Assessing the Effect of Midazolam on the Brain Functional Connectivity using Graph Analysis

Hazim Omar[1], Theodore Kypraios[2], Dorothee Auer[1], and Naranjargal Dashdorj[1]
[1]*Radiological and Imaging Sciences, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom,* [2]*School of Mathematical Sciences, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom*

Introduction: Stimulus-free fMRI allows to detect resting state functional brain networks which were shown to have a small-world architecture (σ) [1, 2]. This small world model is a reflection of a network with multiparallel system properties that processes information both locally and globally while at the same time minimizing the energy and resource involved in certain network functions [3]. This small world model was characterized by high clustering coefficient (Cp) and low average minimum path length. Small-world architecture has been shown to be altered during aging, and following drug intervention [4, 5]. However, this has not been widely confirmed. In this study we investigate the effect of midazolam, a hypnotic and sedative benzodiazepine leading to transient impairment of consciousness and memory, on the functional brain network by using graph analysis.

Method: Resting state data from twelve healthy male volunteers undergoing midazolam challenge study were used. All subjects gave written informed consent and the study was approved by the University of Nottingham Research Ethics Committee. Volunteers were scanned at baseline and after i.v. midazolam (0.05mg/kg body weight) application outside the scanner. Sedation was scored using the Ramsay scale. Scanning was done at 3T (Philips Achieva) using an 8-channel head coil and a standard EPI sequence with TR/TE = 2100/35 ms, 64x64 matrix, 35 axial slices and voxel dimensions 3.25x3.25x3 mm. Resting state fMRI scans lasted 9 minutes. Image analysis was carried out by FSL4.0 software (FMRIB Oxford, UK). Images were preprocessed using high and low pass filtering, spatial smoothing and motion correction in the FSL 4.0 environment. After carrying out Melodic ICA component analysis, independent components were visually inspected for noise and selected noise components were removed. Image registration was achieved by FLIRT function of FSL4.0 software. Regional parcellation using the anatomically labeled template image validated previously by Tzourio-Mazoyer et al [6] . The derived time series were then further corrected for spurious correlations using white matter and CSF time series as repressors of no interest. Individual correlation matrices consisting of 90 nodes (brain regions) were created, and thresholded using a range of cut-off (0.2 to 0.5) values for calculating the graph theoretical attributes using R software packages [7]. The graph attributes for clustering coefficient, global and local efficiency were calculated using "SNA", "igraph", "Brainwaver" and "waveslim". A student T-Test comparison was used for each attributes before and after midazolam administration

Result: A small-world network characteristic was found for the resting state network in both conditions pre (σ = 2.83) and post (σ = 2.06) midazolam administration using a correlation coefficient threshold of 0.5. There was a significant increase in the clustering coefficient, C_p upon midazolam administration (C_p pre = 0.520 and C_p post= 0.585, $p< 0.01$; Figure 1). In addition, there was a significant increase in local efficiency after midazolam administration (Figure 2; $p = 0.006$) with unchanged global efficiency.

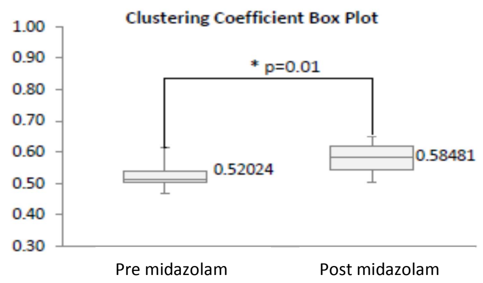

Figure 1: A significant increase in clustering coefficient (p=0.01) was found after midazolam administration.

Discussion: We confirmed small-world properties in the resting state functional network by demonstrating a combination of strong local clustering C_p and short characteristic path lengths. This means that the connectivity is local but the small world remains highly integrated with the presence of a small number of long range connections which confers optimal information processing and flow in the complex brain system. Our finding of an increased clustering coefficient following midazolam induced light sedation suggests that the synchronized functional network behaves increasingly as cliquishness during transition from wakefulness to sleep characterised by reduced attention and consciousness. Network efficiency describes the information flow in the brain network as a disconnected or nonsparse graph. The global efficiency is a measure of the transfer speed of parallel information in the brain while local efficiency measures the information integration in each sub graph [3]. The observed increase in the local efficiency after midazolam may thus be a reflection of enhanced local information integration. Further studies are needed to investigate whether these graph properties underpin the known sedative and cognitive effects of midazolam and whether they correlate with the EEG signature of benzodiazepines.

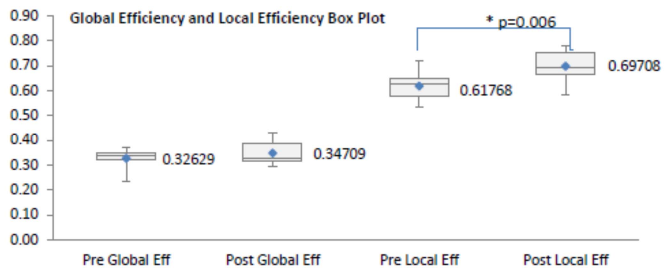

Figure 2: A comparison of global and local efficiency box plot which show a significant increase for local efficiency attribute after midazolam administration (p<0.01).

Conclusion: Our study provides further evidence that brain functional networks have a small-world characteristics and our finding suggest that graph theory analysis can provide an insight in exploring the sedation and hypnotic effect in functional brain connectivity.

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