences are used (Curran, 1997b; Fletcher et al., 2004), sequence learning depends primarily on fronto-striatal-cerebellar circuits.

The study has several limitations. CBS is a rare disorder, and the number of subjects in the present study is small, so the findings need replication. Nonetheless, the tasks in the present study involved having participants respond to many trials; for example, participants responded to 1,400 trials on the ASRT task, and in the contextual cueing they responded to 264 trials. Therefore, these tasks generated data that allowed for examining learning at the individual subjects level. As described above, such analyses revealed the reverse pattern for the accuracy measure on the ASRT task for CBS patients, but not controls, indicating that this pattern emerged even at the individual subjects level.

Finally, it is important to note that CBS patients showed relatively preserved contextual cueing. These results are consistent with the clinico-neuropathological findings of corticobasal degeneration that have shown a relatively intact medial temporal lobe system as well as memory function (see Boeve, 2000). Thus, this intact system might be used to help design programs to increase the period during which patients can be relatively independent. Further, implicit learning, with its multiple forms, could be useful in the differential diagnosis of CBS. That is, if some forms of implicit learning are spared while others are not, this pattern could help to differentiate CBS from other types of dementia, thereby aiding in early diagnosis of CBS.

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