FINAL REPORT

Study Title: Examining Neural Mechanisms of Motivated Learning and Cognitive Performance in Individuals with Multiple Sclerosis: A Functional MRI Study

Study Team: PI: Christopher Cagna, PhD
Associate Research Scientist
Center for Neuropsychology and Neuroscience Research
Kessler Foundation

Co-I: Ekaterina Dobryakova, PhD
Assistant Director of Neuroscience Research
Center for Traumatic Brain Injury Research
Kessler Foundation

RA: Kai Sucich, MA
Senior Research Assistant
Center for Traumatic Brain Injury Research
Kessler Foundation

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Statement of the Problem

A common, but significant, challenge experienced by people with multiple sclerosis (MS) is cognitive impairment, with prevalence estimates as high as 90% (DeLuca et al., 2020; Chiaravalloti & DeLuca, 2008; Korakas & Tsolaki, 2016). To remediate such impairment and improve everyday functioning, people with MS often undergo cognitive rehabilitation. To achieve optimal treatment gain, participants must be able to effectively learn from information provided about their performance throughout rehabilitation. While feedback itself provides information that is instrumental for this learning, it is important to consider the motivation of the learner to engage with that information. The learning utility of feedback will be limited if the learner does not value the information that feedback provides. When individuals place high value on a stimulus, they are more motivated to approach and engage with it. Thus, greater value assigned to performance feedback increases the odds of better learning from it, since the learner is more motivated to receive it. Our previous work utilizing a feedback value task has indicated that the value attributed to feedback is relatively spared in individuals with MS. That is, they display comparable levels of motivation to receive feedback about their cognitive performance as neurologically healthy individuals (Cagna et al., 2023).

While behavioral evidence for motivated learning from feedback in people with MS is informative, it does not shed light on neural mechanisms that facilitate such learning. The current study addressed this need by investigating how the brain facilitates the perceived value placed on feedback and then translates this value into motivated learning from it. Specifically, we examined brain activity using functional MRI in participants with MS, as they completed a memory task that required them to make decisions about whether they wished to receive performance feedback while learning word matches. We quantified perceived value of feedback by assigning monetary costs to feedback, which were deducted from winnings that participants could earn during a later test phase. Findings from this study will contribute to both basic research and applied clinical translation in people with MS. Specifically, this work will elucidate brain regions critical to the interaction between motivated learning and cognitive performance in people with MS (basic research) and will also identify potential neural targets for promoting engagement to learn from their performance throughout rehabilitation and improve their treatment outcomes (applied translation).

Research Questions and Hypotheses

The overarching goal of this study was to characterize brain mechanisms underlying the subjective valuation of cognitive performance feedback in people with MS. Participants with MS completed a willingness-to-pay (WTP; Kable & Glimcher, 2007, 2009; Peters & Büchel, 2010; Rangel et al., 2008) associative memory task (Cagna et al., 2023; Cagna & Bhanji et al., 2024) while undergoing fMRI, during which they learned arbitrary pairs of words and were later tested on them. Participants earned a monetary bonus that was contingent on their performance during the test phase. Participants had the opportunity to see feedback related to their performance (i.e., response accuracy) during the learning phase at varying monetary costs. Any feedback purchased was deducted from winnings earned during the test phase. Thus, a greater proportion of decisions to purchase feedback is indicative of greater subjective value assigned to it.

The current study addressed three specific aims. **1) Characterize local activation of, and functional connections between, corticostriatal brain regions in response to performance feedback valuation in people with MS.** Given extensive evidence of the involvement of the ventral striatum (VS), caudate nucleus, and ventromedial prefrontal cortex (vmPFC) in both feedback learning (Tricomi et al., 2006; Tricomi & Fiez, 2008) and subjective valuation (Bartra et al., 2013), we hypothesized that these regions would display increased activation and functional connectivity during decisions to purchase feedback, compared to decisions to decline it, due to the higher subjective value of feedback that is motivating a decision to purchase it. Deciding to purchase feedback, with the knowledge that its cost will be deducted from any future winnings, indicates that the participant recognizes the value of the information provided by it for future test performance. Thus, these regions would likely facilitate the valuation that contributes to the motivation to purchase feedback. **2) Examine the relationship between corticostriatal brain activity and performance feedback choice behavior in people with MS.** In addition to becoming more active during decisions to purchase feedback, the VS, caudate, vmPFC, and their connections were hypothesized to predict decisions to purchase feedback. While the first aim identified whether the hypothesized regions were responsive during decisions to purchase feedback, this aim tested whether corticostriatal activity contributes to those decisions. Given the importance of corticostriatal circuitry to subjective valuation, reward, and motivated behavior (Bartra et al., 2013; Haber, 2016; Liljeholm & O'Doherty, 2012), we hypothesized that significantly greater activity in these regions would predict decisions to purchase feedback. **3) Identify individual differences in cognition that may predict differences in performance feedback valuation in people with MS.** As an additional exploratory aim, cognitive assessment using the Woodcock Johnson IV (WJ-IV) Cognitive test battery was used to identify potential contributions of other cognitive functions to subjective valuation of feedback and motivated learning in MS. Such data can be used for future work aimed at establishing cognitive profiles for people with MS who are most receptive to the value of performance feedback. Such work can potentially identify individuals who will be most (and least) responsive to cognitive rehabilitation, allowing for more precise tailoring of individualized treatments. As this aim was exploratory, we did not have explicit hypotheses for it.

Study Sample Characteristics

Sixteen participants (age range: 18-65) with relapsing-remitting MS (RRMS) were recruited. The study sample was constrained to RRMS, given its high prevalence in the MS population (Lublin et al., 2014) and differences in cognitive impairment between RRMS and other phenotypes (Johnen et al., 2017). There were no restrictions based on sex, gender, race, or ethnicity. Exclusion criteria included diagnosis of a neurological disease other than MS (e.g., epilepsy); significant history of alcohol, drug abuse, or psychiatric illness; current diagnosis of major depressive disorder, schizophrenia, or bipolar disorder; use of steroids, benzodiazepines, or neuroleptics within the past four weeks; and an exacerbation of symptoms within the past four weeks. MRI exclusion criteria included presence of ferrous metal or implanted devices in the body; claustrophobia; and pregnancy. One participant was excluded prior to data analysis due to misunderstanding the task (see "Project Challenges"). Thus, the final sample comprised the original intended sample of 15 participants. Demographic data for the final sample appear in the accompanying table.

Age (Years)	52.00 (11.01)
Education (Years)	16.27 (1.98)
Sex	60% Female 40% Male
Race/Ethnicity	73.3% Caucasian 13.3% Black/African-American 6.7% Hispanic 6.7% Other
Years Since MS Diagnosis	15.40 (10.25) Mdn. = 13.00 IQR = 15.00
Time Since Last Flare-up (Years)	4.24 (4.62) Mdn. = 2.50 IQR = 5.06

Values for age, education, years since diagnosis, and years since last flare-up of symptoms are reported as mean (standard deviation). The median (Mdn.) value and interquartile range (IQR) values are also provided for years since diagnosis and last flare-up. Percentages are provided for sex and race/ethnicity.

Principal Findings

Data analysis is ongoing. We highlight some of the principal findings in relation to each study aim below.

Aim 1: Characterize local activation of, and functional connections between, corticostriatal brain regions in response to performance feedback valuation in people with MS.

An important finding that emerged from this study was that people with MS display stronger functional connectivity between the VS (nucleus accumbens) and the vmPFC during decisions to purchase feedback, compared to decisions to decline feedback. As displayed in Figure 1, the vmPFC is indicated in blue-green, and brain areas displaying stronger connectivity with it are displayed in warm colors. <u>This supports our hypothesis that brain regions historically associated with reward and value integration are recruited during motivated learning in people with MS (i.e., when participants are willing to buy performance feedback information)</u>. Other regions that the vmPFC shared stronger connectivity with during Purchase (vs. Decline) decisions include the thalamus, medial temporal gyrus, and insula.

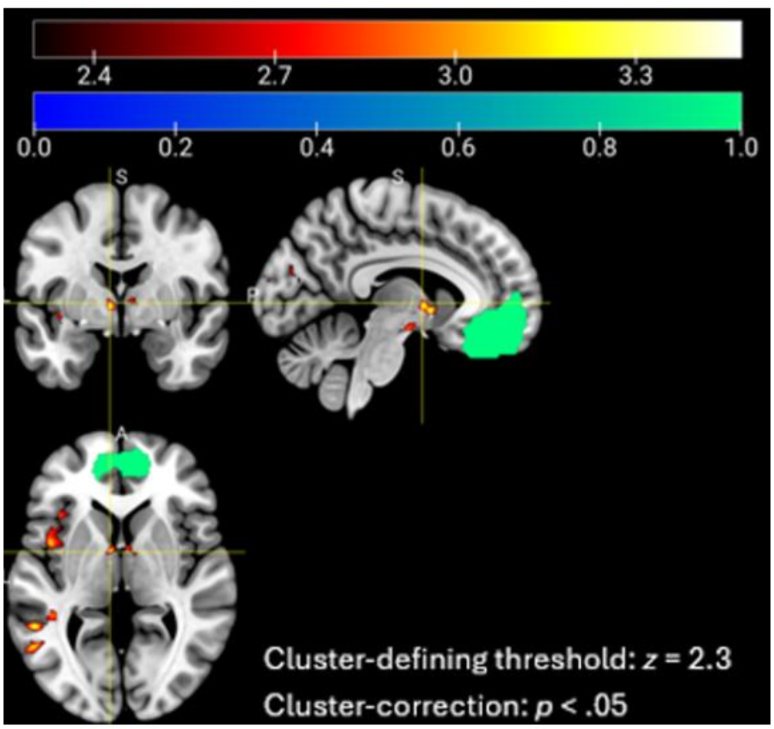

Fig. 1

2) Examine the relationship between corticostriatal brain activity and performance feedback choice behavior in people with MS.

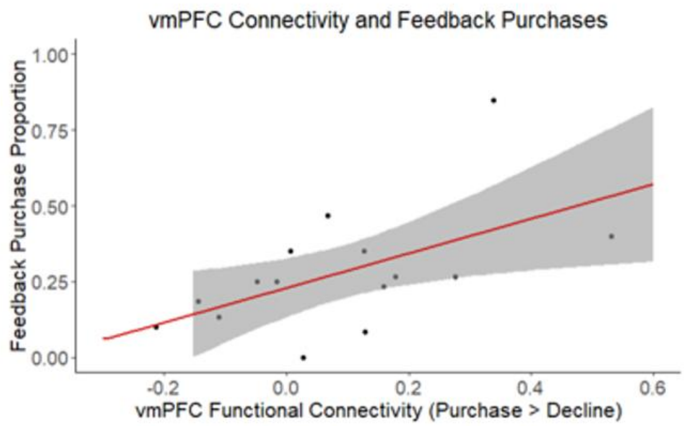

Fig. 2

Importantly, this stronger vmPFC connectivity during Feedback Purchase vs. Decline decisions significantly <u>predicted</u> feedback choice behavior. We constructed a generalized logistic mixed model with the following parameters: outcome variable: binary feedback choice (purchase, decline); fixed effects: age, education, sex, VAS-F fatigue rating (i.e., self-reported fatigue during the task), confidence ratings, feedback cost, and parameter estimates of the aforementioned vmPFC connectivity. Likelihood ratio tests revealed that the stronger vmPFC connectivity that occurred during "Purchase" decisions made a significantly independent contribution to predicting the likelihood of a participant opting to purchase feedback [$X^2(1) = 5.23$, $p = .02$] – above and beyond the influences of age, education, sex, task fatigue, feedback cost, and confidence. Parameter estimates of this effect indicated that this stronger vmPFC connectivity predicted <u>higher</u> likelihood of choosing to purchase feedback ($b = 9.02$, $b_{SE} = 3.58$). These results further bolster confidence that the differential brain activation occurring during Purchase decisions is actually influencing the willingness to buy feedback (and more broadly, the motivation to learn from it.). Scatterplot displaying subject-level relationships between these variables appears in Figure 2.

3) Identify individual differences in cognition that may predict differences in performance feedback valuation in people with MS.

For this exploratory aim, we conducted trial-level generalized logistic mixed models and subject-level Pearson correlation analyses to identify potential individual differences in cognitive capacities that could predict motivated learning (i.e., feedback purchases) in people with MS. Binary feedback choice (purchase, decline) was the dependent variable in mixed models. Feedback purchase proportion (i.e., number of "Purchase" decisions divided by 60) were used in Pearson correlation analyses. We constructed models for the following tests of the WJ-IV Cognitive battery: Letter-Pattern Matching, General Information, Picture Recognition, and Memory for Words. We also did the same for other neuropsychological measures, including the Symbol Digit Modalities Test (SDMT; Smith et al., 1982), California Verbal Learning Test – Second Edition (CVLT-II; Delis et al., 2000), Brief Visuospatial Memory Test – Revised (BVMT-R; Benedict et

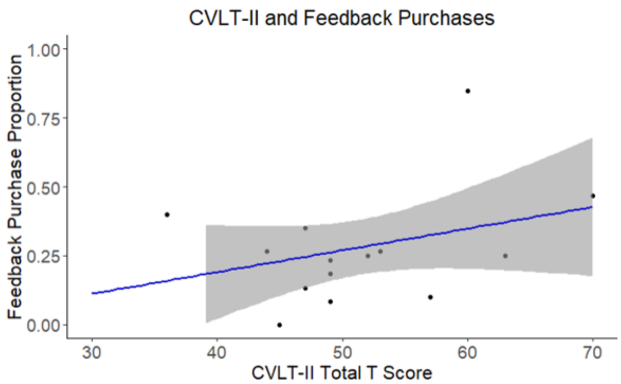

Fig. 3

al., 1996); and the Wechsler Adult Scale of Intelligence – Second Edition (WASI-II; Wechsler, 2011) Vocabulary Test. The only test to emerge as a *marginal* predictor of feedback purchase likelihood was the CVLT-II [$X^2(1) = 3.06$, $p = .08$], such that individuals who performed better on the CVLT-II (total score) were marginally more likely to purchase feedback throughout the task ($b = 0.16$, $b_{SE} = 0.09$) (Fig. 3). This finding suggests the possibility that individuals with MS whose verbal learning and memory abilities are intact may be more likely to recognize the learning utility of feedback for aiding performance on a verbal associative memory task. Future work will need to examine whether this effect is due to a unique contribution of verbal learning and memory or simply due to the verbal nature of the task. Thus, we advise caution with this finding, as it is exploratory, marginally significant, and is derived from a small sample.

We also examined potential cognitive influences on task performance – trial-level accuracy during the test phase (correct, incorrect) for mixed models and percentage of correct responses during the test phase for subject-level Pearson correlation analyses. The WJ-IV Picture Recognition Test and the WASI-II Vocabulary Test each displayed positive moderate associations with test performance. Individuals who scored higher on WJ-IV Picture Recognition ($r = .67$, $p = .01$; Fig. 4) and on the WASI-II Vocabulary Test ($r = .58$, $p = .04$; Fig. 5) tended to correctly recall more words during the test phase of the WTP task. The WASI-II Vocabulary Test is a measure of premorbid verbal intelligence; therefore, it makes sense that individuals with MS with higher levels of it would also do well on this task. The WJ-IV Picture Recognition Test assesses visual memory, specifically for objects and pictures. The fact that participants who scored higher on this test also tended to perform well on the verbal-based study task might suggest a more "generalized" benefit across different memory types in aiding performance. While these results are interesting, we also advise caution with each of them, given the small sample size, though they may be interesting avenues for future work.

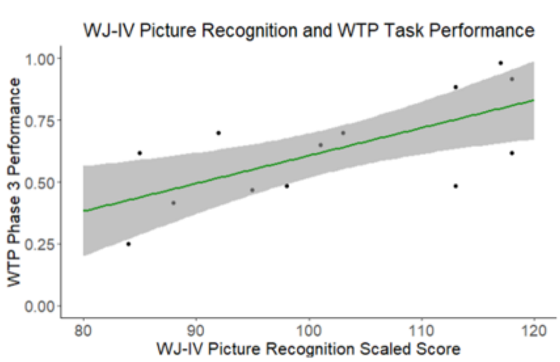

Fig. 4

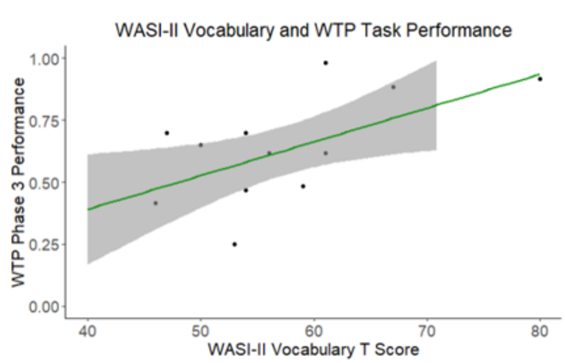

Fig. 5

Implications for Research and Clinical Practice

The results from this study demonstrate the importance of the vmPFC and its functional connections in encoding the perceived value assigned to performance feedback and facilitating motivated learning from it in people with MS. Our study provides neural evidence that well-established value regions (vmPFC) are not only active when determining feedback value but that this activity *contributes to* the motivation to learn from it. This work also indicates the potential importance of verbal learning and memory. Rehabilitation efforts are most effective when tailored to the needs of an individual. Thus, this work indicates that individuals with MS who display reduced verbal learning and memory capacities may require additional efforts to engage motivated learning throughout an intervention. This is sensible given that performance feedback provided by clinicians or therapists in rehabilitation settings is typically conveyed verbally (either spoken or in writing). Future work with larger samples will be needed to investigate this possibility further.

Collectively, the results of this investigation provide an exciting avenue for future research to examine other factors that might directly influence these neural circuits and their relationship with motivated learning. They also provide insight to clinical settings by identifying certain cognitive profiles to consider when working with individuals with MS.

Project Successes

This pilot investigation yielded critical preliminary data for the previously "missing piece" of brain mechanisms underlying the motivation to learn from cognitive performance feedback in people with MS. On a broader level, this work provides neural insights for better understanding the motivated learning that is integral for rehabilitation success in MS and other clinical groups. It also sheds light on individual difference factors that may influence this motivated learning, which can further inform the tailoring of rehabilitation protocols to maximize treatment gain.

With respect to additional funding successes stemming from this Research Grant, data from this project were used as preliminary data for a National Multiple Sclerosis Society Career Transition Award application, which was recently funded (PI: Cagna; $620,000 total costs). This 5-year award will build upon the findings from this project by examining how mental effort influences brain mechanisms underlying motivated learning in people with MS. The Woodcock Institute Research Grant played a pivotal role in spearheading this line of research and also in securing additional funding to continue it. The research team extends its sincerest appreciation to the Woodcock Institute.

Project Challenges

As is possible with any research project, there were minor challenges that delayed the intended timeline of the project. Participant recruitment was more challenging than expected for a single-day, single-session study. In addition to more typical issues such as participant last-minute cancellations/rescheduling, there was also the additional challenge of summer weather slowing down recruitment during those months (Flare-ups in relapsing-remitting MS are more common in hotter temperatures). While we were able to successfully recruit the entire sample within the funding period, it was at a later date than we had planned. Additionally, one participant needed to be excluded from the final sample after they reported a fundamental misunderstanding of the task paradigm after the scan (despite the participant reporting understanding during the practice task beforehand). Thus, their performance data (and accompanying brain data) were invalid. In response, we received approval from the Woodcock Institute to re-allocate surplus funds in our award to include an additional participant. Thus, we were able to acquire our intended sample of 15 participants. Despite these minor delays and challenges, we are now actively preparing conference abstracts and publications (as described below).

Papers and Presentations

Presentations: Oral presentation/poster abstracts based on this project's work will be submitted for the next annual meetings of the Society for Neuroscience and the International Neuropsychological Society. Titles TBD.

Publications: Manuscript preparation for this project has begun, with the goal to submit by Fall 2026. Title TBD.

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