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Motor Adaptation Deficits in Ideomotor Apraxia

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Abstract

Objectives: The cardinal motor deficits seen in ideomotor limb apraxia are thought to arise from damage to internal representations for actions developed through learning and experience. However, whether apraxic patients learn to develop new representations with training is not well understood. We studied the capacity of apraxic patients for motor adaptation, a process associated with the development of a new internal representation of the relationship between movements and their sensory effects. **Methods:** Thirteen healthy adults and 23 patients with left hemisphere stroke (12 apraxic, 11 nonapraxic) adapted to a 30-degree visuomotor rotation. **Results:** While healthy and nonapraxic participants successfully adapted, apraxics did not. Rather, they showed a rapid decrease in error early but no further improvement thereafter, suggesting a deficit in the slow, but not the fast component of a dual-process model of adaptation. The magnitude of this late learning deficit was predicted by the degree of apraxia, and was correlated with the volume of damage in parietal cortex. Apraxics also demonstrated an initial after-effect similar to the other groups likely reflecting the early learning, but this after-effect was not sustained and performance returned to baseline levels more rapidly, consistent with a disrupted slow learning process. **Conclusions:** These findings suggest that the early phase of learning may be intact in apraxia, but this leads to the development of a fragile representation that is rapidly forgotten. The association between this deficit and left parietal damage points to a key role for this region in learning to form stable internal representations. (*JINS*, 2017, *23*, 139–149)

Keywords: Reaching, Movement, Learning, Internal representation, Stroke, Parietal cortex

INTRODUCTION

The notion that purposeful actions depend on internal representations developed through experience has gained prominence in motor control and neuropsychology (Haaland, Harrington, & Knight, 2000; Shadmehr & Mussa-Ivaldi, 2012; Wolpert & Ghahramani, 2000). While a clear description of what exactly these representations contain has been lacking, new research supports the idea that they might incorporate properties of the body, the environment, and their interaction. Such representations are thought to carry immense functional benefits (Kumar & Mutha, 2016; Shadmehr, Smith, & Krakauer, 2010; Wolpert & Kowato, 1998); for instance, they might enable the brain to predict the sensory consequences of movement commands. Regions around the left intraparietal sulcus have been widely suggested as the site for such representations (Buxbaum, Johnson-Frey, & Bartlett-Williams, 2005; Buxbaum, Kyle, Grossman, & Coslett, 2007; Goldenberg, 2009; Haaland et al., 2000), although some studies have also emphasized a role for inferior frontal regions particularly for retrieval of the stored information (Haaland et al., 2000; Serino et al., 2010; Tranel, Manzel, Asp, & Kemmerer, 2008). Ideomotor limb apraxia, a movement disorder that occurs most commonly after left hemisphere damage, is thought to arise, in part, from damage to these representations (Buxbaum, 2014; Heilman, Roghi, & Valenstein, 1982; Heilman & Rothi, 1993; Pazzaglia, Smania, Corato, & Aglioti, 2008; Rothi, Ochipa, & Heilman, 1991). Disruption of these representations leads to impaired planning of transitive, object-related actions (Clark et al., 1994; Mozaz, Rothi, Anderson, Crulcian, & Heilman, 2002; Vingerhoets, 2014), and also learned intransitive movements such as waving goodbye (Goldenberg, 1999; Toraldo, Reverberi, &

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Rumiati, 2001). Planning deficits have also been reported when apraxics perform motor sequences (Harrington & Haaland, 1992) and when their reaching movements require greater interjoint coordination (Mutha, Sainburg, & Haaland, 2010).

Given the view that these deficits arise from deficient internal representations, and that these representations are developed with learning, it is surprising that so few studies have investigated whether apraxics can develop new representations through motor learning. This is critical, particularly for understanding whether motor difficulties in apraxics can be improved with rehabilitation, especially since apraxia is associated with significant functional deficits (Buxbaum et al., 2008; Goldenberg, Daumuller, & Hagmann, 2001; Hanna-Pladdy, Heilman, & Foundas, 2003). The few studies that have examined motor learning in apraxics have yielded controversial results. Dovern and colleagues (2011) reported that implicit learning of a motor sequence was intact in apraxics, but intentional recall of the sequence was impaired, suggesting that apraxics retain the ability to learn and consolidate a new motor skill. However, others (Motomura, Seo, Asaba, & Sakai, 1989; Rothi & Hielman, 1984) reported that apraxics fail to learn sequences of manual gestures. Heilman, Schwartz, and Geschwind (1975) have also shown marginal evidence for difficulty with rotary pursuit learning in apraxic patients. Thus, based on these limited and inconsistent findings, it is unclear how apraxia affects the ability to develop representations necessary for coordinated, goal-directed actions.

Therefore, we assessed the capacity for learning in apraxics using a paradigm in which adaptation of movements to a novel visuomotor relationship is required. Such learning is thought to result in an update of the internal representation that maps movement commands to their sensory consequences. We predicted that these patients would be unable to build a new representation and would, therefore, demonstrate greater adaptation deficits than patients without apraxia.

METHOD

Participants

The Institutional Review Board of the University of New Mexico and the New Mexico Veterans Affairs Healthcare System approved the study. Data were obtained in compliance with the Declaration of Helsinki. Thirteen healthy elderly adults and 23 stroke patients participated after providing informed consent. Patients were right handed before stroke as established using the Edinburgh inventory (Oldfield, 1971). Patients also had to be at least 6 months post-stroke and have no neurological diagnoses other than a left hemisphere lesion to be included. They were enrolled after lesion location, extent and volume derived using neuroimaging (MRI or CT) were verified by a neuroradiologist. Furthermore, patients could not have had any hospitalizations for substance abuse in the past 10 years and no peripheral movement restrictions. Patients were referred by private neurologists and local hospitals after we thoroughly screened the medical records. We did not recruit subjects with a particular language deficit or any other specific cognitive or behavioral deficit. If the above criteria were satisfied, they were enrolled and neuropsychological and behavioral measures were obtained later. Healthy participants met the same criteria except that they had not had a stroke.

Stroke patients were divided into apraxic ($N = 12$) and nonapraxic ($N = 11$) groups based upon their performance with the left, ipsilesional limb on a 15-item imitation battery with 5 meaningless, 5 intransitive, and 5 object-use movements. Movements were videotaped for analysis and subjects were defined as apraxic if they made 4 or more errors, which was at least 2 standard deviations below a normative sample (Haaland & Flaherty, 1984; Haaland et al., 2000). The Fugl-Meyer test of motor impairment was administered on the contralesional arm of the patients (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975) and auditory comprehension was assessed using the Western Aphasia Battery (WAB) Sequential Commands (Kertesz, 1982). Table 1 gives the mean scores on these tests along with demographic and clinical data for all three groups, and statistical confirmation that the groups were comparable in terms of age, education, sex, and degree of right-handedness. A total of 6 of 11 nonapraxics, and 5 of 12 apraxics also participated in our previous study (Mutha et al., 2010).

Lesion Characterization

For neuroimaging, 21 patients had MRIs and 2 had CT scans due to medical contraindications for MRI. T1-weighted MRIs were normalized to the MNI-ICBM 152 template using routines in SPM8 (Ashburner & Friston, 2005) and custom Matlab scripts. Lesions were then reconstructed on the anatomical images (MRI) or the ICBM 152 template (CT) in Adobe Photoshop and the traced lesions were converted back into volumes of interest (VOIs). Using MRIcroN (Rorden & Brett, 2000), lesions were overlaid to create images showing the distribution of lesions in apraxic (Figure 1A) and nonapraxic patients (Figure 1B). These images represent the regions that were damaged in 1% (magenta) to 100% (red) of patients in each group. We also subtracted the lesions of the two groups (Figure 1C) to represent regions that were damaged in a larger number of apraxics than nonapraxics.

Additionally, the Anatomy toolbox for SPM (Eickhoff et al., 2005) was used to create anatomical regions of interest (ROIs) from probablistic cytoarchitectonic maps. Individual ROIs were created for different parietal regions because prior studies have suggested that these regions are likely to show greater damage in apraxics. The parietal ROI included inferior parietal cortex [Brodmann area (BA) 39, 40], intraparietal sulcus, and parietal operculum/SII (anterior BA 40).

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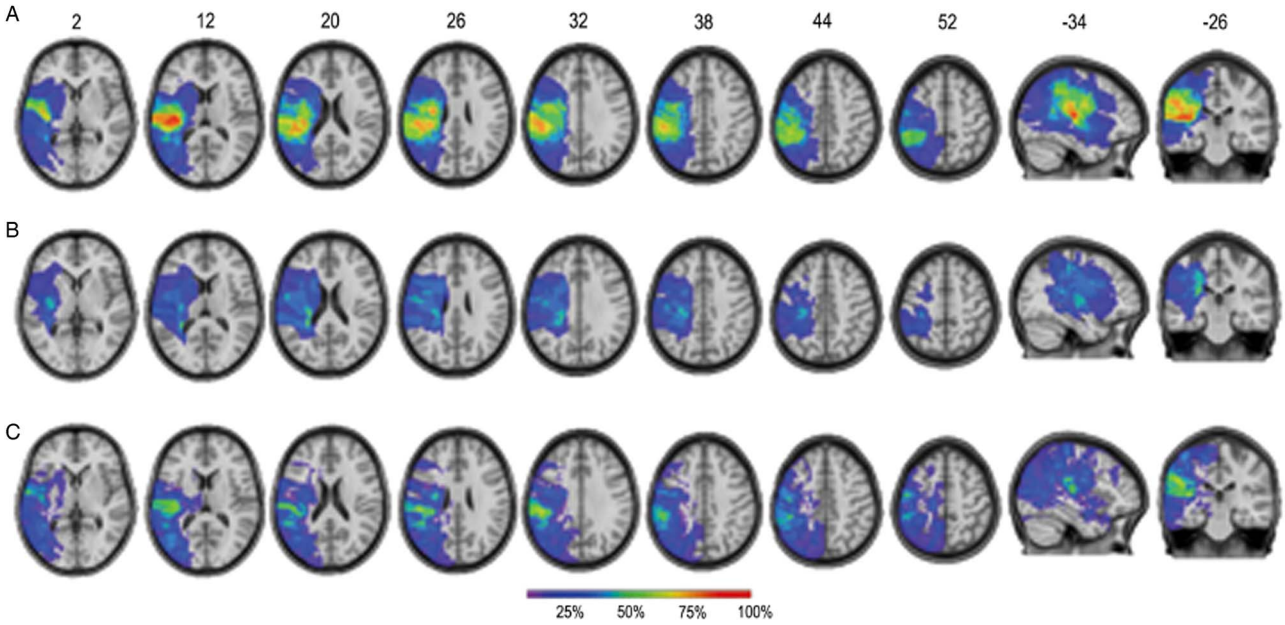

Fig. 1. Lesion distributions. **A:** Lesion overlap in the apraxics. **B:** Lesion overlap in the nonapraxics. **C:** Subtraction of the lesion distributions in each group reflecting the areas that are damaged more in the apraxics than the nonapraxics.

Each subject's reconstructed VOI was then intersected with each of the ROIs within MRIcroN to get the number of voxels damaged in each region; these were then compared statistically across groups. Note that several studies have also implicated frontal regions in apraxia but our patients did not have extensive frontal damage, and these regions were, therefore, not considered in this analysis.

Experimental Task

The experimental setup was similar to our previous study (Mutha et al., 2010) (Figure 2A). Briefly, each participant sat in a chair and placed their arm in an airsled system that moved on a tabletop. The tabletop restricted movements to the horizontal plane, while the airsled minimized friction. A cursor, a start circle and targets were projected using a horizontally mounted HDTV onto a mirror placed beneath it. The mirror blocked vision of the arm and also provided the illusion that the display was in the same plane as the arm. Reaching movements were performed on the tabletop below the mirror. The positions of the index fingertip, the lateral epicondyle of the humerus and the acromion directly posterior to the acromioclavicular joint were recorded using a Flock of Birds system (Ascension Technology), and the X-Y coordinates of the fingertip was used to define the projected cursor position. The cursor was the only movement related feedback available during the experiment. Data were collected at 130 Hz.

The experimental task is shown in Figure 2B. All subjects performed the task with their left arm, which was the ipsilesional arm for the stroke patients. All targets were presented in the left hemispace to avoid the influence of any potential hemispatial neglect. The task required reaching movements from a central start position to one of eight targets (radial distance of 12 cm) arranged 45-degrees apart along the circumference of an invisible circle. Targets were individually displayed in a pseudo-random order. Subjects brought the cursor into the start circle to initiate a trial and were instructed to move it to the target when the target appeared after a brief

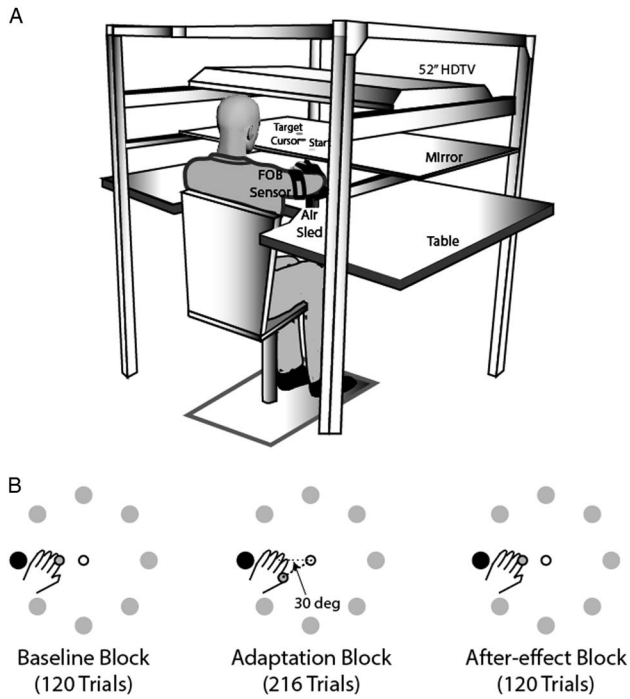

Fig. 2. Experimental setup. Note that while the picture shows a person using the right arm, participants in the current study used their left arm during the task. **A:** Apparatus. **B:** Display of display for Baseline, Adaptation, and After-Effects Blocks.

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delay along with an audiovisual "go" signal. Velocity feedback was provided and subjects were encouraged to attain a peak speed of at least 0.5 m/s. If the speed requirement was satisfied, subjects were given points based on their final position accuracy. Each subject performed three blocks of trials (Figure 2B) (1) A baseline block (120 trials) in which cursor and hand motion were veridical (2) An adaptation block (216 trials) in which the cursor was rotated counterclockwise by 30 degrees relative to hand motion, and (3) An after-effect block (120 trials) which was identical to baseline. Note that our apraxic patients had weaker comprehension (Table 1), so we wished to ensure that any performance deficit was not related to a problem understanding task instructions. An experimenter, therefore, guided the subjects' arm to the target for a couple of trials initially and confirmed that they understood the type of movement they had to perform. When this was affirmed, subjects were instructed to continue independently. The experimenter monitored performance throughout and occasionally checked with the subjects to ensure they had no questions. Our results indicated that subjects understood the instructions well and complied with them.

Data Analysis

All kinematic data were low-pass filtered at 8 Hz, and position data were differentiated to yield velocity and acceleration values. Movement start and end were, respectively, determined by identifying the time of peak velocity and searching backward and forward in time for the first minimum in velocity below 3% of peak tangential velocity. Adaptation was quantified in terms of changes in direction errors at peak acceleration ("initial direction errors"). These errors were quantified as the angle between the line joining the start circle center and finger position at peak acceleration and the line from the start circle center to the target.

Within each block of trials, we analyzed cycles of movements. A cycle was defined as a series of movements to each of the eight targets. Thus, the baseline, rotation and after-effects blocks included 15, 27, and 15 cycles, respectively. The first two cycles of the baseline block were considered practice and were not analyzed. Statistical analyses were conducted using repeated-measures analyses of variance (ANOVAs) with group (Healthy control, Apraxic, Non-apraxic) and cycle as factors. Tukey's *post hoc* tests were conducted when warranted by significant effects.

RESULTS

Participant Characteristics

Table 1 shows the demographic and clinical data for the three groups. Limb apraxia scores are also provided, and based upon the selection criteria, apraxics had worse scores compared to the nonapraxics ($p < .001$) and the healthy controls ($p < .001$). The two stroke groups were not significantly different in time post stroke ($p = .274$). Lesion volume, although larger in the apraxics, was not significantly different from that of the nonapraxics ($p = .127$). We also compared lesion volume non-parametrically and found no group differences (Mann Whitney U Test; $U = 40$; $p = .1164$). However, the apraxics had greater auditory comprehension deficits than the nonapraxics ($p = .037$) and the control group ($p = .012$). Hemiparesis was somewhat greater in the apraxics based on the Fugl-Meyer measure, but these differences were not reliable ($p = .079$). Nonetheless, contralesional hemiparesis is not expected to have affected task execution since the ipsilesional arm was used during the task.

Task Performance

Baseline

Figure 3A shows the cursor trajectories on the last baseline cycle for representative subjects in each group. As can be seen,

Table 1. Demographic and clinical data

Parameter	Healthy controls	Nonapraxics	Apraxics	Statistical results
N	13	11	12	
Age (years)	61.5 (7.4)	63.8 (11.4)	65.0 (9.3)	$F_{2,33} = 0.44$, $p = 0.646$
Sex, N (% female)	1 (8%)	1 (9%)	4 (33%)	$\chi^2 = 3.61$, $p = 0.165$
Education	15.1 (2.4)	15.3 (2.5)	15.0 (2.7)	$F_{2,33} = 0.05$, $p = 0.965$
Edinburgh laterality quotient[a]	90.2 (10.8)	90.2 (13.2)	97.4 (6.5)	$F_{2,33} = 1.93$, $p = 0.162$
Limb apraxia[b]	13.3 (1.3)	13.6 (1.0)	8.9 (1.7)[4,5]	$F_{2,33} = 42.55$, $p < 0.001$
Comprehension[c]	80 (0)	78.2 (6.0)	64.9 (20.5)[d,e]	$F_{2,33} = 5.44$, $p = 0.009$
Years post-stroke	N/A	7.5 (6.4)	4.7 (5.7)	$F_{1,21} = 1.26$, $p = 0.274$
Lesion volume (cc)	N/A	75.6 (69.6)	123.3 (74.1)	$F_{1,21} = 2.53$, $p = 0.127$
Fugl-Meyer motor[d]	N/A	59.5 (6.5)	47.2 (20.4)	$F_{1,21} = 3.41$, $p = 0.079$

All the data given are means, and numbers in parentheses are standard deviations unless otherwise indicated.
[a]Laterality quotient ranges from +100 (strongly right handed) to –100 (strongly left handed).
[b]Maximum score is 15 correct (Haaland and Flaherty1984).
[c]Western Aphasia Battery, Sequential Commands, maximum score is 80 (Kertesz1982).
[d]Impaired relative to other stroke group.
[e]Impaired relative to control group.
N/A = not applicable.

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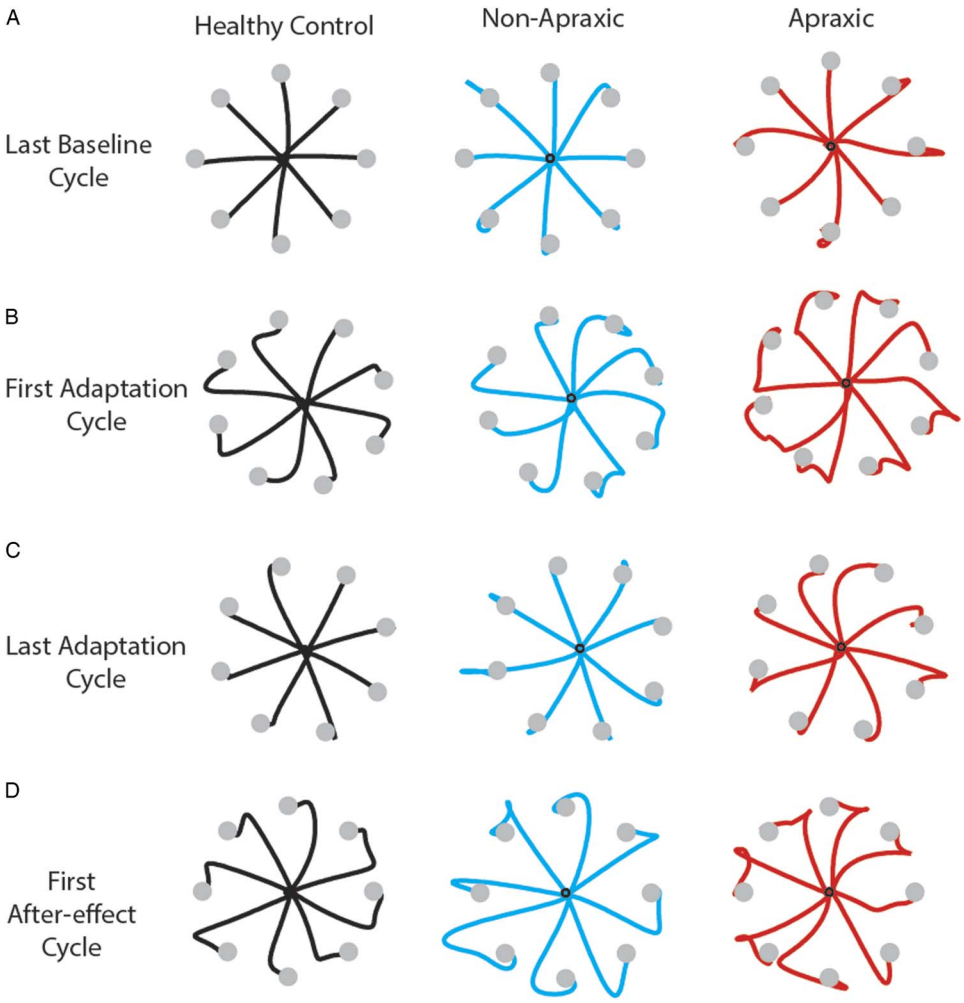

Fig. 3. Trajectories for individual representative participants from the control (black), nonapraxic (blue) and apraxic (red) groups. **A:** The last baseline cycle. **B:** The first adaptation cycle. **C:** The last adaptation cycle. **D:** The first after-effect cycle.

subjects' movements were smooth, directed straight toward the target, and on most trials, ended accurately at the target location. Overall, there were only marginal differences in peak velocity among the three groups ($F_{2,33} = 2.6354$; $p = .0867$; partial eta-squared = 0.1366). The mean peak velocity of the control subjects was 0.51 ± 0.026 m/s while that of the non-apraxics and apraxics was 0.48 ± 0.028 and 0.43 ± 0.027 m/s, respectively. Importantly, these subtle velocity differences, which were observed across all blocks, did not correlate with the amount of learning (see next section). There were no group differences in initial movement direction either ($F_{2,33} = 0.5165$; $p = .6013$), indicating that movements were similarly directed during the initial portion of the reach. There was a marginal group difference in movement accuracy ($F_{2,33} = 3.0510$; $p = .0608$; partial eta-squared = 0.1548), but the mean final position error for all groups was less than 1 cm. Thus, baseline movements were performed quite well and consistently across all groups. For apraxics, this consistency indicated understanding of and compliance with task instructions despite weaker comprehension (Table 1).

Adaptation

Figure 3B shows the cursor paths for the representative subjects when they were first exposed to the rotation. As expected, large initial direction errors occurred due to the imposed rotation. These errors were close to 30 degrees across all groups; there was neither a significant group × cycle (last baseline, first adaptation) interaction ($F_{2,33} = 0.0796$; $p = .9237$) nor a significant group effect ($F_{2,33} = 1.1389$; $p = .3324$). Subjects then modified their ongoing movement to correct the rotation-induced errors and bring the cursor to the target, resulting in the curved trajectories of Figure 3B. As rotation experience continued, all subjects began to modify their hand trajectories to account for its effects. Figure 3C shows the cursor trajectories for our representative subjects on the last cycle of the adaptation block. As shown, the healthy subject (black) and nonapraxic patient (blue) made straight movements despite the presence of the rotation suggesting that they had developed an internal representation of the perturbation and had predictively accounted for its effects. In contrast, the apraxic patient

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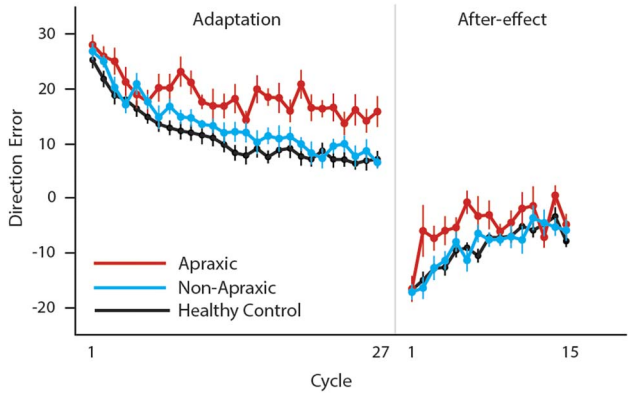

Fig. 4. Group data. Initial direction errors for the apraxic (red), nonapraxic (blue), and control (black) groups during the adaptation and after-effect sessions. Data shown are mean ± SEM.

showed only a modest improvement in movement direction; this patient's movements (red) remained substantially curved even at the end of the adaptation block. The consistency of these observations is shown in Figure 4 (left panel), which plots the change in initial direction error for all adaptation cycles across all subjects in the three groups. The controls (black) and nonapraxics (blue) reduced their direction errors from ~30 degrees to ~7 degrees. However, the apraxics (red) did not show such a large improvement (Mean ± *SE* direction error on the last cycle = 15.72 ± 1.72 degrees). Our group × cycle (first, last adaptation) ANOVA showed significant group ($F_{2,33} = 6.6838$; $p = .0037$; partial eta-squared = 0.1717) and cycle ($F_{1,33} = 142.92$; $p < .0001$, partial eta-squared = 0.6788) effects, and a marginal group × cycle interaction ($F_{2,33} = 2.89$; $p = .06$; partial eta-squared = 0.0789). *Post hoc* tests for the significant group effect indicated that the apraxics showed greater errors compared to the controls ($p = .0009$; Cohen's $d = 0.5516$) as well as the nonapraxics ($p = .0058$; Cohen's $d = 0.4734$). We also noted that the interaction effect could have been marginal because of the pattern of direction error reduction in the apraxic patients, which we explored further (see next paragraph). We then asked whether some of the group differences in learning could be explained by other measures that differed between the groups, particularly lesion volume and WAB comprehension score. However, neither of these measures correlated significantly with the overall amount of learning (change in direction error between the first and last cycles) (r = 0.15; $p = .4725$ for lesion volume, r = 0.05; $p = .8161$ for WAB score). Similarly, while peak velocity was marginally different between the groups (healthy controls: 0.50 ± 0.031 m/s, nonapraxics: 0.47 ± 0.034 m/s, apraxics: 0.40 ± 0.032 m/s; $F_{2,33} = 2.6312$; $p = .0870$, partial eta-squared = 0.1381), it did not correlate with the amount of learning (r = 0.24; $p = .1561$). In summary, our findings indicated that apraxic patients did not improve their movement direction to the same degree as healthy controls or nonapraxic patients and this deficit was unlikely to be due to greater stroke severity (based on lesion volume, auditory comprehension and speed differences) in the apraxic group.

A closer inspection of the learning curve of the apraxics revealed that they showed a rapid improvement over the first few cycles, but asymptoted to show no substantial improvement thereafter. We conceptualized these results, in an exploratory and *post hoc* manner, in terms of the model proposed by Smith, Ghazizadeh, and Shadmehr (2006) in which adaptation occurs *via* the operation of two processes: a fast-process that learns rapidly (but also forgets rapidly) and a slow process that learns slowly (but retains well). The intact initial learning but disrupted late learning suggested an intact fast process, but an impaired slow process in these subjects. We noted that they showed a pattern of error-reduction that was similar to healthy controls for the first 6 cycles (group × cycle interaction: $F_{2,33} = 0.1017$; $p = .9036$), but not thereafter (group × cycle interaction: $F_{2,33} = 4.8934$; $p = .0138$). We, therefore, considered the error reduction during the first 6 cycles as mediated by the fast process, while cycle 6 to cycle 27 (last cycle) were considered as the slow phase. Of interest, Krakauer et al. (2006) also used the first six cycles of movements to eight different targets to assess the initial time course of rotation adaptation, suggesting that this time duration might effectively capture early learning processes. Because the learning deficit was seen in the slow phase, we investigated whether this deficit was related to the degree of apraxia reflected by the apraxia score. For this analysis, we treated apraxia score as ordinal rather than continuous because this score was always an integer within a certain range, and participants could be rank ordered in terms of their deficit based on their apraxia score. We then performed a Spearman's correlation between the amount of learning in the slow phase (change in direction error from the 6th to the 27th cycle) and apraxia score. We found a significant relationship between these two measures (Spearman's rho = 0.4097; $p = .0131$) while noting that the amount of learning increased as apraxia severity decreased (apraxia score increased). Such a relationship was not observed for the fast phase (Spearman's rho = 0.0542; $p = .7535$).

After-effects

Figure 3D shows the first cycle of movements during the after-effects block for our representative subjects. The control (black) and nonapraxic subjects (blue) showed movements that were in the learned direction, as seen during the last adaptation cycle. A similar pattern was seen for the apraxic patient (red), who also demonstrated large after-effects despite not having fully learned the rotation. Surprisingly, the magnitude of the after-effect, quantified as the error on the first after-effect cycle, was similar for all three groups (one-way ANOVA; $F_{2,33} = 0.0199$; $p = .9803$) as demonstrated in Figure 4 (right panel). Despite this similarity, we observed that apraxics returned to baseline performance levels much faster than controls, suggesting that they tended to more quickly forget what they had

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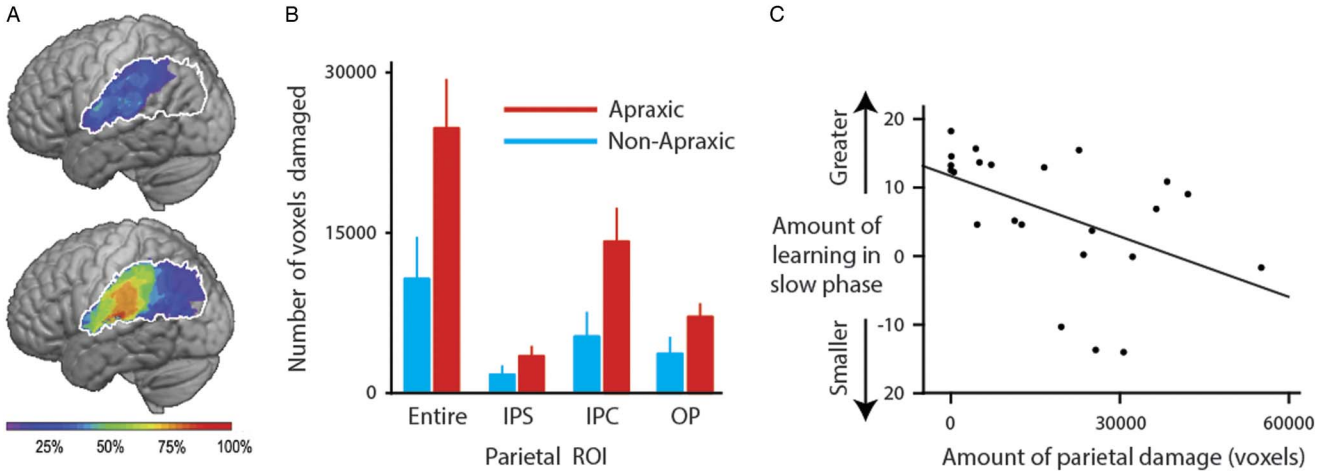

Fig. 5. Lesion analysis. **A:** 3D reconstructions of the parietal ROI (including the inferior parietal cortex, intraparietal sulcus and the parietal operculum/SII regions) in the nonapraxic (top) and apraxic (bottom) groups. **B:** Comparison of the number of voxels damaged in the entire parietal ROI, and specifically, the intraparietal sulcus (IPS), the inferior parietal cortex (IPC) and the parietal operculum (OP) in the nonapraxic (blue) and apraxic (red) patients. **C:** Relationship between volume of parietal damage and deficit seen in the slow phase of learning. The deficit was defined as the difference in direction error between the 6th and 27th adaptation cycles. A value of zero indicates no change in performance between these two time points. Positive values indicate that error decreased, indicating continued learning while negative values indicate that performance became worse over time.

learned. To statistically confirm this, we performed a group × cycle ANOVA comparing the after-effect magnitude during the initial portion of the after-effects session (first six cycles, as in the adaptation session). This interaction was significant ($F_{2,33} = 4.3311$; $p = .0214$), and *post hoc* tests revealed that while errors were similar for all groups on the first cycle, by the sixth cycle, they were significantly smaller for the apraxics compared to both controls ($p = .0186$) and non-apraxics ($p = .0037$). This suggested rapid de-adaptation and faster return to baseline in apraxics relative to others. Importantly, this finding was not due to any group differences in peak velocity during the early phases (first six cycles) of the after-effect block (mean peak velocity for healthy controls = 0.51 ± 0.027 m/s, nonapraxics = 0.50 ± 0.039 m/s and apraxics = 0.42 ± 0.041 m/s; $F_{2,33} = 2.2337$; $p = .1252$, partial eta-squared = 0.1334; correlation with change in error over first 6 cycles: r = 0.012; $p = .9478$).

In summary, behaviorally, we found a reduced amount of learning and more rapid forgetting in patients with ideomotor apraxia.

Lesion Analysis

We then wished to examine whether some of the behavioral deficits seen in the apraxics were related to the extent of their brain damage. We focused on the parietal regions since these have been most commonly implicated in ideomotor apraxia (Buxbaum et al., 2005; Haaland et al., 2000). Figure 5A shows the 3D reconstructions of our parietal ROI in the nonapraxic (top) and apraxic (bottom) groups. Note that superior parietal damage was not present in enough of our sample to be considered. Apraxics had greater damage in the parietal ROI relative to the nonapraxics, as shown in Figure 5B [t = –2.35; $p = .029$; apraxic mean = 24.8 cc ($SD = 15.8$ cc) or 44.3% ($SD = 28.4\%$); nonapraxic mean = 10.7 cc ($SD = 13.0$ cc) or 19.1% ($SD = 23.2$)]. When we examined which of the three parietal areas might account for this difference, we found that apraxics had greater damage only in the inferior parietal area (t = –2.28; $p = .033$), consistent with many prior studies (Buxbaum et al., 2005, 2007; Muhlau et al., 2005; Pazzaglia et al., 2008; Vingerhoets, 2014). We then examined the relationship between the amount of learning in the slow phase and the magnitude of parietal damage. This relationship, shown in Figure 5C, was statistically significant (r = 0.5; $p = .0151$) and indicated that the amount of learning in the slow phase decreased as the volume of parietal damage increased. Thus, greater learning deficits were associated with greater parietal damage.

DISCUSSION

Motor deficits in ideomotor limb apraxia have largely been attributed to damage to internal representations of actions developed through learning (Buxbaum, 2014; Goldenberg, 2013; Heilman & Rothi, 1993; Rothi et al., 1991). We show here that apraxics also demonstrate a diminished ability to develop new, stable motor representations through learning. In our study, apraxic patients demonstrated an initial rapid improvement in performance, but failed to refine performance thereafter. They also demonstrated an early after-effect likely reflecting the initial learning, but this after-effect was not sustained and performance rapidly returned to baseline levels. These patients had greater damage to

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left inferior parietal regions, pointing toward a key role for these regions in learning to develop such internal representations.

Neuroanatomical Substrates of Apraxia

Our finding of greater left inferior parietal cortex damage in apraxics is consistent with numerous prior studies in patients (Buxbaum et al., 2005, 2007; Haaland et al., 2000; Pazzaglia et al., 2008) and functional imaging studies in healthy individuals (Moll et al., 2000; Muhlau et al., 2005; Vingerhoets, 2014). The most prevalent explanation of left inferior parietal function in praxis (Buxbaum & Kalenine, 2010; Heilman et al., 1982) emphasizes it as the site for internal representations crucial for action. Damage to these representations primarily affects familiar, well-learned actions, deficits in which are the most sensitive markers of limb apraxia (Buxbaum & Kalenine, 2010; Haaland et al., 2000). Voxel-based lesion symptom mapping findings demonstrating that left inferior parietal cortex damage is associated with impaired recognition of tool-use gestures are consistent with this notion (Buxbaum et al., 2005, 2007; Buxbaum & Kalenine, 2010).

While inferior parietal cortex has been most strongly emphasized as the critical substrate, other studies have also highlighted the importance of left frontal regions (Dovern et al., 2011; Haaland et al., 2000; Pazzaglia et al., 2008) and left temporal regions (Tarhan, Watson, & Buxbaum, 2015) in praxis. Importantly, the temporal lobe findings appear to be associated with knowledge of tool function more than spatiotemporal knowledge of how to move (Canessa et al., 2008; Sirigu, Duhamel, & Poncet, 1991). In contrast, the differential role of frontal *versus* parietal regions in apraxia, and particularly in the context of motor learning, has not been identified. It is possible that, while parietal regions store learned representations, frontal regions play a larger role in the selection of task-appropriate learned responses (Schluter, Rushworth, Passingham, & Mills, 1998). Our current results further extend this notion and suggest that parietal lesions also prevent the development and storage of new representations. Additionally, the magnitude of this deficit appears to be related to the volume of parietal damage, especially of the inferior parietal region.

Multiple Timescales of Adaptation and Apraxia

Adaptation deficits identified in our apraxics can be best understood in the context of the multi-rate learning model proposed by Smith et al. (2006). Here, adaptation is driven by two processes, a fast process that leads to rapid reduction in motor errors and a slow process that leads to further smaller improvements. Based on our observations, apraxia appears to spare the fast process, while adversely impacting the slow one. Although this needs to be more definitively established in future studies, it is then likely that operation of the intact fast process leads to the improvement in performance early in learning, but a disruption of the slow component prevents significant subsequent improvement. Crucially, the magnitude of improvement during the slow phase seems to depend on the degree of apraxia.

Our findings also have implications for the neural substrates mediating the fast and slow components of adaptation. Typically, damage to the cerebellum impairs adaptation to large, abruptly introduced perturbations, as we used here (Martin, Keating, Goodkin, Bastian, & Thach, 1996; Thach & Bastian, 2004; Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). However, cerebellar patients can adapt to gradually induced perturbations because such adaptation presumably engages only the slow process (Criscimagna-Hemminger, Bastian, & Shadmehr, 2010). Thus, cerebellar damage appears to primarily disrupt the fast process, while leaving the slow component intact. In contrast, our recent findings have shown that patients with damage largely restricted to left parietal cortex show a small improvement early in adaptation, but no additional refinement thereafter (Mutha, Sainburg, & Haaland, 2011a). Our apraxic patients, who had maximum lesion overlap in inferior parietal cortex, and whose deficit correlated with their parietal lesion volume, showed a similar trend: first, they demonstrated rapid learning early (of larger magnitude than previously seen in our focal parietal lesion patients), and second, they failed to make any substantial improvements during the later stages of the task. Thus, it appears that left inferior parietal damage largely spares the ability to learn *via* the fast process, while primarily affecting the action of the slow process. It is thus plausible that the cerebellum and the inferior parietal regions mediate the fast and slow components of learning, respectively.

Despite similarities between the current group of apraxics and our prior patients with focal parietal lesions (Mutha et al., 2011a) as noted above, the pattern of after-effects was somewhat different. In our previous work, we did not observe clear after-effects with the contralesional arm (Mutha, Sainburg, & Haaland, 2011b), but did note a small after-effect when the ipsilesional arm was used (Mutha et al., 2011a). In contrast, here, in the apraxics, the magnitude of the after effect initially was as large as the other groups. This is most likely related to the greater degree of the initial, fast learning in the apraxics compared to focal parietal damaged patients in our previous studies; such an association has been suggested before (Della-Maggiore, Malfait, Ostry, & Pauss, 2004; Shadmehr & Mussa-Ivaldi, 1994). Another finding that was different from our prior work was that of our apraxic patients' rapid return to baseline performance. We interpreted this finding as reflecting rapid forgetting of whatever was learned. Prior work has in fact argued that learning driven by the fast process also decays rapidly (Smith et al., 2006). Furthermore, rapid de-adaptation of visuomotor learning was demonstrated (Hadipour-Niktarash, Lee, Desmond, & Shadmehr, 2007) with TMS over primary motor cortex. While it is still unclear whether adaptation and retention are mediated by distinct mechanisms and different neural substrates, recent research (Galea, Vazquez, Pasricha, Orban de Xivry, & Celnik, 2011; Huang, Haith, Mazzoni, & Krakauer, 2011)

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suggests that this might be the case: adaptation may be dependent on cerebellar and parietal regions, but retention, at least of the fast learning, may be dependent on motor regions. While our apraxic patients had somewhat greater damage to sensorimotor regions of cortex relative to nonapraxics (apraxic mean = 16.3 cc (*SD* = 13.8 cc), nonapraxic mean = 7.6 cc (*SD* = 6.9 cc)), the lack of reliable group differences in sensorimotor lesion volume ($p = .071$) suggests that our study may have been under-powered to detect a robust relationship between retention and amount of sensorimotor cortex damage. This can be more conclusively established in the future.

Motor Learning Deficits in Apraxia

There are only a limited number of learning studies in apraxia, and none to our knowledge that examine motor adaptation, considered to be a form of implicit learning that updates internal representations of the body and the environment. Our current findings are consistent with work that showed marginal learning deficits in apraxics when learning rotary pursuit, another implicit task (Heilman et al., 1975). However, while our apraxic patients showed both impaired learning and rapid forgetting, Heilman et al.'s (1975) results were statistically significant only when retention and learning were combined. In contrast, Dovern et al. (2011) found no evidence of impaired implicit learning in apraxics using a serial reaction time task. In their study, however, apraxic and nonapraxic patients were differentiated by left premotor and not parietal damage, suggesting that parietal damage may be more influential in determining implicit learning deficits. Interestingly, this same study reported deficits in explicit memory for the sequence, consistent with two other studies that found impaired explicit learning of gesture sequences in apraxics (Motomura et al., 1989; Rothi & Hielman, 1984). However, neither of these studies directly examined potential neuroanatomical correlates. Our study is the first to begin to differentiate what aspects of learning are disrupted in patients with apraxia. We show that early learning appears to be intact in apraxics, which we speculate may lead to the development of a fragile internal representation that is rapidly forgotten. A deficit in refining this representation over time is likely associated with lesions to inferior parietal cortex, which are most common in limb apraxia. More research is needed to conclusively establish these findings. The specific nature of motor learning deficits in patients with apraxia resulting from frontal lesions also requires detailed further investigation in the context of explicit *versus* implicit memory deficits. Tasks that assess recall of learning may be crucial in this regard. Finally, if we can better understand the mechanisms underlying these deficits, it could potentially offer an opportunity to develop more effective rehabilitation programs for apraxic patients whose deficits are strongly associated with deficits in daily functioning (Buxbaum et al., 2008; Goldenberg et al., 2001; Hanna-Pladdy et al., 2003).

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