Using neurostimulation to understand the impact of pre-morbid individual differences on post-lesion outcomes

Anna M. Woollams, Gaston Madrid, and Matthew A. Lambon Ralph

*Neuroscience and Aphasia Research Unit, Division of Neuroscience and Experimental Psychology, School of Biological Sciences, University of Manchester, Manchester, M13 9PL, England

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Neuropsychological data have proven invaluable in advancing our understanding of higher cognition. The interpretation of such data is, however, complicated by the fact that post-lesion behavioral abnormalities could reflect pre-morbid individual differences in the cognitive domain of interest. Here we exploited the virtual lesion methodology offered by transcranial magnetic stimulation (TMS) to explore the impact of pre-morbid individual differences on post-lesion performance. We applied this approach to the domain of reading, a crucial ability in which there are known to be considerable individual differences in the normal population. As predicted by neuropsychological studies of surface dyslexia in semantic dementia and the connectionist triangle model of reading, previous empirical work has shown that healthy participants vary in their reliance on meaning for reading words with atypical correspondences between spelling and sound. We therefore selected participants who varied along this dimension and applied a virtual lesion to the left anterior temporal lobe. As expected, we observed a significant three-way interaction between “pre-morbid” reading status, stimulation, and word type, such that TMS increased the disadvantage for spelling-sound atypical words more for the individuals with stronger semantic reliance. This successful test-case study provides an approach to understanding the impact of pre-morbid individual variation on post-lesion outcomes that could be fruitfully applied to a variety of cognitive domains.

transcranial magnetic stimulation | anterior temporal lobe | surface dyslexia | semantic dementia | reading

The study of neuropsychological patients to inform models of normal cognitive function has proven highly productive. A major issue, however, that arises in this research is the possibility of systematic individual differences in normal pre-morbid performance impacting significantly on post-damage neuropsychological profiles. Such differences can complicate the interpretation of behavior in terms of its implications for both cognitive and neural models (1), particularly because neuropsychological conclusions are often based on single cases. Estimation of these differences is challenging because they are conflated with the impact of brain damage; hence, one cannot retrospectively assess pre-morbid performance. A three-pronged approach is needed to establish and understand the impact of these individual differences. Firstly, detailed data on the full spectrum of patients’ performance is needed from large-scale case-series studies. Secondly, computational models that implement the core cognitive framework and incorporate an account of individual variation are required. Finally, new approaches, such as neurostimulation techniques that can transiently mimic patient performance, are necessary to relate pre-morbid individual differences directly to post-damage performance. In this paper, we illustrate the key challenges and potential solutions to the issue of pre-morbid individual differences within the domain of reading aloud, where there is already extensive neuropsychological data linking semantic deficits to surface dyslexia and an implemented computational model of individual differences in semantic reliance (SR) in normal reading and its post-damage consequences. Until now, however, there has not been a direct test of the model’s hypothesis, and here we provide this by exploiting the “virtual lesion” approach offered by repetitive transcranial magnetic stimulation (rTMS).

Reading is a particularly mature and sophisticated area of research because competing alternative accounts have been implemented as computational models, allowing direct quantitative simulation of behavior. It is also a key ability in which there are considerable individual differences among the normal population (2). Reading aloud in English constitutes a quasi-regular domain (3), such that most words have predictable pronunciations according to the most typical subword correspondences between spelling and sound (e.g., *pink, scribe*), but there are nevertheless many words that contain atypical correspondences that render their pronunciations unpredictable (e.g., *pint, scarce*). Current models of reading vary in how they propose the human reading systems deals with this quasi-regularity (3, 4).

The connectionist triangle model proposes a direct subword pathway between spelling and sound that contains representations of orthography and phonology distributed over a set of units (3, 5, 6). These units are linked by connections, with the weights on these learned through probabilistic exposure on a representative corpus. When trained in isolation, this pathway can successfully translate...
all known words and also novel letter strings (3). However, when the model is trained with an additional semantic pathway to emulate access to word meaning, then a division of labor emerges such that this whole-word information comes to support pronunciation of atypical words, allowing the direct pathway to partially specialize to typical subword mappings (3, 5, 7, 8). Evidence for this account is provided by reports of stronger semantic effects for reading aloud atypical than typical words (9–13), which has been simulated in the connectionist triangle model (5). In this model then, semantic damage results in deficits in reading atypical words, a pattern called surface dyslexia (3, 7).

The connectionist triangle model account therefore makes the strong prediction that semantic deficits should compromise reading of words with atypical spelling–sound mappings (3). This prediction is supported by the observation that the vast majority of patients with semantic dementia, a progressive and selective deterioration of semantic memory due to atrophy and hypometabolism of the anterior temporal lobes (ATLs) (14, 15), show a reading profile of surface dyslexia (16, 17). The causes of this association have been hotly debated, however, because there have been a small minority of cases of semantic dementia who show preserved atypical word reading (18–21).

The connectionist triangle model account proposes that, in addition to degree of semantic damage, a key factor in explaining variation in the degree of surface dyslexia seen in semantic dementia is pre-morbid individual differences in the degree of semantic involvement in reading aloud (7, 8). Previous work on individual differences in reading styles had been framed in terms of differential reliance on whole-word and subword strategies (22, 23), rather than the involvement of semantic information, and had yielded inconsistent cognitive correlates (2). More recently, Graves et al. (21) have considered individual variation in degree of SR during reading and found this to be related to white matter connectivity within the left hemisphere reading network. The connectionist triangle model account of variation in surface dyslexia in semantic dementia focuses particularly on individual differences in SR specifically for words with atypical spelling–sound mappings.

As noted earlier, to explore the proposal derived from the connectionist triangle model, large-scale case-series neuro-psychological data are needed to quantify the strength of the relationship between semantic and reading impairments and the incidence of atypical cases and map across the scale of variation around the central tendency of the association. This was provided by the largest case-series study of this issue performance to date, based on 100 observations of reading behavior from 51 semantic dementia patients (8). This study found an extremely strong association between semantic deficits and surface dyslexia, with the degree of semantic impairment accounting for half the variance in patients’ reading of atypical words. While there were three cases showing preserved atypical word reading at initial testing, all progressed to a surface dyslexic reading pattern at follow-up. However, despite the strength of the association between semantics and atypical word reading in this study, there was nevertheless considerable variation in reading performance between patients with the same degree of semantic impairment.

To further our understanding of the role of individual differences, we also need a computational model that implements the role of semantic information in normal reading and incorporates a formal mechanism and simulation of how pre-morbid variation in SR can impact upon post-damage performance. Woollams et al. (8) simulated their case-series data using a sample of different instantiations of the connectionist triangle model that varied in the degree of semantic support provided during training of the direct pathway. For models trained with strong semantic support, lesioning in the semantic pathway had a marked negative impact on atypical word reading. For models trained with weak semantic support, lesioning had a much milder effect on atypical word reading. For models trained with weak semantic support, lesioning had a much milder effect on atypical word reading.

In this study, we exploit the virtual lesion methodology to understand the impact of pre-morbid individual differences on post-damage performance. This approach allows us to circumvent concerns about variation in the location/extent of damage and also in adapting to surface dyslexia, both of which are inherent in neuro-psychological research. We applied rTMS to the left ATL of normal readers to determine how variation in SR for atypical word reading impacts upon deficits after disruption. We selected normal readers for their low or high SR using a behavioral measure previously shown to predict the size of imageability and semantic priming effects in reading (2). We therefore used rTMS to target the anterior MTG of low and high SR readers for virtual lesioning. The individual differences hypothesis predicts that the disadvantage for atypical words should be increased by ATL rTMS more for the high SR readers than the low SR readers and that this pattern should be particularly apparent for low-frequency words.

Results
An ANOVA on reaction time data for low-frequency words (Table 1) with reader type (low SR/high SR) as a between-participants variable and rTMS (pre/post) and typicality (typical/atypical) as within-participant variables revealed that the critical expected three-way interaction between reader type, stimulation, and typicality was significant, $F(1, 16) = 0.23, P = 0.036$. There was also a two-way interaction between typicality and reader type, $F(1, 16) = 4.90, P = 0.042$, a significant main effect of typicality, $F(1, 16) = 35.15, P < 0.0005$, and a marginally significant main effect of reader type, $F(1, 16) = 4.20, P = 0.057$.

An ANOVA on the data for low-frequency words before TMS with reader type (low SR/high SR) as a between-participants variable and typicality (typical/atypical) as a within-participant variable revealed no significant interactions or main effects. For the low SR readers, there was a marginally significant effect of reader type, $F(1, 16) = 3.76, P = 0.072$, the critical three-way interaction between reader type, stimulation, and typicality was significant, $F(1, 16) = 3.68, P = 0.072$, and there was a marginally significant main effect of reader type, $F(1, 16) = 3.25, P = 0.088$.

Table 1. Millisecond RTs of low and high SR readers on the frequency by typicality reading list completed pre-TMS and post-TMS

| Reader type | Frequency | Typicality | Pre-TMS Mean | Pre-TMS SD | Post-TMS Mean | Post-TMS SD |
|-------------|-----------|------------|--------------|------------|---------------|------------|
| Low SR      | High      | Typical   | 502          | 63         | 507           | 67         |
|             |           | Atypical   | 508          | 63         | 508           | 67         |
| Low SR      | High      | Typical   | 519          | 67         | 527           | 79         |
|             |           | Atypical   | 545          | 82         | 540           | 87         |
| High SR     | High      | Typical   | 555          | 55         | 543           | 61         |
|             |           | Atypical   | 565          | 62         | 552           | 54         |
| Low SR      | High      | Typical   | 587          | 73         | 578           | 74         |
|             |           | Atypical   | 622          | 67         | 629           | 83         |
variable revealed only significant main effects of typicality, $F(1, 16) = 19.31, P < 0.0005$, and reader group, $F(1, 16) = 4.72, P = 0.045$, with no interaction, $F(1, 16) = 0.42, P = 0.528$. After rTMS, there was a significant interaction between typicality and reader group, $F(1, 16) = 13.36, P = 0.002$, indicating that the typicality effect for the high SR readers was now significantly larger than that for the low SR readers, as can be seen in Fig. 1. There was also a significant main effect of typicality, $F(1, 16) = 38.21, P < 0.0005$, and a trend toward an effect of reader group, $F(1, 16) = 3.41, P = 0.083$. Follow-up paired $t$ tests demonstrated that the typicality effect for low-frequency words after TMS was not significant for the low SR readers, $t(1, 8) = 1.6, P = 0.148$, but was highly significant for the high SR readers, $t(1, 8) = 8.0, P < 0.0005$.

This pattern of results was confirmed by using regression to consider the extent to which degree of SR, as a continuous variable, predicted the size of typicality effects for low-frequency words. Before rTMS, there was no significant relationship between SR and the typicality effect for low-frequency words, $F(1, 16) = 0.37, P = 0.554$. In contrast, after rTMS, there was a significant relationship between SR and the typicality effect for low-frequency words, $F(1, 16) = 7.14, P = 0.017, R^2 = 31\%$. Essentially, the two groups were reading atypical words in different ways before rTMS, and disruption of semantic processing only affected the high SR readers, producing a relationship between the SR measure and the size of the typicality effect after stimulation.

An ANOVA on reaction time data for high-frequency words (Table 1) with reader type (low SR/high SR) as a between-participants variable and rTMS (pre/post) and typicality (typical/atypical) as within-participant variables revealed only a main effect of typicality, $F(1, 16) = 5.95, P = 0.027$.

Results for high- and low-frequency words were compared using an omnibus ANOVA on reaction times, with reader type (low SR/high SR) as a between-participants variable and rTMS (pre/post), typicality (typical/atypical), and frequency (high/low) as within-participant variables, and revealed a marginally significant four-way interaction, $F(1, 16) = 3.83, P = 0.068$. This result supports the previous analysis and indicates that, as predicted, the disruptive effect of TMS on atypical word reading for the high SR readers was most apparent for low-frequency words.

An omnibus ANOVA on error rates, presented in Table 2, with reader type (low SR/high SR) as a between-participants variable and rTMS (pre/post), typicality (typical/atypical), and frequency (high/low) as within-participant variables revealed only significant effects of typicality, $F(1, 16) = 50.59, P < 0.0005$, frequency, $F(1, 16) = 64.54, P < 0.0005$, and an interaction between them, $F(1, 16) = 36.18, P < 0.0005$. No other effects approached significance.

### Discussion

The influence of pre-morbid individual differences on the interpretation of post-damage neuropsychological profiles is a critical issue. Here we addressed this challenge in the domain of reading, where there is already a large body of case-series evidence showing the distribution of reading deficits observed after semantic damage and an implemented computational model that explains the variation in these deficits (7, 8). We employed rTMS to the left ATL to test the hypothesis that individual differences in degree of SR when reading atypical words produces appreciable variation in the impact of a virtual lesion. Before ATL stimulation, the two groups did not differ in their reading performance, whereas after stimulation, the typicality effect for low-frequency words was significantly greater for the high than low SR readers. In addition, the size of the typicality effect for low-frequency words was predicted by the individual differences measure.

The finding that stimulation had no appreciable impact on high-frequency words for any participants illustrates that left ATL rTMS does not interfere with reading in general. It also argues against an account of variation in stimulation effects according to SR in terms of individual differences in global susceptibility to ATL stimulation. The reading deficit we observed for the high SR readers was manifested in reaction times, as is the case for most cognitive TMS studies, including those involving ATL stimulation (25, 27, 28). Although this contrasts with the accuracy effects seen in semantic dementia patients, this is to be expected given that the neural impact of rTMS is more anatomically and temporally punctuate than that of any neurodegenerative condition.

The results of the present study are consistent with the neuropsychological data concerning atypical word reading deficits in semantic dementia (8, 29). Structural neuroimaging shows reading deficits to be associated with damage to the left ATL (ref. 30 and

| Reader type | Frequency | Typicality  | Pre-TMS Mean | SD | Post-TMS Mean | SD |
|-------------|-----------|------------|--------------|----|---------------|----|
| Low SR      | High      | Typical    | 0.53         | 1.68 | 0.53          | 1.68 |
|             |           | Atypical   | 0.53         | 1.68 | 1.06          | 2.20 |
| Low        | Low       | Typical    | 1.59         | 2.46 | 1.59          | 2.46 |
|            |           | Atypical   | 11.64        | 7.09 | 10.58         | 8.02 |
| High SR    | High      | Typical    | 0.53         | 1.68 | 1.59          | 2.46 |
|            |           | Atypical   | 3.70         | 3.37 | 3.17          | 2.20 |
| Low        | Low       | Typical    | 2.65         | 2.55 | 1.59          | 2.46 |
|            |           | Atypical   | 11.64        | 6.23 | 10.58         | 5.36 |

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A comparison of activated by atypical word reading (warm colors) and showing a positive relationship with degree of SR (cool colors) based on data from Hoffman et al. (Fig. 2).

Fig. 2. A comparison of (A) areas of left ATL atrophy in semantic dementia patients with surface dyslexia (reproduced with permission by Oxford University Press from ref. 30); (B) the area of rTMS stimulation previously shown to disrupt semantic processing (27) and targeted in the current study; and (C) the areas activated by atypical word reading (warm colors) and showing a positive relationship with degree of SR (cool colors) based on data from Hoffman et al. (31).
we report here. Specifically, lower SR readers may initially show a dissociation between impaired semantic processing and relatively intact reading performance (18–20), while higher SR readers may initially show a dissociation between impaired reading performance and relatively intact semantic processing (50, 51). Taken together, these cases provide a double dissociation between reading and meaning, the gold standard of evidence for functional independence. However, the account proposed and supported here is instead of a graded relationship between reading and meaning in the healthy population that affects the degree of association between the two capacities seen after brain damage.

While the individual differences we have reported here do pose some challenges to the traditional interpretation of neuropsychological data, these merely emphasize the importance of considering the full range of performance across a case series of patients (52). Although Shallice (1) was skeptical that individual differences could speak directly to the functional architecture, we would suggest that the individual differences in reading that we have reported are extremely theoretically informative in showing a key relationship between atypical word reading and semantic processing. This study and its linked papers (2, 8, 31) indicate that individual differences can speak directly to issues of functional architecture as long as the relevant theory has a formal way to consider individual variation. The exploration of individual differences within the implemented triangle model of reading provides a tangible example of how this can be achieved (7, 8, 44). The underlying causes for this variation have yet to be determined (2), but the connectionist triangle model is well placed to explore this issue given its focus on learnt representations. Our results suggest any neurocognitive model needs to incorporate mechanisms that permit substantial systematic individual differences in the dynamics of the reading network. Given that reading is a late-acquired skill both phylogenetically and ontogenetically (53, 54), it is a prime example of a domain in which individual differences in the normal healthy population may be at their most marked, behaviorally (2) and neurally (21, 31, 48). However, substantial normal variation is apparent in a variety of higher cognitive capacities, and the neurostimulation approach we present could be harnessed to explore the nature of individual differences in other domains.

Materials and Methods

Participants. An initial pool of 129 individuals completed a reading-aloud task designed to assess their degree of SR for atypical word reading, as described in Computation of the Individual Differences Index. Stimulus properties are provided in Table S1. All participants were University of Manchester undergraduate or postgraduate students. We recruited as many TMS eligible and willing participants as possible from the upper and lower ends of the SR distribution. We also recruited participants born to one of which was presented before TMS and one of which was presented afterward. The order of lists was balanced within group across participants.

Stimuli. The stimuli used in the TMS experiment were the 168 words from the Surface List (17). This list contains a factorial manipulation of frequency and spelling–sound and regularity, with 48 items in each cell, with properties of the stimuli provided in Table S4. This list is the same as that (i) used to quantify surface dyslexia in semantic dementia (17), (ii) to simulate this pattern within the connectionist triangle model (8), and also (iii) to determine neural activation among normal readers varying in degree of SR using fMRI (31). Accordingly, our TMS study can be directly related to these three previous, key studies. To prevent item repetition, the words were divided into two sets of 84 items, with one of which was presented before TMS and one of which was presented afterward. The order of lists was balanced within group across participants.

Procedure. The DMDX experimental software package (55) was used to record RTs and vocal responses and to display instructions and stimuli. Responses were collected by a voice-key plus headset connected to an IBM compatible Pentium III computer with a 60 Hz refresh rate at 1,280 × 1,024 pixel screen resolution. Vocal responses were recorded from the beginning of the trial for a period of 1,000 ms after the voice key triggered. Trials from all conditions were presented mixed together in a pre-stimulatur and post-stimulation block, with the order of trial presentation within each block randomized anew for each participant, and stimuli were presented in white on a black background. The assignment of item sets to pre- or post-stimulation was counterbalanced across participants. Mispronunciations and measurement errors were recorded by hand. Participants were instructed to name the centrally presented words as rapidly and accurately as possible. Trials began with a 500-ms fixation cross followed by the word that disappeared from the screen upon response or after 2,000 ms.

The study used the virtual lesion method in which there was (i) a reading-aloud task (baseline), then (ii) rTMS stimulation, and immediately after (iii) an analogous reading-aloud task (probe). This meant that rTMS was delivered without a concurrent task and all were given after either 80, 100, or 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 320, 340, 360, 380, 400, 420, 440, 460, 480, 500, 520, 540, 560, 580, 600, 620, 640, 660, 680, 700, 720, 740, 760, 780, 800, 820, 840, 860, 880, 900, 920, 940, 960, 980, 1,000, 1,020, 1,040, 1,060, 1,080, 1,100, 1,120, 1,140, 1,160, 1,180, 1,200 ms. Stimulation intensity for the experiment was determined for every participant, and stimuli were presented during the rTMS refractory period, which has been estimated to last for approximately 20 min (27). Focal magnetic stimulation was delivered using a 70-mm figure-of-eight coil attached to a MagStim Rapid2 stimulator (Magstim). Before experimental stimulation, motor threshold (MT) was determined for every participant as a visible twitch in the relaxed contralateral abductor pollicis brevis muscle in three out of six trials. Stimulation intensity for the experiment was therefore set at 20% of MT for each participant and each stimulation site. rTMS stimulation. A structural T1-weighted MRI scan was acquired for each participant to guide rTMS stimulation. The Atlas site was defined as the region 10 mm posterior from the tip of the left temporal lobe along the MTG, consistent with previous studies where left ATL stimulation has been shown to disrupt semantic processing (25–27). The average Montreal Neurological Institute coordinate for the stimulated site were −53, 13, −32 (Fig. 2B). For stimulation, this site was determined by coregistering the cortical surface with 11 anatomical landmarks (inion, tip of the nose, left/right ear canals, and left/right ear projections), some of which were marked before the scan with oil capsules (vertex, nasion, left/right ear tragus, and beneath lip in chin indentation). Coregistration was made using Ascention minibird magnetic tracking system and MriReg software (www.cabri.at/minicore/microminreg/index.html).

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