Evaluating effect of Citosine Arabinoside on functional brain connectivity in patients with acute myeloid leukemia using s-LORETA

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Objective:
Quantitative analysis of background EEG frequencies is a standard method used to evaluate the toxicity of a drug in the Central Nervous System (CNS); however, this method is unable to provide valuable information about brain activity source location and connections between different areas or neuronal populations.
Low resolution brain electromagnetic tomography (LORETA) represents a software that permits a truly three-dimensional tomography of the brain's electrical activity that can better study drug-induced changes in functional brain connectivity.
Cytosine Arabinoside (Ara-C), is a nucleoside analog used for treatment of Acute Myeloid Leukemia (AML). A high intravenous dose of Ara-C has been noted to produce a number of CNS toxicities and can contribute to changes in brain function.
For this reason, the aim of this study was to evaluate the possible effect of Ara-C on connectivity in the resting state, in patients with AML using LORETA.

Methods:
Patients
We studied eight patients with newly diagnosed AML (3 male and 5 female with a median age of 56 years, range 42-74).
Four patients were treated with induction standard dose of Ara-C and the other 4 with high-dose Ara-C

EEG recording
All patients underwent an EEG evaluation before and after six months of treatment with Ara-C ev.
Nineteen scalp-electrodes were placed according to 10–20 International System
The recording session were performed in all patients at rest with eyes closed for 10 minutes
The EEG recordings were exported into American Standard Code for Information Interchange (ASCII) files and imported into the s-LORETA software.
Three Region of Interests (ROIs) corresponding to specific combinations of Broadman areas, *using the Tailarach Brain Atlas,* were defined (see Table 1)
For each couple of ROIs, a s-LORETA connectivity analysis was performed.

Analysis of resting-state EEG functional connectivity
The connectivity analysis was based on the lagged linear temporal correlation between two or more Broadman areas, across successive 2-s epochs over the investigated sample

Statistical analysis
T-thresholds, corresponding to statistically significant thresholds ($p < 0.05$ and $p < 0.01$), were calculated by the statistical algorithm implemented in the sLORETA software

Results:
The oncological disease and the neurological status remained stables in all patients.

•In the first group of patients (standard dose): no statistical significant differences after 6 month of therapy were obtained for all frequency bands in all ROIs.

•In the second group (high dose): a significant modification was observed in the beta2 band after 6 months (20.5-30 Hz) (Fig. 1). This modification consisted in a decrease of linear lagged phase synchronization between the cortical areas identified by ROI1 ($T = 2.9$, $p < 0.05$). Similarly, a decrease of non-linear lagged phase synchronization was obtained between the cortical areas identified by ROI2.
•No significant differences were observed in the other frequency bands for both ROI1 and ROI2.
•Concerning ROI3, t-test gave no significant differences for all frequency bands.

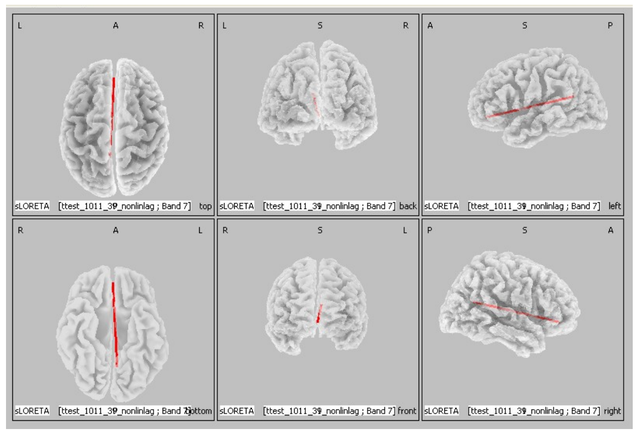
Table 1

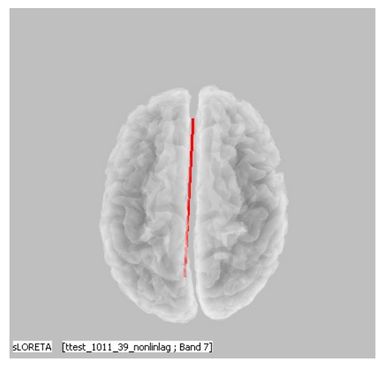
Brodman area

BA 31: the posterior cingulate cortex (PCC)
BA 7: precuneus
BA 39: inferior parietal cortices
BA 10-BA 11: medial prefrontal cortex (MPFC)

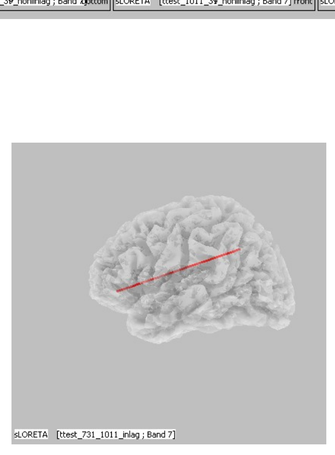
ROI	BA	t (p<0.01)	t (p<0.05)	t	Significance
1	10,11 vs 39	3.18	2.58	2.92	yes
2	7,31 vs 10,11	3.15	2.63	2.91	yes
3	7,31 vs 39	3.27	2.63	2.61	no

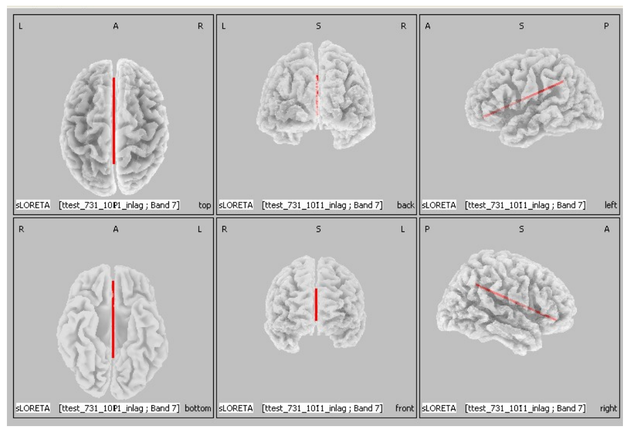
ROI 1 10-11vs 39





ROI2 7,31 vs 10,11





Discussion:
Our findings suggest that high dose of Ara-C, can decrease resting EEG functional connectivity, especially the fronto-parietal network, in patients with AML, and can contribuite to changes in the functional state of brain.

Since beta2 is correlated with attention, our findings suggest that Ara-C can decrease resting EEG functional connectivity.

Further studies will be needed to confirm these findings in a larger patients' cohort, using also neuropsychological assessment.

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