Cognitive neuropsychological and neuroanatomic predictors of naturalistic action performance in left hemisphere stroke: a retrospective analysis

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Abstract

Individuals who have experienced a left hemisphere cerebrovascular accident (LCVA) have been shown to make errors in naturalistic action tasks designed to assess the ability to perform everyday activities such as preparing a cup of coffee. Naturalistic action errors in this population are often attributed to limb apraxia, a common deficit in the representation and performance of object-related actions. However, naturalistic action impairments are also observed in right hemisphere stroke and traumatic brain injury, populations infrequently associated with apraxia, and errors across all these populations are influenced by overall severity. Based on these and other data, an alternative (though not mutually exclusive) account is that naturalistic action errors in LCVA are also a consequence of deficits in general attentional resource availability or allocation. In this study, we conducted a retrospective analysis of data from a large group of 51 individuals with LCVA who had completed a test of naturalistic action, along with a battery of tests assessing praxis, attention allocation and control, reasoning, and language abilities to determine which of these capacities contribute uniquely to naturalistic action impairments. Using a regularized regression method, we found that naturalistic action impairments are predicted by both praxis deficits (hand posture sequencing and gesture recognition), as well as attention allocation and control deficits (orienting and dividing attention), along with language comprehension ability and age. Using support vector regression-lesion symptom mapping (SVR-LSM), we also demonstrated that naturalistic action impairments are associated with lesions to posterior middle temporal gyrus and anterior inferior parietal lobule – regions known to be implicated in praxis; as well the middle frontal gyrus that has been implicated in both praxis and attention allocation and control. Taken together, these

findings support the hypothesis that naturalistic action impairments in LCVA are a consequence of apraxia as well as deficits in attention allocation and control.

Introduction

Naturalistic actions such as preparing toast with butter and jam require the use of different manipulable objects (e.g. knife, spoon, toaster). Each object in turn requires knowledge about how it should be used. This manipulation knowledge is known to be subserved by a so-called *praxis system* that enables the production and recognition of tool-related actions (e.g., pantomiming how a tool is to be used) and the imitation of both meaningful and meaningless actions (Binkofski and Buxbaum, 2013; Buxbaum and Kalénine, 2022, 2010). The praxis system is primarily supported by the left hemisphere (e.g., Binkofski and Buxbaum, 2013; Buxbaum and Kalénine, 2010; Johnson-Frey, 2004; Lewis, 2006; Orban and Caruana, 2014). It is therefore perhaps unsurprising that people who have experienced a left hemisphere cerebrovascular accident (LCVA) make errors in naturalistic action tasks at rates higher than neurotypicals (Buxbaum et al., 1998). Such errors include omitting a step in the task (e.g., failing to put butter on toast) or inverting the appropriate order of task steps (e.g., spreading butter on the bread before toasting it; Buxbaum et al., 1998). It has also been demonstrated that gesture pantomime, a task commonly used to assess praxis function, correlates with performance in naturalistic actions in LCVA (Bienkiewicz et al., 2015; Hartmann et al., 2005; Poole et al., 2011).

However, naturalistic action impairments have also been observed in individuals less likely to have praxis deficits such as those who have suffered a right cerebral vascular accident (RCVA; (Bickerton et al., 2012, 2007; Bienkiewicz et al., 2015; Hartmann et al., 2005), traumatic brain injury (TBI; Buxbaum et al., 1998; Schwartz et al., 1998), Parkinson's disease (Balouch and Rusted, 2014; Giovannetti et al., 2012, 2008, 2002; Roll et al., 2017). Moreover, patterns of error types are highly similar across these populations

(Buxbaum et al., 1998; Giovannetti et al., 2002; Jarry et al., 2021; Schwartz et al., 1999, 1998). These data suggest that naturalistic action impairments may arise for reasons additional to deficits of the left-lateralized praxis system. Based in part on evidence that dividing attention with a secondary task disrupts performance of the primary naturalistic action task (Giovannetti et al., 2007; Humphreys and Riddoch, 2000), the limited-capacity resources theory proposes that errors in naturalistic tasks may instead arise because of a reduction in general attentional resources after damage to the brain (Giovannetti et al., 2007; Reason, 1984; Robertson et al., 1997; Schwartz et al., 1998).

Research on attention distinguishes between attention control and attention allocation. Attention control (also termed cognitive control, executive control, or executive attention, e.g., Burgoyne and Engle, 2020) is the ability to select relevant thoughts and behaviors and suppress inappropriate thoughts and behaviors based on current goals and task demands (Miller and Cohen, 2001). Attention control is particularly relevant in situations of increased cognitive demand, such as during distraction. Attention allocation (sometimes referred to as "alerting"), a lower-level function that does not depend on volition (Anderson, 2021), is the ability to replace a resting state with a state of preparation to detect and respond to inputs (Petersen and Posner, 2012). These two different processes are highly interdependent and provide the foundation for other cognitive functions such as working memory and decision-making (Boshra and Kastner, 2022). From a neuroanatomic perspective, attention allocation and control are known to rely on a bilateral brain network involving fronto-temporo-parietal areas, midline structures such as the anterior cingulate, and subcortical connections with the brainstem and thalamus (Boshra and Kastner, 2022; Fan et al., 2005). The bilateral involvement of the brain in attention allocation and control

could explain why these processes are impaired in a number of neurological conditions (Manohar et al., 2014). However, whether such deficits contribute to naturalistic action impairments remains a matter of debate. Indeed, most of the evidence in dementia populations have not distinguished between specific attention allocation or control deficits and overall disease severity (Giovannetti et al., 2002; Jarry et al., 2021).

In this study, we assessed whether naturalistic action impairments in LCVA arise from a combination of praxis and attention allocation and control deficits using a retrospective analysis of data from 51 people with chronic LCVA. The extensive dataset included performance on a test of naturalistic action along with 20 predictors derived from a battery of tests measuring praxis, attention processes, reasoning, and language; we also included participant demographics. We tested which predictors accounted for naturalistic action impairments. We also assessed whether performance on our test of naturalistic action had any relationship to individuals' reports of difficulties in daily activities. Finally, using a machine-learning based approach, we performed an exploratory analysis of the lesion correlates of naturalistic action impairments.

Material and Methods

Participants

Data for the study were collected in 2003-2006 but remained unpublished. Participants were recruited from the Research Registry of the Moss Rehabilitation Research Institute and from outpatient admissions at MossRehab. Included participants were between the ages of 18 and 80, had sustained a single left-hemisphere cerebrovascular accident (LCVA) more than six months prior to participation, and did not have a history of major psychiatric diagnosis, dementia, or current drug/alcohol abuse. Informed consent was obtained for all participants in accordance with the policies of the Institutional Review Board of Einstein Healthcare Network. Participants were assessed to ensure that they exhibited at least some residual neurological impairment as determined by a score greater than 0 on the National Institutes of Health (NIH) stroke scale (Brott et al., 1989), but did not have severe language comprehension deficits as determined by a score of four or more on the comprehension subscale of the Western Aphasia Battery (WAB; Kertesz and Hooper, 1982). This retrospective dataset included a total of 64 participants who performed the main task (Naturalistic Action Test – NAT; Schwartz et al., 2002). Of those individuals, 12 individuals did not complete one or more of the relevant tests from the behavioral test battery, and another participant was found to have a secondary lesion in the right hemisphere after behavioral testing. The remaining 51 participants were included in our analyses. Demographic information for these participants is shown in Table 1.

Table 1: Demographic information

	LCVA (N=*51*)
Age	
Mean (SD)	59.25 (9.94)
Range	35-79
Education (years)	
Mean (SD)	12.88 (3.00)
Range	8-20
Gender	
No. Males	35
No. Females	16
Handedness	
No. Left-Handed	4
No. Right-Handed	47
Months post-onset	
Mean (SD)	43.17 (41.27)
Range	5.95-150.18

Table 2: Overview of the Naturalistic Action Test

Item		*Objects arrayed on table*	*Additional requirements*
1	Make toast with butter and jelly and instant coffee with cream and sugar	Target objects	None
2	Wrap a gift as a present	Target objects and distractors*	None
3	Prepare and pack a child's lunchbox (with sandwich, drink, and cookies); pack a child's schoolbag (with notebook and stocked pencil case)	Target objects and closed drawer containing more targets plus distractors**	Signal end of each task by activating bell attached to underside of tabletop

*Electric tape, stapler, paper bag, gardening shears; **Contents of drawer: (targets) knife, thermos lid, thermos cup; (distractors) envelope, spoon, fork, extra knife, coupons, spatula, retractable tape measure, spool of thread, screwdriver, toothbrush, and tongs.

Naturalistic Action Test (NAT)

The NAT (Schwartz et al., 2002) quantifies performance during three naturalistic tasks of increasing complexity: preparing a cup of coffee and toast with butter and jam, wrapping a gift, and preparing a lunchbox (Table 1). To ensure comprehension, instructions were read aloud to participants while they viewed black-and-white drawings of the completed task (e.g., a slice of toast with butter and jam). Following instructions, the examiner asked if the participant understood what he/she was expected to do; if not, the instructions were repeated until the participant indicated that he/she understood them. Physical assistance with bimanual aspects of the task (e.g., stabilization of objects) was provided for individuals who required it. According to a detailed scoring protocol (Schwartz et al., 2002), participants received a total NAT score from zero to 18 (zero to six on each part of the test). A score of 18 indicated perfect performance. After informed consent was obtained, the NAT was administered during an initial session that also included the Western Aphasia Battery and NIH stroke scale. This session required approximately 1.5 hours to complete.

Behavioral Test Battery

To examine predictors of NAT performance, participants also completed a battery of tests assessing praxis, attention allocation and control, reasoning, and language. The tests are described below and were administered in randomized order over three separate testing sessions within two weeks. Because praxis is typically assessed with the hand ipsilesional to the stroke to avoid the confound of motor impairments, participants used their less-impaired left hand in the praxis tasks (Hand Posture Sequencing, Gesture to Sight, and

Gesture Imitation). All other tasks allowed participants to respond with their preferred hand.

Praxis Tasks

Function and Manipulation Similarity Test

Each test item consisted of a pair of black-and-white drawings of common manipulable objects presented using Psycope (Boronat et al., 2005). Participants were asked to decide whether the two depicted objects had the same function (Function condition; e.g., air conditioner and fan) or the same manner of manipulation (Manipulation condition; e.g., computer keyboard and piano). Participants were scored on the correct proportion of responses on the 64 items in each condition.

Gesture recognition

The gesture recognition test was closely based on a test developed by Heilman and colleagues (Heilman et al., 1982; see Tarhan et al., 2015). On each trial, participants saw the printed name of a gesture (e.g., "hammering") for 5000 ms and heard the name of the gesture spoken twice. Participants then watched two sequential videos of object-related gestures being pantomimed and had to decide which of the two viewed gestures matched the named gesture. In the Semantic condition (24 items), one of the gestures in the pair was incorrect by virtue of a semantic relationship to the target gesture (e.g., sawing). In the Spatiotemporal condition (24 items), one of the gestures in the pair was incorrect by virtue of a spatial error in hand posture (eight items), arm posture/trajectory (eight items), or amplitude and/or timing (eight items). The conditions were blocked, and the order of

correct and incorrect videos on each trial was randomized. Performance was scored as the number of gestures correctly recognized in each condition.

Gesture to Sight of Object

Participants were shown an object on each of 10 trials and were asked to pantomime its use using their left hand (Buxbaum et al., 2005, 2000). Participants were not allowed to touch or manipulate the object. Scoring was analogous to that of the meaningless gesture imitation task, with the addition of a "content" category. Content was scored as zero if another recognizable gesture was substituted for the target gesture (e.g., brushing teeth when the object was a comb) and one otherwise. Test items that received a content score of zero were not scored on the other four spatiotemporal components. Using a detailed scoring protocol performed by trained, reliable coders (Buxbaum et al., 2000), the percentage of correct gestures was calculated across items that received a content score of one.

Hand Posture Sequencing Task

Participants were asked to produce 20 sequences of five hand postures each using the left hand (task modeled after Harrington and Haaland, 1991). Each hand posture sequence comprised some combination of handle grasping, button pressing, and palming a computer mouse in non-repeating order, as indicated by a series of five symbols displayed on a computer screen. The symbols were semi-abstract in that the symbol for palming was a solid square, the symbol for button press was a dot within a circle, and the symbol for grasping the handle was a handle-shaped "U". The task was administered using Psyscope

on a Macintosh computer. Before beginning the task, participants were trained to criterion to identify the symbols associated with each action in the sequence. They began each trial with the ipsilesional left hand resting on the space bar of a computer keyboard while they viewed a fixation cross on the monitor. The cross brightened to alert the participants to an upcoming trial. A series of five symbols was displayed to denote the sequence of postures to be made. After a jittered delay (1000-2000 ms), a tone signaled the participants to lift the hand and produce the series of movements on the apparatus, which contained a row of five handles, a row of five doorbells, and a row of five computer mice. The symbols remained on the monitor during the response. Responses were videotaped; accuracy was scored offline using these videos. Errors included 1) taking more than 2000 ms to initiate a movement during the RT interval, 2) executing an incorrect hand posture, or 3) executing an incorrect hand posture before correction (i.e., corrected errors). These three error sub-types were summed to produce a total error score.

Meaningless Gesture Imitation

Participants were asked to imitate gestures performed by a videotaped model as precisely as possible, using their less impaired (ipsilesional) left hand (Goldenberg and Hagmann, 1997). The model used their right hand, to allow mirror-image imitation by the subject. Test stimuli consisted of 15 meaningless gestures. Performance on each trial was scored by two independent coders as “correct” (one point) or “incorrect” (zero point) for four aspects of the movement: hand posture, arm posture, amplitude, and timing (Buxbaum et al., 2000). Thus, a maximum of four points could be earned for each gesture (60 total points).

Novel Tools Test

This test required participants to select and use novel tools to manipulate novel cylindrical objects (Goldenberg and Hagmann, 1998). Each wooden cylinder had a metal or wooden part to which one of the tools must be fitted (e.g., a "hook" tool fits in the "eye" of a cylinder) to lift the cylinder from a platform. Participants were shown a single cylinder at a time, along with an array of three tools, and asked to select the tool best suited for lifting the cylinder. On each trial, participants received two points for correctly selecting the tool on the first attempt but lost one point each time they made a wrong choice. Once the correct tool was identified, participants were then asked to apply that tool to lift the cylinder from the base. Participants earned two points for successfully lifting the cylinder but lost points for incorrect or failed attempts. In our dataset, the selection and application scores were combined to create a Novel Tools Total score (maximum score = 24).

Attention allocation and control tasks

Attention Network Test (ANT)

In the Attention Network Task (ANT; Fan et al., 2002) participants depressed a left or right button on a button box to indicate the orientation of a center arrow presented on a computer monitor while inhibiting a response based on the orientation of flanking arrows. The center arrow direction could be the same (i.e., congruent) or different from the flanking arrows. There was also a neutral condition where the flankers were dashes without any arrowheads. Stimuli appeared either at the bottom or the top of the screen. On some trials, the stimulus could be preceded by a cue orienting participants to the spatial location of the upcoming

stimulus (i.e., a star appearing at the top or bottom of the screen). In other trials, the cue alerted individuals that a stimulus was coming but was uninformative about the stimulus location, either presented as a single star appearing at the center of the screen or as stars appearing at both the top and bottom of the screen (i.e., a double cue). Finally, in the remaining trials no cue was presented. Participants were scored on accuracy and reaction time (RT). RT was calculated separately for each of the three congruency conditions (congruent/incongruent/neutral) and four cue location conditions (center/double/spatial cue/no cue), for a total of 12 different mean response times. Within each condition, any RTs that fell three standard deviations above or below the mean were removed, as were any RTs less than 100 ms. Following from Fan et al. (2002), we examined three different scores for analysis. Total accuracy measured a participant's ability to indicate the orientation of the center arrow and ignore the flanking arrows across all conditions. The alerting score was computed by subtracting, for correct trials, the RT in the double cue condition from the RT in the no cue condition; this difference was then divided by the average RT of the two conditions. Finally, the orienting score was computed by subtracting the RT in the spatial cue condition from the RT in the center cue condition, then dividing by the average RT of these two conditions.

Digit Span

This task was taken from the Wechsler Adult Intelligence Scale – III (Weschsler, 1997). Participants had to repeat a gradually increasing sequence of digits spoken at one second intervals by the experimenter, starting with a sequence of two digits. The number of digits in the sequence increased by one after each successful trial. The task terminated when the

participant failed two attempts to correctly repeat the sequence of digits. The longest sequence successfully repeated was taken as the digit span measure.

Dual Task Test

In a baseline condition, black dots (1-cm diameter) appeared in random locations on a computer screen at intervals of 0.5, 1.0, 1.5, or 2.0 s. Participants had to press the space bar whenever a dot appeared. In a subsequent dual-task condition, the dot detection task was performed while participants were required to repeat digit strings of length span-minus-one, where the span was taken from the prior Digit Span task. Participants had to respond to 64 dots in each condition. RTs less than 150 ms or greater than 10,000 ms were trimmed. A dual-task interference score was computed by subtracting the mean baseline RT from the mean dual-task RT.

Self-Ordered Pointing Test

In this measure of non-verbal working memory, participants were shown twelve black-and-white abstract designs in a 3x4 array on a single sheet of paper. The participants were asked to look over the designs and point to any one of them. The experimenter then turned the page, revealing the same designs in different positions in the array. Participants were asked to point to a different design than any of their previous choices. The test continued in this fashion for twelve trials. Participants received one point each time they chose a design that was different from the previous choices (revised from Petrides and Milner, 1982).

Sustained Attention to Response Test (SART)

In this continuous performance test, 225 single digits were presented serially over a period of 4.3 minutes on a computer screen running E-Prime (Robertson et al., 1997). Participants were asked to respond by pressing a key to all digits except "3," which appeared 25 times according to a predetermined, quasi-random schedule. The digits varied in size. Each digit was presented for 250 ms, followed by a 900 ms mask. This task was scored as the number of commission errors (i.e., incorrect presses to 3) and the number of omission errors (i.e., lack of response to numbers other than 3). From these two scores we calculated a sensitivity index (d-prime).

Reasoning Tasks

Brixton Test

This test (Burgess and Shallice, 1997) employed a testing book consisting of 56 pages (55 trials). On each trial, participants were presented with two rows of five circles each, equally spaced and equal in size. The circles were numbered sequentially based on position. On each page, one circle was colored blue. Participants had to deduce the pattern of movement of the blue circle and predict where the blue circle would appear on the next page. The pattern changed periodically, at which point participants were required to deduce the new pattern and predict the next movement accordingly. The test was scored as the number of trials on which the blue circle's position was not correctly predicted; better performance is indicated by lower scores.

Tower of London

Participants had to move a stack of balls among three posts to produce a specified configuration, indicated with a colored drawing, within a limited number of moves (Shallice, 1982). There were 12 problems increasing in complexity and number of moves required. Performance was scored as the number of problems solved on the first try and in under 60 seconds.

Test of Functional Independence

Older American Resources and Services – Multidimensional Functional Assessment Questionnaire (OARS-MFAQ)

To examine the relationship of the NAT with impairments in activities of daily living (ADL), participants completed the OARS-MFAQ, a questionnaire measuring functional independence in ADL (Fillenbaum and Smyer, 1981). A subset of seven questions measuring instrumental ADLs (i.e., temporally-extended tasks, such as using the telephone, shopping for groceries, meal preparation, and housework) was administered. Participants were required to select from among three response options: absence of impairment (two points; e.g., "without help, including looking up numbers and dialing a telephone"), some impairment (one point; e.g., "can answer the phone or dial the operator in an emergency, but need a special phone or help in getting the number or dialing"), or inability to perform the task (zero point; e.g., "completely unable to use the telephone"). The total score was calculated from the sum of the seven items, with a maximum score of 14 indicating no ADL impairments.

Imaging

Of the 51 participants included in this dataset, 45 had a hand-drawn lesion map obtained from a research-quality MRI or CT scan. Participants received their scan at the Hospital of the University of Pennsylvania. Research MRI scans included whole-brain T1-weighted MR images collected on a 3T (Siemens Trio, Erlangen, Germany; repetition time =1620 msec, echo time = 3.87 msec, field of view = 192 × 256 mm, 1 × 1 × 1 mm voxels) or 1.5T (Siemens Sonata, repetition time = 3,000 msec, echo time=3.54msec, field of view= 24 cm, 1.25 × 1.25 × 1.25 mm voxels) scanner, using a Siemens eight-channel head coil. Participants who were contraindicated for MRI underwent whole-brain research CT scans without contrast (60 axial slices, 3–5 mm slice thickness) on a 64-slice Siemens SOMATOM Sensation scanner. For MRI scans, a team member manually segmented lesions to produce a 3-D lesion mask. The binarized lesion drawings were then warped to a 1×1×1 mm common template brain (Montreal Neurological Institute "Colin27") using a symmetric diffeomorphic registration algorithm (Avants et al., 2008) to translate manual lesion segmentations to standardized space via a two-step process: First, they were registered to an intermediate template comprising healthy brain images acquired from the same scanner at the Hospital of the University of Pennsylvania that was used to collect MRI scans from the patients; then, volumes were mapped from the intermediate template to the "Colin27" template (i.e., Montreal Neurological Institute – MNI – space). A neurologist naive to the behavioral data (Dr. Branch Coslett) inspected all warped lesions to ensure that no errors had occurred. Lesions from research CT or clinical scans were drawn by the same neurologist directly onto the template brain, which had been rotated to match the pitch of the patient's scan. This method achieved high intra- and interrater reliability in a previous study (Schnur et al., 2009).

Analyses

Least Absolute Shrinkage and Selection Operator (LASSO) Regression

Our dataset consisted of many potential predictors that could explain performance on the NAT. We were interested in assessing which subset of variables meaningfully predicted NAT performance. To do this in a principled manner without overfitting the data, and to address potential collinearities between predictors, we used a LASSO regression approach. LASSO is a regularized regression technique that applies a penalty term to the residual sum of squares of the regression to achieve a relatively sparse model (Tibshirani, 1996). That is, this penalty term pushes most coefficient (i.e., beta) estimates toward zero; any remaining non-zero beta estimates are then assumed to contribute to the model.

Our LASSO regression model was used to test which of 20 variables (Table 3) predicted total NAT performance (i.e., resulted in non-zero model coefficients). Variables included outcome measures from the Behavioral Test Battery, as well as demographic variables including Age and Months post-stroke onset. LASSO regressions were fitted in R using the package *glmnet* (Friedman et al., 2010). Using this package, we first estimated a penalty coefficient (λ) that reflects the amount of shrinkage to apply in the model to minimize mean squared error. Lambda was estimated using a 10-fold cross-validation approach using the *cv.glmnet* function. The estimated minimum λ was used to run the subsequent LASSO regression using the function *glmnet* to estimate the model coefficients. The functions *cv.glmnet* and *glmnet* separately normalize each variable by default, thus accounting for differences in the scale and range of the various battery test scores. Importantly, these functions return non-normalized coefficients that are appropriately

scaled for each independent variable (analogous to a conventional regression approach) and do not provide a coefficient uncertainty estimate (e.g., standard error); thus, it is not possible to interpret the magnitude of each coefficient as reflecting its relative importance in the model.

Prediction quality

The LASSO regression method does not provide an estimate for the uncertainty of the resulting parameter estimates (e.g., standard errors for the beta coefficients). Thus, to ensure that the resulting model (i.e., the non-zero parameters) described the data well, we performed a leave-one-out cross validation prediction analysis. On each iteration one subject was pulled out of the sample, and model coefficient parameters were estimated using the rest of the sample (i.e., n=50) using a classic General Linear Model (GLM). This subset model was then used to predict the NAT score of the withheld subject, and the quality of the prediction was compared to the true observed NAT score. This procedure was repeated for all participants in the data set. We applied this procedure twice; once including only the non-zero terms identified from the original LASSO regression, and once including all 20 possible variables. We measured Spearman's correlation between the actual and predicted NAT scores for each model. To test whether the two Spearman correlations were significantly different (i.e., that the model with non-zero terms was superior to the full model), we applied a permutation approach. We first computed the observed rho difference between each prediction analysis. To test if this difference score was different from a null distribution, we permuted with replacement the NAT scores 10,000 times. For each permutation we calculated the correlation between the predicted

NAT scores and the permuted ones under both models, deriving a null distribution of the difference in rho values between the two models. Finally, we estimated the probability that the observed rho difference was null as the number of values from the null distribution that were greater than our true observed rho difference (i.e., the tail probability of observing the actual difference in rho values between the two models). A probability less than 5% ($p = 0.05$) was considered significant.

Lesion Symptom-Mapping analyses

To examine lesions associated with poor performance on the NAT, we performed lesion-symptom mapping using Support Vector Regression-Lesion Symptom Mapping (SVR-LSM) using the SVR-LSM Matlab toolbox developed by DeMarco and Turkeltaub (2018). SVR-LSM is a multivariate analysis technique that uses machine learning to determine the association between lesioned voxels and behavior across all voxels and participants simultaneously. Using this approach, we analyzed data from the 45 participants in our dataset that had a hand-drawn lesion map. Only voxels lesioned in at least 10% (i.e., 4) of participants were included in the analysis. Total lesion volume was regressed from both the behavioral scores and the lesion maps. Voxelwise statistical significance was determined using a Monte Carlo style permutation analysis (10,000 iterations) in which the association between behavioral data and lesion map was randomized. A voxelwise threshold of $P < 0.005$ one-sided was applied to determine chance-level likelihood of a lesion-symptom relationship. A cluster size threshold was subsequently applied to keep only clusters with at least 100 voxels (i.e., 100 mm^3). The neuroanatomic label of the surviving clusters was checked with the third version of the Automated Anatomical

Labelling atlas (AAL3 atlas; Rolls et al., 2019). We report the maximum statistic (Z-value) observed in each cluster, as well as the coordinates of the cluster centroid (Table 4).

Correlation between NAT and ADL functional independence questionnaire

To examine the degree to which performance on the NAT relates to an individual's functional independence in instrumental activities of daily living, we ran a Spearman correlation between the OARS-MFAQ and the NAT.

Results

NAT performance is predicted by measures of praxis and attention allocation and control

In our retrospective dataset, we first examined the relationship between performance on the Naturalistic Action Test (NAT) and the 20 measures from our background test battery. Using a LASSO regression model, we obtained six non-null predictors (Table 3). These predictors included the number of errors in the Hand Posture Sequencing Task (HPST), the number of items correctly recognized in the Semantic version of the Gesture Recognition Task (Semantic GR), the attention orienting score from the Attention Network Test (ANT), the reaction time difference between the dual-task test and its baseline (hereafter, Dual Task interference), the comprehension subtest of the Western Aphasia Battery (WAB Comprehension) and participant age. Importantly, the sign of the coefficient of each predictor matched the expected direction (e.g., positive coefficients for tasks where higher scores indicate better performance).

Table 3: List of the variables used in the LASSO regression model. In bold are the predictors for which the LASSO regression returned a non-null coefficient.

Variable	*Coefficient estimate*
Praxis	
Hand Posture Sequence Test	**-0.0954**
Semantic Gesture Recognition	**0.0689**
Function Knowledge	null
Manipulation Knowledge	null
Spatial Gesture Recognition	null
Gesture to Sight	null
Meaningless Imitation	null
Novel Tool Use[1]	null
Attention allocation and control	
ANT orienting	**-14.4229**
Dual Task Interference	**-0.0004**
ANT alerting	null
ANT accuracy	null
Digit Span	null
SOPT	null
SART	null
Reasoning	
Brixton Test	null
Tower of London	null
Language	

WAB Comprehension	**0.7245**
Demographics	
Age	**-0.0235**
Months Post Stroke onset	null

[1]The Novel Tool Use task is sometimes referred to as a reasoning task (Goldenberg and Hagmann, 1998), but also relies on praxis system integrity as revealed by correlations in the ability to use novel tools and to use or pantomime familiar tools (Goldenberg and Hagmann, 1998).

To confirm that these six predictors account reliably for NAT performance, we ran a prediction analysis using a leave-one-out cross-validation procedure. Overall, we found that our model predicted actual NAT performance with good accuracy (Spearman correlation between the predicted and actual NAT values, rho = 0.46; $p < 0.001$ one-sided; Fig. 1A). In comparison, the same cross-validation approach using all 20 predictors led to an inferior prediction of NAT performance (rho = 0.27; $p = 0.03$ one-sided; Fig. 1B). Using a permutation test, we confirmed that the difference in Spearman's correlation scores for these two regressions was significantly different (rho difference score = 0.19; $p = 0.01$ one-sided; Fig; 1C), indicating that the reduced model was a significantly better fit to the data than the full model, potentially due to overfitting by the full model.

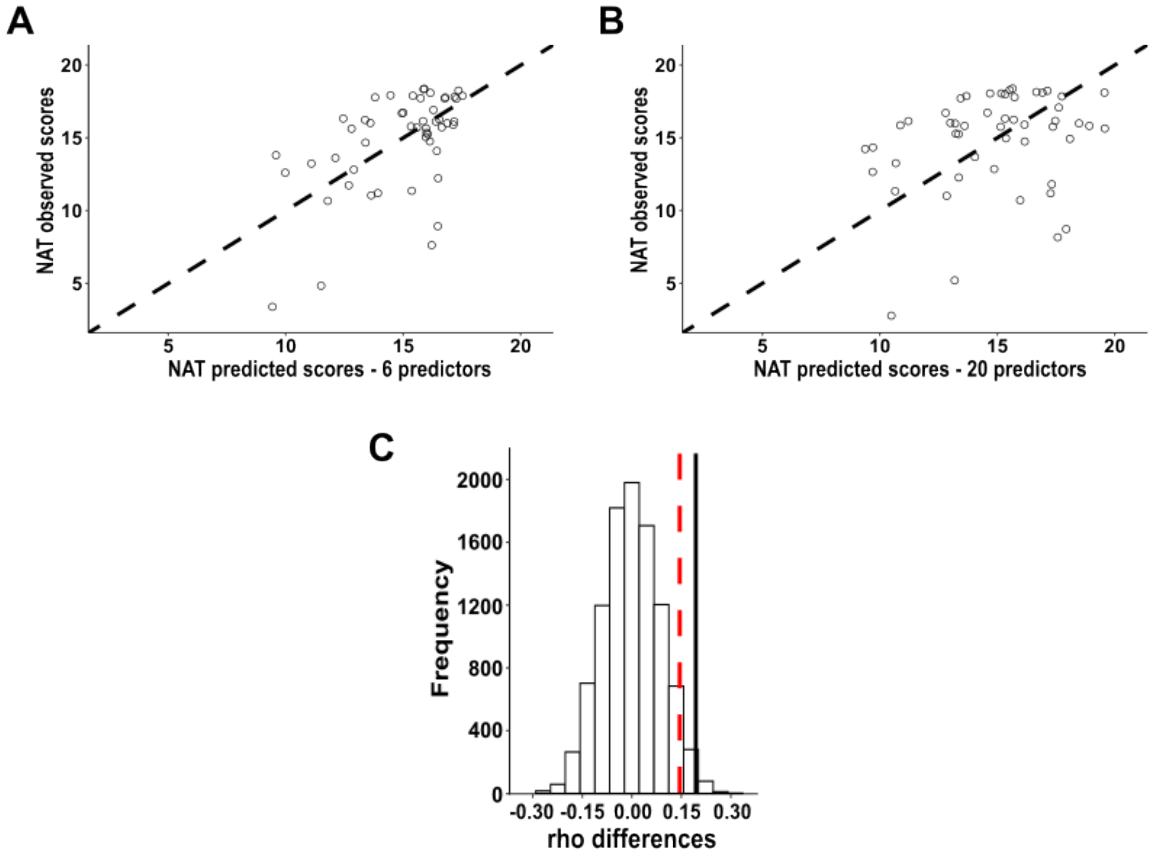

Figure 1: NAT score prediction was better predicted with a classic regression model that included only the non-zero predictors identified by the LASSO regression. Predicted NAT scores were estimated with a classic regression model including A) only the six non-zero predictors from the LASSO regression and, B) all 20 predictors. The black dashed lines depict the unity line. C) The difference between Spearman's rho scores for each model was calculated and tested for significance compared to a null distribution obtained after 10,000 permutations. The solid black line is the observed rho score difference. The red dashed line reflects an alpha value of 0.05, indicating that the observed rho difference is significantly larger than chance.

NAT performance relates to impairments in instrumental activities of daily living

Using Spearman's correlation, we found that NAT performance was significantly correlated with the OARS-MFAQ, a self-report measure of ADL impairments (rho = 0.35; p = 0.01). This positive correlation suggests that participants who performed better on the NAT reported fewer impairments on instrumental activities of daily living.

Lesions associated with poor NAT performance are associated with praxis and attentional processes

We conducted Support Vector Regression- Lesion Symptom Mapping (SVR-LSM) to examine the relationship between lesion location and performance on the NAT (Fig. 2, Table 4). This analysis indicated that impaired NAT performance was associated with lesions to three brain regions. First, there was an association between impaired NAT performance and left posterior Middle Temporal Gyrus (pMTG). There was also a cluster

in the anterior Inferior Parietal Lobule (aIPL), which included voxels in both the Supramarginal Gyrus and the Postcentral Gyrus. Finally, we observed a cluster in the Middle Frontal Gyrus (MFG) extending to the *pars triangularis* of the Inferior Frontal Gyrus (IFG), with 20% of the voxels of that cluster located within the IFG.

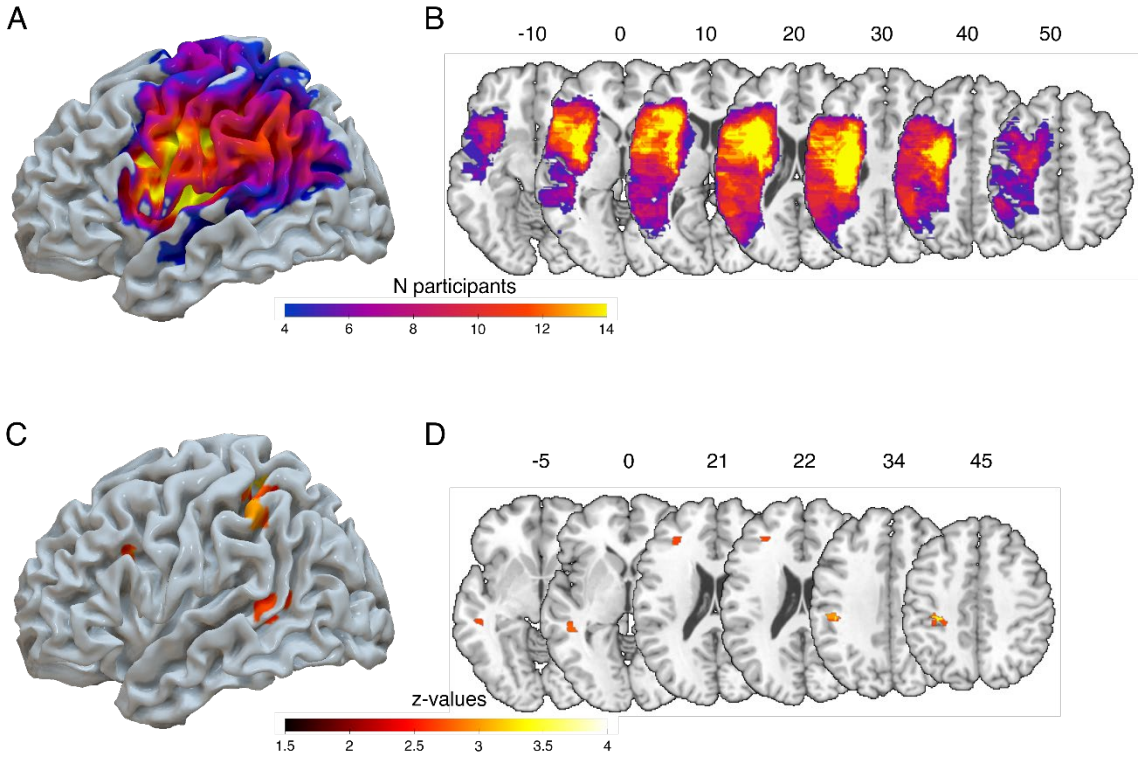

Figure 2: Naturalistic actions impairments are associated with lesions in the frontal, parietal and temporal lobes. Inflated brain render (A) and axial-view brain slices (B) are shown for the lesion overlap map depicting voxels lesioned in at least four of the 45 participants; the color reflects the number of individuals for whom that voxel is lesioned (range: 4-14). Slice numbers reflect the corresponding z coordinates in MNI space. Inflated brain render (C) and axial brain slices (D) are shown for the thresholded map of areas associated with naturalistic action impairments with significant voxels at p-value < 0.005 one-sided,

corresponding to a z-value < -2.57 and a cluster size with at least 100 voxels (i.e., 100 mm^3). The analyses revealed three main clusters in the pMTG, the aIPL and the MFG.

Table 4: Neural correlates associated with impaired NAT performance. The coordinates for the cluster centroid are in MNI space.

Brain area(s)	*Cluster extent (mm^3)*	*Peak Z-value*	*Cluster centroid coordinates*
Inferior Parietal Lobule	711	-3.72	-38; -29; 42
Middle Temporal Gyrus	339	-2.78	-48; -34; -1
Middle Frontal Gyrus	128	-3.12	-32; 35; 22

Discussion

Based on a retrospective analysis of previously-collected data, we examined the predictors of naturalistic action impairments in an LCVA population using a regularized regression approach (LASSO regression) that accounted for collinearities in the dataset. As expected, we found that naturalistic action impairments in people with LCVA were predicted by praxis deficits. We also found that naturalistic action impairments in this population were predicted by deficits in attentional control and allocation. Finally, language comprehension and age were also predictive of NAT performance.

Praxis is an important contributor to naturalistic action performance. Specifically, we found naturalistic action performance was driven by the ability to recognize tool-related gestures – a measure of praxis knowledge, and the ability to properly produce a series of object-directed hand postures – a measure of posture sequence production. Regarding tool-use gestures, we specifically observed that the inability to distinguish between semantically-related tool-use gestures (e.g., use of hammer versus saw) was predictive of naturalistic action deficits. Loss of knowledge of the actions associated with manipulable objects has historically been viewed as a core component of so-called "ideational apraxia" (e.g., De Renzi and Lucchelli, 1988; Ochipa et al., 1989) In naturalistic tasks, appropriate objects must be selected in a timely manner from arrays that often contain task-irrelevant but semantically-related objects (e.g., various kitchen utensils in a breakfast preparation task). We speculate that degradation of tool action knowledge makes such selection difficult, contributing to poor task performance.

We also found that the ability to produce a sequence of object-related hand postures plays a role in naturalistic action impairment. Previous studies have shown that individuals

with LCVA are particularly impaired in this task with respect to neurotypicals and RCVA (Haaland and Harrington, 1994; Harrington and Haaland, 1992, 1991). The task requires translation from a sequence of semi-abstract visual symbols to a sequence of hand postures. Poor performance may reflect slow retrieval of the individual hand-posture elements within each sequence and/or a deficit in representing the order of the elements within sequences. We speculate that hand posture sequencing is relevant to naturalistic action by virtue of the fact that in naturalistic action tasks, visual information (i.e., an object in the array) is used to inform the appropriate selection of a hand posture for use of that object. Moreover, naturalistic tasks, like the hand posture sequencing task, contain numerous objects for which the correct hand posture (e.g., cutting butter, spreading butter, and spreading jam with a knife) must be produced sequentially (Botvinick and Plaut, 2004; Cooper and Shallice, 2000; Cooper et al., 2005). Thus, it is possible that naturalistic action suffers from a reduced ability to produce actions in the correct order, over and above any difficulties with retrieval of the individual elements in the sequence. Further investigation is needed to disentangle the precise role of hand posture sequencing deficits in naturalistic actions.

In addition to praxis deficits, we found that attentional allocation and control deficits were also predictive of naturalistic action impairments. Specifically, we observed a relationship with the ability to select information from visual input (orienting) and the ability to divide attention between two simultaneous tasks (dual-task decrements). The orienting measure suggests that a reduced ability to respond to exogenous cues to orient spatial attention contributed to naturalistic action errors. A previous report showed that attention orienting on an auditory version of the Attention Network Test was disrupted in LCVA compared to neurotypicals (LaCroix et al., 2020). Attention orienting is typically

conceptualized as occurring in response to suddenly-appearing stimuli (e.g., Posner, 1980). While sudden changes of state do occasionally occur in the NAT (e.g., the toast pops up when toasting is complete), in the context of naturalistic tasks we speculate that reductions in orienting attention more broadly impact the degree to which any object in the array provides a "bottom-up" signal of the need to shift attention to its location.

We also found that naturalistic action impairments were related to attention control; specifically, the ability to respond to stimuli despite interference by a secondary task. As noted in the Introduction, a previous study showed that neurotypical individuals made more errors when required to perform a naturalistic action in parallel with another attention-demanding task (Giovannetti et al., 2007). In the naturalistic action tasks performed in the present study, there was no explicit secondary cognitive task. However, naturalistic actions inherently require the division of attention across multiple simultaneously-occurring events. For instance, when preparing breakfast, one can slice butter or open a jam container while simultaneously attending to the status of bread in the toaster. Consistent with prior evidence of dual task impairments in stroke (Feld and Plummer, 2021; Mullick et al., 2021), deficits in the ability to divide attention across the different subparts of naturalistic action tasks may be impaired in the LCVA population.

We additionally found that language comprehension is predictive of naturalistic action performance. It is worth noting that the NAT is designed to limit verbal instructions by showing people visual pictures of the task goal (e.g., a picture of toast with butter and jam) and also includes a phase where the experimenter checks whether the instructions are understood. Despite these methodological considerations, we cannot fully reject the possibility that some language comprehension deficits affected task performance, as both

the WAB and the NAT involve remembering and following complex multi-step instructions. This account is consistent with a previous study in LCVA that found a correlation between measures of language comprehension and performance in a coffee preparation task (Hartmann et al., 2005). Finally, we found that (older) age was also predictive of greater naturalistic action impairments. In neurotypicals, performance of naturalistic actions is slower for older participants compared to younger ones (Giovannetti et al., 2019). This result is perhaps unsurprising given that aging affects overall brain health, which in turn affects "general" cognitive functions such as processing speed (Brayne et al., 1995).

In addition to examining the predictors of NAT performance, we also assessed whether the Naturalistic Action Test is a valid measure of participants' assessment of their abilities in temporally-extended activities of daily living. We observed a moderate correlation between the NAT and self-reported responses on the OARS-MFAQ. On that basis, we suggest that the results of this study have relevance not just for laboratory-based tests of naturalistic actions, but for real-world activities more broadly.

Lastly, we conducted a lesion-symptom mapping analysis to explore which brain regions may be involved in naturalistic action deficits. Our analysis revealed that lesions to portions of the praxis (tool-use) network including the pMTG, the aIPL and the MFG are associated with naturalistic action impairments. The contribution of these areas is consistent with our behavioral data showing that praxis deficits predict naturalistic action impairments, and with previous neuroimaging studies in which neurotypicals observed naturalistic actions (see Bienkiewicz et al., 2014 for a meta-analysis). The left pMTG plays a role in action observation and recognition (Papeo et al., 2019; Wurm and Lingnau, 2015)

and subserves representations for tools and hands; lesions to the left pMTG contribute to impaired gesture knowledge (Kalénine et al., 2010; Tarhan et al., 2015). Based on our finding that impaired semantic gesture recognition contributed to poorer naturalistic action performance, we suggest that lesions to the pMTG contribute to degraded tool-use representations that impact naturalistic action.

Lesions to the aIPL, in contrast, are associated with errors in the production of hand postures in tool-use pantomime (Hoeren et al., 2014; Tarhan et al., 2015). While in our study tool-use pantomime (i.e. Gesture-to-Sight task) was not a contributing predictor to naturalistic action impairments, we may speculate that lesions to the aIPL contribute to an inability to select hand postures appropriate to objects in the naturalistic array and may reflect the contribution of the Hand Posture Sequencing Task to the prediction of overall NAT performance.

The MFG is known to be involved in the execution of tool-related actions (Brandi et al., 2014; Chen et al., 2023; Gallivan et al., 2013), although the specific cognitive process supported by this area remains unclear. The MFG is also involved in dual task performance (Worringer et al., 2019). Thus, this area may contribute to both attention and praxis computations that are critical for naturalistic action.

Note that the use of lesion-symptom mapping techniques is limited by the lesion map overlap within a sample, which in our case tends to be sparse for more posterior areas such the occipito-temporal cortex involved in praxis (Brandi et al., 2014; Peeters et al., 2009) and for prefrontal areas involved in attentional control (Dove et al., 2000; MacDonald et al., 2000). Functional connectivity analyses in LCVA or neurotypicals may

be useful in further clarifying the brain networks involved in the performance of naturalistic action.

Despite the strength and the novelty of the multivariate LASSO regression approach employed, the current study has some limitations. The analysis of a retrospective dataset limited our access to fine-grained details about administration and data pre-processing for some tasks, as well as trial-level data that might allow for more sophisticated statistical modeling approaches. Future research can address these limitations by taking advantage of recent progress in the development of large publicly-available datasets that can be analyzed with contemporary statistical approaches.

Taken together, findings from this study provide evidence that naturalistic action impairments in LCVA are related to praxis deficits as well as deficits in attention allocation and control, language comprehension, and age. These data contradict the traditional view in the praxis literature that naturalistic action tasks are simple extensions of single object pantomime and use tasks (De Renzi and Lucchelli, 1988; Poeck, 1983), and help to explain why naturalistic action impairments are also observed in people with right hemisphere stroke, traumatic brain injury, and dementia. Finally, the current findings point to several cognitive processes that play a key role in the successful production of naturalistic actions, including knowledge of object manipulation, the ability to produce object-appropriate hand postures in response to environmental input, the allocation of attention in response to visual cues, and the ability to resist cognitive interference.

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Data availability

The retrospective database used for the analyses is available at https://osf.io/rk9c6/. The brain lesion data can be found at https://osf.io/dz5av/.

Code availability

The code used to analyze the behavioral data is available at https://osf.io/w8tc7/. The neuroimaging data were analyzed with the SVR-LSM toolbox available at https://github.com/atdemarco/svrlsmgui/tree/svrlsmgui2.

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