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Feasibility of an online cognitive rehabilitation program in patients with a haematological malignancy undergoing autologous stem cell transplantation

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Abstract

Background: Chemotherapy related cognitive impairment (CRCI) is a known adverse event that can impact cancer survivors, resulting in long-standing effect on quality of life (QOL) and activities of daily living (ADL). Currently, there is limited knowledge regarding the etiology and therapy for CRCI. Although CRCI following autologous stem cell transplantation (AuSCT) is emerging as a potentially significant concern for patients with underlying haematological malignancies, it is an area that requires further research.

Aims: This pilot study assessed 1) the prevalence of CRCI in patients with haematological malignancies both pre-AuSCT and post-AuSCT, 2) the feasibility of a cognitive rehabilitation program (CRP) in survivorship care post-AuSCT.

Methods: Over a 12 month period, consecutive patients planned for AuSCT were approached for the study. Enrolled patients were administered a nine-week course of CRP, commencing day 40±5 post-AuSCT. Participants were evaluated using a neuropsychological tool and validated questionnaires at baseline, pre-CRP (day 40±5 post-AuSCT), post-CRP and six months post-CRP.

Results: Thirty-two patients were enrolled. The mean age was 59 years (SD=11.5), 23 (72%) were male and 18 (56%) had multiple myeloma. Participants reported high satisfaction using the CRP, and most devoted significant amount of time as requested.

Conclusions: While there appeared to be a low incidence of significant CRCI in our patient population, the incorporation of CRP in survivorship care appeared to be feasible. A larger randomised study examining the efficacy of CRP should be further explored.

Key words: Cognitive rehabilitation, cognitive impairment, chemotherapy, survivorship, haematological malignancy.

Introduction

Chemotherapy related cognitive impairment (CRCI) is a highly distressing and disabling adverse event commonly reported by cancer patients (1, 2). The incidence varies, but studies in solid tumour patients suggested that up to 70% of patients receiving chemotherapy self-report some degree of CRCI (1-6). The cognitive domains most commonly affected are memory, concentration, information processing speed and executive function (1, 6, 7-9). For some, CRCI may be subtle and transient, but for many these symptoms can be long-standing and have a major impact on quality of life (QOL) and activities of daily living (ADL) (2).

Haematopoietic stem cell transplantation is utilised for many haematological malignancies. It is preceded by high-dose conditioning chemotherapy, and patients are at risk of developing CRCI (10-12). Autologous stem cell transplantation (AuSCT) involves harvesting the patients' own stem cells, with subsequent reinfusion back into the patients post high-dose chemotherapy. CRCI following AuSCT is emerging as a potentially significant concern for these patients (10-12). While a few studies have investigated neuropsychological functioning in haematopoietic transplant recipients (10-12, 16-23), the effect of CRCI post-AuSCT has not been fully elucidated and needs further research (14-23). Moreover, currently no specific treatment strategy for CRCI is in routine practice.

Cognitive rehabilitation programs (CRPs) aim to improve or restore cognitive function, and have the potential to increase QOL for those with CRCI (24-29). A number of studies have examined CRPs as a potential tool to enhance the cognitive abilities of patients, including cancer survivors post chemotherapy, with encouraging results (27-29). Many have also reported improvements in psychological, physical and social functions (24, 26). A recent randomised controlled trial (RCT) evaluated the efficacy of an online CRP in survivors of solid tumours. The study reported a significant improvement in perceived cognitive impairment in the CRP group compared to the non-CRP group. There was also significantly lower levels of anxiety, depression and fatigue favouring the CRP intervention (30). Online

CRP also enables access to a validated health tool in the community, ideally linked into an existing survivorship program.

The primary goal of this pilot study was assess the implementation of an online CRP as part of routine post-AuSCT cognitive care for patients treated for a haematological malignancy. The secondary goal was to evaluate the incidence of CRCI in this patient cohort, both pre-AuSCT and post-AuSCT.

Materials and Methods

Study Design

This was a multicentre, single arm pilot study. The lead site was a major tertiary referral hospital with an existing dedicated, multidisciplinary Haematology Survivorship Clinic providing holistic care for patients post treatment completion. The other participating sites were satellite sites referring patients for AuSCT. Figure 1 summarises the routine clinical care (red boxes), the study procedure (blue boxes) and the study assessment time points (green boxes). Consecutive potential AuSCT patients presenting to the lead site were considered for the study. The study was discussed with the patients and those interested were provided with a Patient Information and Consent Form (PICF). Patients enrolled onto the study were administered a baseline cognitive assessment pre-AuSCT (T1). A post-AuSCT cognitive assessment was performed on day 40±5 post-AuSCT (T2), giving the patients adequate time to recover from their transplant. During T2 assessment participants were educated and trained about the online CRP. The target usage time was 120-minutes per week for nine consecutive weeks, which was modified based on published evidence of efficacy with this CRP to improve compliance. An evaluation survey was completed six weeks into the CRP, as well as at the completion of the CRP to determine the patients' perceptions of satisfaction and usability of the CRP. A third cognitive assessment was performed (T3) one-week post

completion of the CRP intervention. A final cognitive assessment occurred at six months to determine the sustainability of findings observed (T4).

Full high-risk ethics approval was obtained in September 2016 from the Human Research Ethics Committee (HREC) of the lead site. This HREC operates in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Research Involving Humans (2007), the Note for Guidance on GCP, the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988.

Cognitive assessment and data collection

Both qualitative and quantitative data were collected and analysed. Demographic data was collected and recorded from the patients' electronic medical records. At each of the four cognitive assessments, patients were evaluated using CogState, a computerised neuropsychological tool. CogState measures objective cognitive function including memory, attention and executive function (31-33). Patients also completed validated questionnaires assessing subjective cognitive function, anxiety and depression, QOL and stress at the four time points. The questionnaires used in this study were:

1. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Cognitive Functioning subscale (EORTC QLQ-CF) (34)
2. Functional Assessment of Cancer Therapy – Cognition subscale (FACT-COG) (35)
3. Functional Assessment of Cancer Therapy – Bone Marrow Transplant subscale (FACT-BMT) (36)
4. Hospital Anxiety and Depression Scale (HADS) (37)
5. The Perceived Stress Scale – 14 items (PSS-14) (38)

A 25-item survey was also developed purposely for this study. It contained seven sections: ease of learning, perceived efficacy, usability, satisfaction, compliance, predicted future use and the World Health Organization 5-item Well-Being Index (WHO-5).

Intervention

The CRP chosen for this study was BrainHQ from Posit Science, an internet accessible CRP designed to enhance multiple cognitive domains such as memory and attention (39, 40). This CRP targets visual and auditory processing systems, aiming to result in cognitive improvement by enhancing information processing (39), and targets specific cognitive domains such as attention, memory and navigation. The program has been validated in cancer populations (26) and was supplied at no cost to the participants.

Statistical Methods

Statistical analyses were undertaken with Stata software V.14IC (StataCorp, College Station, TX, USA). The total compliance outcome was estimated as a proportion of patients achieving the total intervention time of 1080 minutes over the course of nine weeks with corresponding 95% confidence interval. An additional analysis of a percentage of individual compliance weeks per patient (defined as a number of weeks a patient achieving intervention time of 120 minutes over the course of an individual week out of the total of nine weeks) was undertaken. Treatment effects were estimated using a random-effect linear regression model with the value of a given outcome as the dependent variable, individual time points as independent variables (using the baseline time as a reference point), and patients as random effects due to the repeated measures. The effects were reported as mean differences of the outcome value at a given time point compared to the baseline value of the same outcome measure with corresponding 95% confidence intervals.

Results

Between November 2016 and July 2017, 60 patients were assessed for study eligibility. Of these, 47 (78%) patients were eligible. Most common reasons for ineligibility were lack of English skills to follow CRP instructions, or that AuSCT was not within required study timeframe. Thirty-two patients consented to the study (recruitment rate 68%). Major reasons for decline were refusal to travel to lead site and a lack of interest in cognitive rehabilitation.

The demographic and clinical characteristics of the study participants are presented in Table 1. The mean age was 59 years (SD=11.5), 23 (72%) were male, 18 (56%) had multiple myeloma and 12 (38%) had lymphoma. All patients had previously completed chemotherapy, and the mean time since diagnosis was 4.2 years (SD=5.8). 16 out of 18 myeloma patients had received AuSCT upfront, with VCD (bortezomib, cyclophosphamide and dexamethasone) being the most commonly used induction treatment. The remaining two myeloma patients both had 2 prior lines of therapy before their AuSCT. Conversely, all 12 lymphoma patients had undergone AuSCT as part of their salvage therapy (second line treatment), with gemcitabine based regimens and ICE (ifosfamide, carboplatin and etoposide) being the most frequently used salvage chemotherapy. The study population was highly educated, with 20 patients (63%) holding a tertiary degree.

Overall, implementation of the online CRP appeared feasible

Overall, there was high satisfaction with the online CRP. The participants found it to be user-friendly and felt it improved their cognitive functions. The average total training time was 1004 minutes (45 - 3731 minutes), which was within the confidence interval of the recommended 1080 minutes. Nonetheless, only ten (40%) patients completed the recommended CRP prescription in the nine-week timeframe. Furthermore, only about half (48.72%) of the weeks recorded met the 120 minute goal. Reasons for CRP

non-compliance included time constraints due to employment or lifestyle (n=13, 52%), disease progression and/or hospitalisation (n=8, 32%), and lack of internet access or computer issues (n=4, 16%).

The incidence of cognitive impairment pre-AuSCT and post-AuSCT appear to be low

Although the sample size was small, the results demonstrated a lower than expected incidence of CRCI pre-AuSCT. This possibly reflected the fact that the majority of participants had multiple myeloma, and antimyeloma regimens are usually well tolerated. More surprisingly, the incidence of CRCI post-AuSCT was similar to pre-AuSCT, based on both subjective measures with validated questionnaires as well as with objective Cogstate measures. As Table 2 shows, when comparing the various facets of cognition between Time 1 (pre-AuSCT) and Time 2 (40 days post-AuSCT), there did not appear to be significant deterioration overall, except for FACT-BMT total score. Other parameters did not display evidence of worsening CRCI at Time 2 either.

Improved subjective measures of cognitive function and QOL was observed over time

The various domains of the participants' cognitive functions were analysed using validated questionnaires and Cogstate. These scores were compared to T1, and as demonstrated by Table 3 the participants appeared to show an improvement in the subjective measures of cognition, including QOL, stress, and depression scores. In general, the subjective cognitive scores improved over time, and whether that effect was due to CRP efficacy or just recovery due to time could not be definitively answered in this study. Conversely, the Cogstate scores did not reflect objective improvements over time.

Discussion

Cancer-related cognitive impairment (CRCI) is an emerging treatment related toxicity that has been shown to occur in the majority of patients post chemotherapy (1-6). Affected areas include memory, attention and executive function, and effects can be long lasting (1, 6-9). As a result, cancer survivors could be severely impacted with regards to their QOL and activities of daily living.

This multi-site collaborative pilot study is one of the first in the world to not only assess the prevalence of CRCI in haematological patients pre- and post-AuSCT, but also to analyse the feasibility of utilising an online CRP as part of survivorship care in this patient population. Both subjective assessment tools (validated questionnaires) and objective tool (Cogstate) were utilised to assess the study patients.

The prevalence of reported CRCI pre-AuSCT was lower in this cohort than previous studies (16, 17), likely reflecting the tolerability of current antimyeloma regimens, and the fact that AuSCT is now used predominantly in the upfront setting. Therefore the majority of myeloma patients were not heavily pretreated. Given that the lymphoma patients had received more intense chemotherapy prior to the AuSCT, a future study of only lymphoma patients may demonstrate a higher CRCI. More surprisingly, the incidence of CRCI post-AuSCT was lower than expected. Larger studies are required to confirm these findings and more importantly, to elucidate the timepoints of CRCI in this population of patients.

The online CRP was deemed to be favourable by the study cohort, and the implementation appeared to be feasible. The mandated usage time was high, and the average training time was within the confidence intervals of the target. The predominant reasons for noncompliance were due to employment and lifestyle factors, and not flaws identified with the CRP itself. The study demonstrated that it was possible to incorporate CRP in routine survivorship care, despite the low prevalence of CRCI in this cohort. Furthermore, the subjective cognitive improvement post-AuSCT could possibly be related to the natural recovery over time, and a randomised study is needed to further evaluate the efficacy of CRP in this

context. With ever-improving progression free survival and overall survival, cognitive survivorship management will only become increasing relevant in patients with haematological malignancies. Interestingly, a previous study (30) using the same intervention in an oncology cohort also demonstrated subjective improvement only.

Conclusion

In this cohort, the prevalence of reported CRCI both pre-AuSCT and post-AuSCT was found to be lower than expected, which might reflect the tolerability of the chemotherapy administered. While there appeared to be a low incidence of significant CRCI in our patient population, the incorporation of CRP in survivorship care appeared to be feasible. A larger randomised study examining the efficacy of CRP should be further explored.

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Figure 1. Study schema

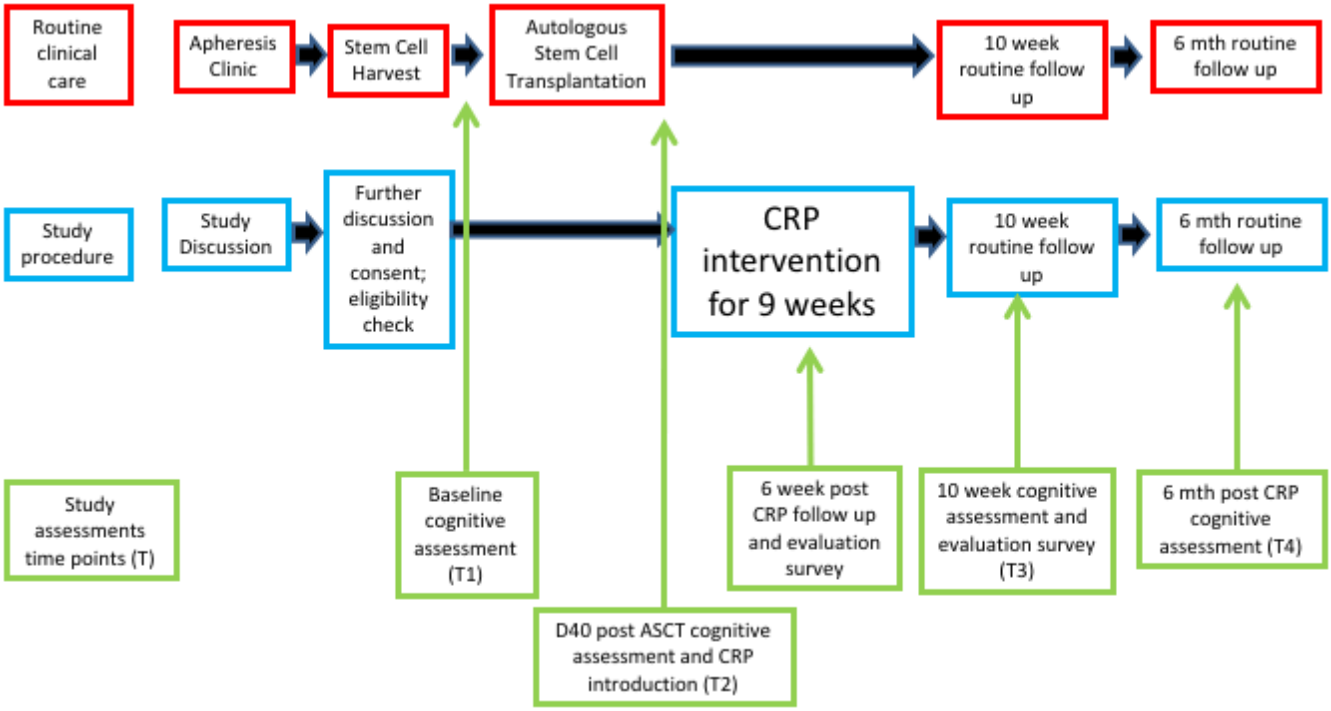

Table 1. Baseline demographic and clinical characteristics (n=32)

Characteristics	n = 32	%
Sex		
Male	23	71.9%
Female	9	28.1%
Age, years		
Mean (SD)	58.7 (11.5)	
Range	28 - 74	
Diagnosis		
Multiple myeloma	18	56.3%
Non-Hodgkin's lymphoma	8	25.0%
Hodgkin's lymphoma	4	12.5%
Amyloidosis	2	6.3%
Time since diagnosis, years		
Mean (SD)	4.2 (5.8)	
Range	0.3 - 20	
Conditioning Regimen		
Melphalan 200mg/m2	14	43.8%
BEAM	10	31.3%
Melphalan 140mg/m2	5	15.6%
Other	3	9.4%
Cancer Treatment Modality		
Chemotherapy	32	100.0%
Chemotherapy & Radiotherapy	21	65.6%
ECOG Performance Status		
0	19	59.4%
1	13	40.6%
Educational attainment		
< Year 12	8	25.0%
Year 12	4	12.5%
Associate's degrees	6	18.8%
Bachelor’s degrees	11	34.4%
Master’s degrees	2	6.3%
Doctoral Degree	1	3.1%
Employment status		
Employed (working >30 hr)	4	12.5%
Employed (working 10 - 30 hr)	6	18.8%
Employed (working <10 hr)	3	9.4%
Employed (leave)	2	6.3%
Retired/pensioner	10	31.3%
Not employed	7	21.9%

Abbreviation: SD, standard deviation; BEAM: BiCNU, etoposide, cytarabine, melphalan; ECOG: Eastern Cooperative Oncology Group.

Table 2 Comparison of findings from Time 1 to Time 2.

Scale	Time 1 (pre-AuSCT)	Time 2 (post-AuSCT)
Cohen Perceived Stress	**n=30**	**n=29**
mean (SD)	12.57 (5.92)	12.59 (6.79)
median (IQR)	12 (8, 18)	15 (6, 17)
EORTC QLO-C30	**n=30**	**n=30**
mean (SD)	77.77 (18.74)	74.99 (17.88)
median (IQR)	83.33 (66.67, 100)	83 (66.67, 83.33)
FACT-BMT total	**n=30**	**n=30**
mean (SD)	112.24 (17.46)	107.04 (19.48)
median (IQR)	111 (102, 123)	106 (91, 123)
PWB domain		
mean (SD)	20.7 (4.02)	19.27 (4.68)
median (IQR)	20.5 (18, 24)	19.5 (15, 23)
SWB domain		
mean (SD)	23.97 (3.34)	23.68 (3.21)
median (IQR)	24 (22, 27)	24 (21, 26)
EWB domain		
mean (SD)	19.4 (3.5)	19.87 (3.77)
median (IQR)	20 (18, 22)	20.5 (18, 23)
FWB domain		
mean (SD)	19.33 (5.53)	17.9 (5.76)
median (IQR)	19.5 (15, 23)	18 (14, 22)
BMTS domain		
mean (SD)	29.17 (4.65)	26 (5.77)
median (IQR)	29 (26, 32)	26 (21, 29)
BMT TOI domain		
mean (SD)	68.87 (12.87)	63.5 (14.51)
median (IQR)	68.5 (61, 79)	62 (56, 76)
FACTG domain		
mean (SD)	83.4 (13.75)	80.71 (14.18)
median (IQR)	84 (75, 91)	80 (72, 91)
FACT-Cog	n=30	n=30
mean (SD)	101.8 (21.25)	102.47 (20.3)
median (IQR)	102 (85, 121)	101 (92, 118)
HADS (Anxiety)	n=29	n=30
mean (SD)	4.69 (3.21)	4.5 (3.28)
median (IQR)	4 (2, 7)	4 (2, 6)
HADS (Depression)	n=29	n=30
mean (SD)	4.1 (3.00)	5.07 (3.44)
median (IQR)	4 (2, 6)	5 (2, 7)
CogState Subdomains		
Detection	n=30	n=30
mean (SD)	103.9 (8.79)	102.27 (8.48)
median (IQR)	106 (100, 110)	102.5 (98, 109)

Identification		
mean (SD)	102.73 (5.02)	102.43 (5.46)
median (IQR)	102 (100, 105)	102 (100, 105)
Learning		
mean (SD)	101.77 (4.99)	103 (6.1)
median (IQR)	103 (98, 104)	103.5 (99, 106)
Speed		
mean (SD)	98.83 (4.71)	99.57 (4.7)
median (IQR)	98 (97, 100)	100 (97, 102)
Accuracy		
mean (SD)	104.67 (7.81)	105.33 (8.83)
median (IQR)	103 (100, 107)	106.5 (103, 116)
Maze		
mean (SD)	97.87 (5.35)	101.2 (7.19)
median (IQR)	98 (95, 101)	102 (97, 106)

Table 3 Findings over subsequent timepoints compared to Time 1

Scales	**Treatment effect**	**95% CI**	**p-value**
Cohen Perceived Stress			
Time 2	0.28	[-1.49, 2.05]	p=0.758
Time 3	-1.68	[-3.55, 0.19]	p=0.078
Time 4	-2.69	[-4.59, -0.79]	p=0.005
EORTC QLO-C30			
Time 2	-2.78	[-9.09, 3.53]	p=0.388
Time 3	5.98	[-0.74, 12.70]	p=0.081
Time 4	5.98	[-0.83, 12.79]	p=0.085
FACT-BMT total			
Time 2	-5.19	[-9.68, -0.71]	p=0.023
Time 3	3.65	[-1.14, 8.46]	p=0.135
Time 4	9.58	[4.71, 14.45]	p<0.00001
PWB domain			
Time 2	-1.43	[-2.87, -0.001]	p=0.050
Time 3	1.06	[-0.47, 2.58]	p=0.175
Time 4	2.5	[0.95, 4.05]	p=0.002
SWB domain			
Time 2	-0.29	[-1.27, 0.69]	p=0.566
Time 3	-0.15	[-1.19, 0.90]	p=0.785
Time 4	0.43	[-0.63, 1.49]	p=0.424
EWB domain			
Time 2	0.47	[-0.31, 1.24]	p=0.237
Time 3	0.28	[-0.55, 1.10]	p=0.512

Time 4	0.74	[-0.10, 1.58]	p=0.085
FWB domain			
Time 2	-1.43	[-2.88, 0.02]	p=0.053
Time 3	1.47	[-0.07, 3.03]	p=0.062
Time 4	2.88	[1.30, 4.45]	p<0.00001
BMTS domain			
Time 2	-3.17	[-4.84, -1.49]	p<0.0001
Time 3	0.45	[-1.33, 2.24]	p=0.617
Time 4	2.51	[0.69, 4.32]	p=0.007
BMT TOI domain			
Time 2	-5.37	[-9.22, -1.52]	p=0.006
Time 3	3.48	[-0.63, 7.59]	p=0.097
Time 4	8.37	[4.20, 12.54]	p<0.0001
FACT-G domain			
Time 2	-2.69	[-5.92, 0.54]	p=0.103
Time 3	2.69	[-0.76, 6.16]	p=0.127
Time 4	6.56	[3.05, 10.08]	p<0.0001
FACT-Cog			
Time 2	0.67	[-5.44, 6.78]	p=0.830
Time 3	5.61	[-0.91, 12.14]	p=0.092
Time 4	4.74	[-1.87, 11.36]	p=0.160
HADS (Anxiety)			
Time 2	-0.46	[-1.35, 0.42]	p=0.307
Time 3	-0.28	[-1.22, 0.67]	p=0.567
Time 4	-0.8	[-1.76, 0.16]	p=0.103
HADS (Depression)			
Time 2	0.78	[-0.30, 1.86]	p=0.158
Time 3	-0.45	[-1.59, 0.71]	p=0.449
Time 4	-1.3	[-2.47, -0.13]	p=0.029
CogState Subdomains			
Detection			
Time 2	-1.63	[-4.08, 0.81]	p=0.191
Time 3	-2.42	[-5.07, 0.23]	p=0.074
Time 4	-1.32	[-3.97, 1.33]	p=0.329
Identification			
Time 2	-0.3	[-1.61, 1.01]	p=0.654
Time 3	1.76	[0.33, 3.18]	p=0.016
Time 4	0.18	[-1.24, 1.6]	p=0.803
Learning			
Time 2	1.23	[-0.85, 3.32]	p=0.246
Time 3	2.68	[0.44, 4.93]	p=0.019
Time 4	1.92	[-0.33, 4.17]	p=0.094
Speed			

Time 2	0.73	[-0.59, 2.06]	p=0.277
Time 3	2.76	[1.33, 4.20]	p<0.00001
Time 4	1.98	[0.55, 3.42]	p=0.007
Accuracy			
Time 2	0.66	[-2.98, 4.31]	p=0.720
Time 3	0.54	[-3.36, 4.45]	p=0.785
Time 4	-0.09	[-3.99, 3.81]	p=0.963
Maze			
Time 2	3.33	[1.21, 5.46]	p=0.002
Time 3	3.64	[1.34, 5.95]	p=0.002
Time 4	2.88	[0.58, 5.19]	p=0.014