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Serial position ratios and Glutamate

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Abstract

Glutamate is the principal excitatory neurotransmitter in the central nervous system, and is thought to be involved in the process of memory encoding and storage. Glutamate disturbances have also been reported in psychiatric disorders, such as schizophrenia and major depressive disorder (MDD), and in Alzheimer's disease. In this paper, we set out to study the relationship between cerebrospinal fluid (CSF) glutamate levels and memory performance, which we believe has not been reported previously. In particular, we focused on recall performance broken down by serial position. Our prediction was that the recency ratio (Rr), a novel cognitive marker of intellectual impairment, would be linked with CSF glutamate levels. We studied data from a group of cognitively intact elderly individuals, 28 of whom had MDD, while 19 were controls. Study results indicated that Rr levels, but no other memory score, were inversely correlated with CSF glutamate levels, although this was found only in individuals with late-life MDD. For comparison, glutamine or GABA were not correlated with any memory performance measure.

Keywords: Memory; Serial Position; Major depressive disorder; Glutamate.

Introduction

Serial position effects in memory refer to the fact that items learned either at the beginning (primacy) or at the end (recency) of a study list tend to be remembered better than items in the middle (Ebbinghaus, 1902; Murdock, 1962), especially when memory is tested immediately after learning (immediate recall). In neurodegenerative disorders, such as Alzheimer's disease (AD), immediate recall serial position patterns are also present, although primacy effects are typically attenuated, whereas recency effects are emphasised (e.g., Foldi, Brickman, Schaefer & Knutelska, 2003). In contrast, after a delay (delayed recall), individuals with AD usually show a pronounced memory deficit for recency items (Carlesimo, Sabbadini, Fadda & Caltagirone, 1995). Based on the discrepancy between immediate and delayed recency in AD, Bruno, Reichert and Pomara (2016a) have proposed that a ratio measure obtained from these two scores, i.e., the recency ratio (Rr), may be a useful cognitive marker of intellectual impairment, with higher ratios linked with more risk of cognitive decline. In support of their claim, Bruno et al. observed that cognitively intact elderly participants with higher baseline Rr scores displayed more pronounced subsequent cognitive decline as compared with participants with lower Rr levels. Similarly, Bruno, Koscik, Pomara and Johnson (2016b) have shown that Rr is also positively associated with risk of a diagnosis of amnestic mild cognitive impairment, a condition thought to anticipate AD.

Bruno et al. (2016a, 2016b) did not investigate the neurobiological mechanisms underlying the link between Rr scores and potential cognitive impairment, but suggested that higher Rr scores may be due to impaired consolidation, as Rr increases when information is learned initially, but then lost over the intervening delay. Synaptic consolidation, referring to the process of creation and maintenance of memory traces, is thought to depend in the first instance on the mechanism of long-term potentiation (LTP; e.g., Bosch et al., 2014). In turn, LTP relies on the release of glutamate (L-glutamic acid; e.g., Luscher & Malenka, 2012), which is the principal excitatory neurotransmitter in the central nervous system (Riedel, Platt & Micheau, 2003). Disrupted glutamatergic neurotransmission has been reported previously in AD (e.g., Butterfield & Pocernich, 2003; Pomara et al., 1992), as well as other disorders, such as schizophrenia (e.g., Hashimoto, 2014; Hashimoto, Engberg, Shimizu, Nordin, Lindström & Iyo, 2005) and late-life major depressive disorder (MDD;

e.g., Hashimoto et al., 2016). Therefore, given the link between Rr, memory plasticity and consolidation, and risk of cognitive decline, we hypothesised that higher Rr scores may also be associated with a disruption of glutamate levels in the central nervous system.

To test this hypothesis, we examined whether Rr (measured with the Buschke Selective Reminding Test, BSRT) was associated with glutamate levels in a group of cognitively intact elderly participants, subdivided into participants who had a diagnosis of MDD, which has been linked with AD risk (e.g., Byers & Yaffe, 2011) and loss of episodic memory (e.g., Fossati et al., 2004), and healthy controls. Glutamate levels were derived from cerebral spinal fluid (CSF), obtained via lumbar puncture. For comparison, we also evaluated ratios at other serial positions, total memory performance, and both glutamine, an amino-acid involved in the glutamate cycle, and GABA (γ-Aminobutyric acid), which is the main inhibitory neurotransmitter in the central nervous system.

Methods

Participants. Recruitment was part of a study on late-life MDD, conducted at the Nathan Kline Institute for Psychiatric Research, and the New York University School of Medicine. Participants provided informed consent before testing and received up to $450.00 in compensation for their time. The initial sample comprised 133 participants, which was then reduced to 47 by removing all individuals for whom no CSF was collected, or presenting MRI evidence of confluent deep or periventricular white matter hyperintensities, or with a Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) score below 28. A total of 28 participants had a diagnosis of MDD, confirmed by a board-certified psychiatrist based on clinical evaluation and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID); 19 participants were healthy controls. None were diagnosed as having cognitive impairment. Demographic characteristics of the two cohorts can be viewed in the Table (see also Pomara et al., 2012).

MRI Acquisition. The MRI acquisition was performed on a 1.5 T Siemens Vision system (Erlangen, Germany) at the Nathan Kline Institute.

Amino acid determination. Measurement of CSF levels of amino acids was carried out using high performance liquid chromatography (HPLC) system (Shimadzu Corporation, Kyoto, Japan) as previously reported (Hashimoto et al., 2016). Similarly, the procedure for determination of glutamine

and glutamate is described in Hashimoto et al. (2016). CSF GABA was determined using GC-MS with a DB-1 column, as previously described by Mann et al. (2014).

Procedure. The study procedure has already been detailed in Pomara et al. (2012). Briefly, the study consisted of three visits on successive weeks. During visit 1, participants provided consent and were then administered a general medical intake questionnaire to obtain medical history information; vital signs were subsequently measured, and an MMSE score was obtained. Severity of depression was measured here with the Hamilton Depression Scale (HAM-D, 21 items). On a second visit, participants received an MRI scan of the head, and a physical exam, routine laboratory tests and urine drug screens were also performed. On a third visit, participants underwent a comprehensive neuropsychological assessment, including memory evaluation with the Buschke Selective Reminding Test (BSRT; Buschke & Fuld, 1974; Deptula, Singh, Goldsmith, Block, Bagne & Pomara, 1990). The BSRT (standard administration) involves the oral presentation of 16 unrelated nouns, which participants are asked to recall over several trials. For the purpose of this study, two trials are relevant: the first trial (immediate recall), in which participants are asked to free recall as many words as possible immediately after presentation of the study list; and the delayed trial, in which participants are asked to free recall the original study list after a 15-20 minutes gap from initial learning and testing. Finally, a lumbar puncture was performed on a fourth visit, between 9am and 10am, after overnight fasting. This research received ethical approval by the institutional review boards of the Nathan Kline Institute for Psychiatric Research, the New York University School of Medicine, and the Research Ethics Committee of the Graduate School of Medicine, Chiba University.

Design and Analysis. Primacy and recency were defined as the first and last four items on the study list, respectively, whereas middle words were the remaining eight words. The immediate/delayed ratios were calculated by dividing the primacy, middle, and recency scores in the immediate recall trial by the corresponding scores in the delayed recall trial. A correction was applied, as in Bruno et al. (*In Press*), to avoid data loss (*numerator* + 0.05 / *denominator* + 0.1). This way we obtained a primacy ratio (Pr), a middle ratio (Mr) and Rr. We then carried out two sets, one for MDD participants and one for controls, of bivariate Spearman correlations between the ratio scores, total BSRT recall, and glutamate, glutamine and GABA. Non-parametric tests were chosen due to the non-

normal distribution of the ratio scores and of the amino acids levels. Since 24 tests were performed, the α level was corrected to 0.002 (Sidak) to account for multiple tests.

Results

The Table reports cross-sectional comparisons of demographic characteristics and memory performance scores. Depression severity was higher in the MDD group, and thus the original diagnosis was consistent with current depressive state of the sample. None of the other demographic characteristics differed across groups. With regards to memory measures, only one index differed across groups, Mr, which was lower for depressed participants than for controls.

Correlations. Within the MDD group, Rr was negatively correlated with glutamate (ρ = -.621, p<.001), but this correlation was not significant within the control group (ρ = -.310, p = .197). In the MDD group, no other correlations reached or neared significance (p's > .160), and the same was true within the control group (p's > .190). The Figure shows the correlations between ratio scores and CSF glutamate in MDD (A) and controls (B). For purposes of illustration, an Rr outlier score was removed from the Figure (A), but included in the analyses – removing the outlier does not affect the overall pattern of results (ρ = -.589, p = .001). Similarly, to maintain consistent ranges across scatterplots, two outliers were removed from Figure (B), but included in the analyses; this did not affect the overall result of the correlation between Rr and glutamate (ρ = -.348, p = .171).

For reference, the correlation between CSF glutamate and Rr was also significant when examining the whole sample (N = 47; ρ = -.458, p = .001).

Reductions in CSF Aβ42, which we previously reported in this group of MDD subjects (Pomara et al., 2012), were not associated with Rr, either when considering MDD participants (p = .558) or controls (p = .527).

Glutamate. Due to the association between CSF glutamate and Rr in the MDD group, we also assessed whether there were differences between groups in total CSF glutamate levels. A Mann-Whitney U test showed that CSF glutamate was significantly higher in controls than in individuals with MDD (U=163.5, Z=1.992, p=0.046). The median for depressed participants was 0.36 (range: 0.23-0.71), whereas the median for controls was 0.44 (range: 0.28-3.97). When excluding one

extreme outlier in the control group, we were also able to carry out a t test (t(44)=2.152, p=0.037), which confirmed these results (MDD=0.38, SD=0.11; controls=0.46, SD=0.14).

Put Table and Figure about here

Discussion

In this paper, we set out to study the relationship between Rr, which Bruno et al. (2016a) have shown to predict cognitive decline in cognitively normal participants, and glutamate, which is the principal excitatory neurotransmitter in the central nervous system and has been implicated in neuronal plasticity and the formation of memories (e.g., Sanacora, Treccani & Popoli, 2012), as measured in the CSF. Our prediction was that increased Rr levels would be accompanied by a disruption of CSF glutamate level. Our results indicate that, indeed, Rr levels are inversely correlated with CSF glutamate levels, although we only found this relationship in individuals with late-life MDD. For comparison, neither glutamine nor GABA were associated with Rr or either of the other ratio measures.

Bruno et al. (2016a) previously suggested that higher Rr scores may be the product of a compensatory mechanism whereby loss of consolidation and increased long term forgetting are accompanied by a paradoxical enhancement of short term memory ability. It is possible to provide some support to this notion by means of analysing the relationship, within the MDD group, between CSF glutamate levels and the separate components of Rr, namely immediate recency and delayed recency. If the compensatory hypothesis is correct, glutamate should be expected to decrease as delayed recency, indexing consolidation, decreases, while being negatively correlated with immediate recency, representing the compensatory mechanism. Consistent with this hypothesis, CSF glutamate levels in the MDD group were found to be positively correlated with delayed recency (ρ = .452, p = .016), but negatively correlated with immediate recency (ρ = -.386, p = .042). These findings therefore suggest that lower CSF glutamate levels may specifically index a loss of consolidation ability, i.e., an inability in the individual to encode long lasting memories. The idea of a compensatory mechanism also suggests that at least two networks (one for processing long term memory and one for short term memory) may be involved as the basis of changes in serial position patterns of performance. Further research should consider a more direct and experimental approach to clarify this

issue, and proponents of single process accounts of serial position may want to test whether single process models are sufficient to explain the present findings.

As far as we are aware, this is the first study to report a correlation between CSF glutamate levels and memory performance. However, a recent study has reported correlations between plasma glutamate levels and memory scores in a large cohort of over 500, young, neurologically healthy individuals (Kamada et al., 2016). Unlike in the present report, the study by Kamada et al. showed *negative* correlations between glutamate levels and memory proficiency (Japanese Wechsler Memory Scale-Revised: verbal memory, general memory & delayed recall), albeit with fairly small effect sizes. A number of reasons may be at the root of this inconsistency. First of all, although plasma and CSF glutamate levels have been found to be positively correlated, exceptions also have been highlighted, particularly with depressed individuals (Palsson et al., 2014). Second, the populations of the two studies are not directly comparable: whereas our study tested older individuals with MDD, Kamada et al. tested a cohort of healthy, younger participants.

Glutamate was only found to associate with Rr, and not with any of the other ratio measures, or the total recall score in the BSRT. We believe this finding highlights the efficacy and sensitivity of Rr as a measure of memory impairment, although more research with this relatively novel marker is warranted. Moreover, we only observed an association between CSF glutamate and memory in the MDD group, but not in the control group. As noted, MDD is associated with alterations in the glutamine-to-glutamate cycle, with a recent report from our group showing that MDD subjects have a higher glutamine-to-glutamate ratio than controls in the absence of cognitive impairment (Hashimoto et al., 2016). Thus, it is possible that associations between glutamate and memory in MDD may be easier to detect due to the existing cycle imbalance and, consistent with Hashimoto et al.'s finding, correlations between Rr and the glutamine-to-glutamate ratio were found in MDD subjects (ρ = .553, p = .002), but not in controls (ρ = .390, p = .099). However, a more prosaic reason might lie simply in the high variability of glutamate levels within the control data. To account for this variability, we employed non-parametric tests; nevertheless, if we remove a control group outlier with a very high glutamate level, the Rr correlations in controls begin approaching or reaching significance with CSF glutamate, ρ = -.451, p = .060, and the CSF glutamine-to-glutamate ratio, ρ = .543, p = .020,

respectively. Similarly, visual inspection of the Figure (B) does hint at a potential relationship between Rr and CSG glutamate in controls that may be masked by relative lack of power. Nevertheless, a power analysis indicates that in order to observe a significant correlation with power $(1 - \beta)$ at 80%, ρ = -.310 (see Results; Correlations), and α set at 0.002 (see Methods; Design and Analysis), we would need as many as 153 participants, which is over five times the number of depressed individuals in this study, thus suggesting that our differential finding is unlikely to be yielded simply by lack of sample size. All in all, these further analyses suggest that our findings should be interpreted with caution and that further research with clinical and non-clinical populations, employing both CSF and plasma, as well as MR spectroscopy allowing for region specific analyses, should be considered as a future direction.

Although not significantly different (see Table), there was a higher proportion of women in the control group than in the MDD group; average age was also numerically higher in controls. Therefore, we elected to run a further correlation between Rr and CSF glutamate levels, within the MDD group, while controlling for sex and age to rule out unwanted confounds. Our results show that the correlation is significant at the $\alpha = 0.050$ level, ρ = -.392, p = .048.

To conclude, in a group of cognitively intact individuals with late-life major depression, we showed that CSF glutamate levels were associated with Rr, a cognitive marker of memory dysfunction, such that more memory loss was correlated with lower glutamate levels. Our paper is the first report showing a link between CSF glutamate and memory performance. More importantly, our results may help elucidate the relationship between AD and MDD, and help the identification of elderly individuals with MDD who carry the highest risk of being at a prodromal stage of AD. Specifically, as noted recently by Leyhe et al. (2016), individuals suffering from a *pure* depressive disorder, i.e., uncontaminated by dementia, do not present deficits of information storage. If Rr indeed signals an issue with consolidation of episodic information, then late-life MDD individuals with abnormally high Rr scores may be showing signs of a *contaminated* profile, and be in a prodromal stage of AD. Alternatively, considering that we did not find Rr to associate with levels of CSF Aβ42, an AD biomarker, it may be that Rr signals factors other than prodromal AD, such as neuroinflammation or oxidative stress. Future research should therefore consider investigating

whether CSF glutamate levels, in combination with other AD-risk indicators, such as abnormal Aβ and tau levels, and reduced hippocampal volume, are a strong predictor of conversion to a neurodegenerative disease in individuals with MDD, from a cognitively healthy baseline. Moreover, as the precise origin of CSF glutamate is not known, it would also be important for future studies to determine how Rr relates to possible brain region-specific alterations in glutamate level and metabotropic glutamate receptor density, which have been implicated in depression, as determined by MRS and PET neuroimaging techniques, respectively.

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Table. *Demographic and Memory Characteristics of Study Participants by MDD diagnosis*

Characteristic	Comparison Group (N=19)	MDD Group (N=28)	p values (t tests)
Age (years)	68.1 ± 7.3	66.5 ± 5.4	0.41
Education (years)[a]	16.7 ± 2.7	16.5 ± 2.7	0.79
21-item HAM-D	1.2 ± 1.9	14.9 ± 8.8	**<0.001**
MMSE	29.5 ± 0.5	29.8 ± 0.6	0.13
Total recall rating	64.4 ± 12.3	64.9 ± 13.9	0.91
Delayed recall rating	8.5 ± 2.8	9.5 ± 2.5	0.22
			p values (χ^2)
Females (n)	12 (63%)	10 (36%)	0.12
			p values (Mann-Whitney)
Primacy ratio	0.8 ± 0.6	0.6 ± 0.4	0.58
Middle ratio	0.5 ± 0.4	0.3 ± 0.2	**0.004**
Recency ratio	1.9 ± 2.3	1.7 ± 1.9	0.85

The data are the mean ± standard deviation (SD).

21-item HAM-D: 21-item Hamilton Depression Rating Scale, MMSE: Mini-Mental State Examination

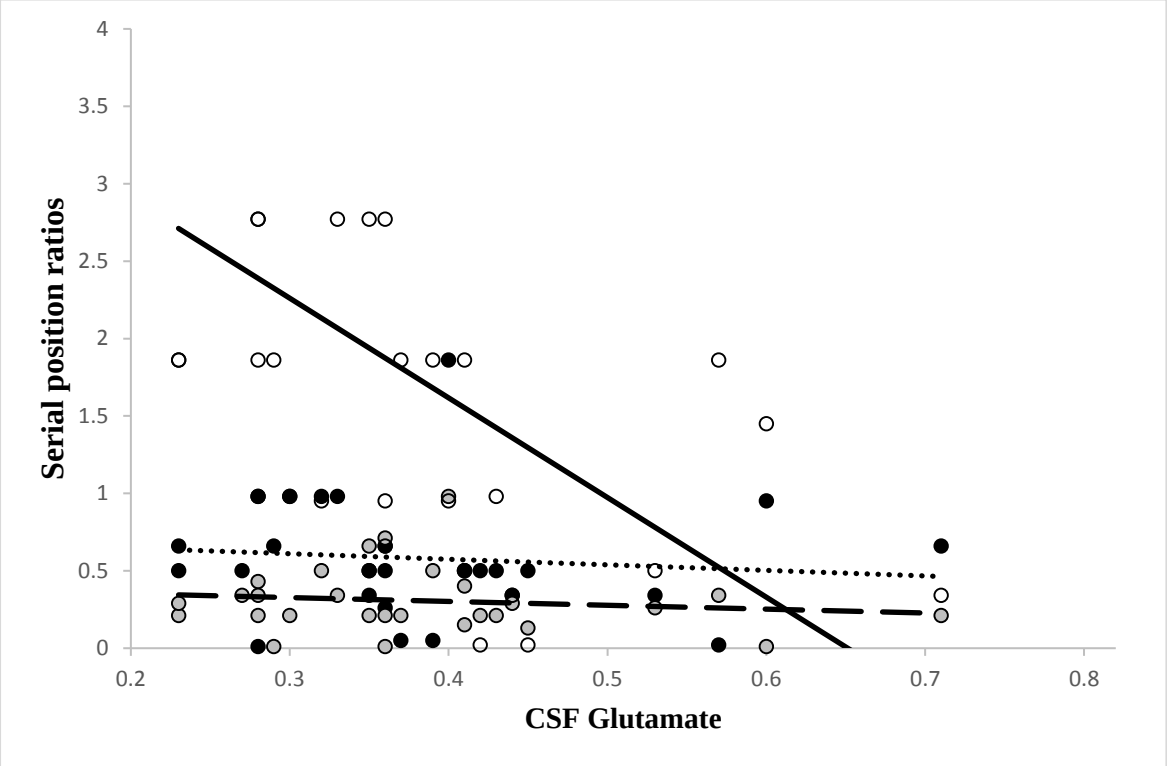
[a] Data for one control subject were not available.

Serial position ratios and Glutamate

Figure. A) Scatterplot of CSF glutamate (x-axis) and the serial position ratios (y-axis) in MDD. Black circles represent the primacy ratio (dotted line); grey circles represent the middle ratio (dashed line); and white circles represent the recency ratio (continuous line). B) Scatterplot of CSF glutamate (x-axis) and the serial position ratios (y-axis) in controls. Black circles represent the primacy ratio (dotted line); grey circles represent the middle ratio (dashed line); and white circles represent the recency ratio (continuous line).

Serial position ratios and Glutamate

A)



B)