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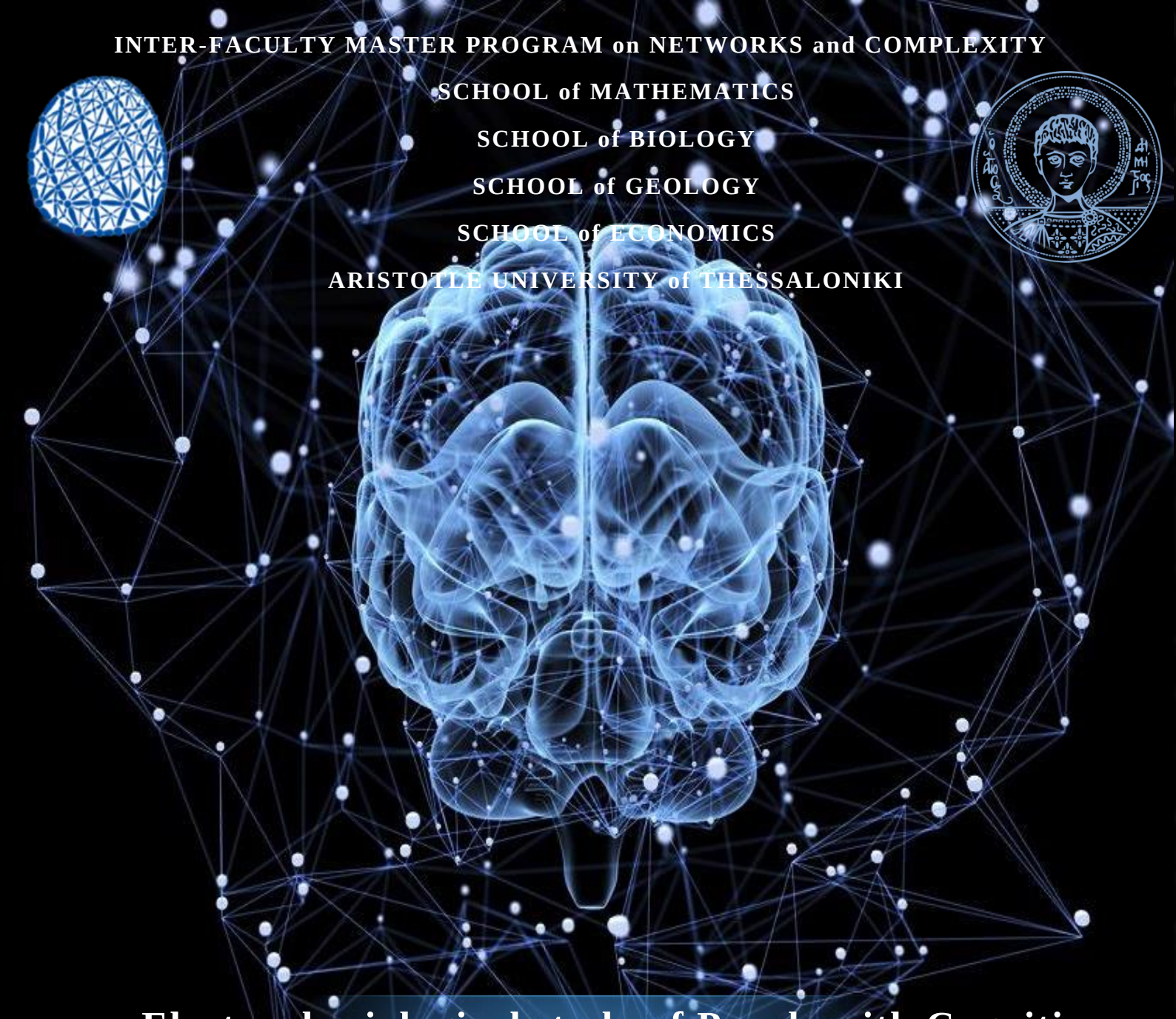

Electrophysiological study of People with Cognitive Impairment related to Alzheimer's Disease by using a High-density EGI GES 300

Ioulietta S. Lazarou

Supervisor: Dimitrios Kugiumtzis, Professor of Polytechnic School, Aristotle University of Thessaloniki

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ΔΙΑΤΜΗΜΑΤΙΚΟ ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ στα ΔΙΚΤΥΑ και ΠΟΛΥΠΛΟΚΟΤΗΤΑ
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Master Thesis

Title:

Electrophysiological study of People with Cognitive Impairment related to Alzheimer's Disease by using a High- density EEG EGI GES 300

Mrs Ioulietta S. Lazarou

SUPERVISOR: Dimitrios Kugiumtzis, Professor, AUTH

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D. Kugiumtzis Professor AUTH	I. Kompatsiaris Senior Researcher A, CERTH	M. Tsolaki Professor AUTH

Thessaloniki, 29th November 2019

ΔΙΑΤΜΗΜΑΤΙΚΟ ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ στα ΔΙΚΤΥΑ και ΠΟΛΥΠΛΟΚΟΤΗΤΑ
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ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Τίτλος Εργασίας:

Μελέτη ηλεκτροεγκεφαλογραφικών ευρημάτων ασθενών με Νοητική Έκπτωση σχετιζόμενη με την Άνοια Τύπου Alzheimer με τη χρήση του υψηλής πυκνότητας EGI GES 300

Κα Ιουλιέττα Σ. Λαζάρου

ΕΠΙΒΛΕΠΩΝ: Δημήτριος Κουγιουμτζής, Αν. Καθηγητής Α.Π.Θ.

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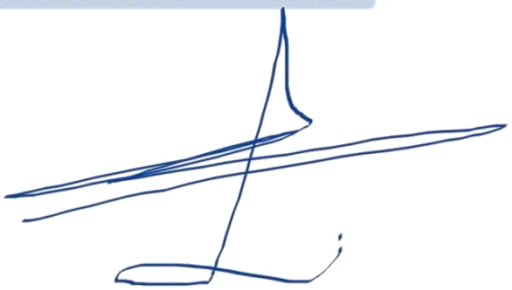
……	……	……
Δ. Κουγιουμτζής Αν. Καθηγητής Α.Π.Θ.	Ι. Κομπατσιάρης Ερευνητής Α' ΕΚΕΤΑ	Μ. Τσολάκη Καθηγήτρια ΑΠΘ

Θεσσαλονίκη , 29 Νοεμβρίου 2019



Κα Ιουλιέττα Λαζάρου
BSc Τμήμα Ψυχολογίας Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
MSc Ιατρική Έρευνα και Μεθοδολογία, Ιατρική Σχολή ΑΠΘ
Υποψ. Διδάκτωρ Ιατρική Σχολή, Τομέας Νευροεπιστημών, Ιατρική Σχολή ΑΠΘ
Ψυχολόγος - Κλινική Ερευνήτρια στο Ινστιτούτο Τεχνολογιών και Πληροφορικής στο Εθνικό Κέντρο Έρευνας και Τεχνολογικής Ανάπτυξης, εργαστήριο Πολυμέσων και Κοινωνικών Δικτύων

ABSTRACT

Background: Subjective Cognitive Decline (SCD) is a largely unknown state thought to represent a preclinical stage of Alzheimer's disease (AD) previous to mild cognitive impairment (MCI). However, the course of network disruption in all stages is scarcely investigated. In order to explore neurophysiological biomarkers of AD spectrum, we investigated resting state HD-EEG (EEG) of SCD, MCI and AD patients.

Methods: We employed resting state EEG to extract correlation matrices for each subject, construct weighted undirected networks and calculate network clustering and strength at global and local level from parietal electrodes. Network measures were compared between groups. 70 patients (20 SCD, 30 MCI and 20 AD) and 22 healthy controls (HC) were enrolled. All participants underwent a detailed neuropsychological assessment and 10 minutes resting state HD-EEG (EGI GES 300) with 256 channels.

Results: The SCD group exhibited decreased clustering coefficient and strength at local level but exhibited no difference at global level compared to HC. However, SCD showed similar but smaller changes in clustering and strength compared to MCI. Also, MCI and AD showed disrupted both clustering and strength compared to HC. SCD exhibit a significant network disruption at local level, showing intermediate values between HC and MCI groups in multiple parameters. These results highlight the relevance of cognitive concerns in the clinical setting and suggest that network disorganization in AD could start in the preclinical stages before the onset of cognitive symptoms.

Conclusion: The above findings reveal a disrupted pattern of the AD connectome that starts in parietal regions, when patients show memory concerns. This pattern provides evidence that disruptions in brain connectome at parietal organization are a key factor in the progression of AD that can dynamically reflect the progression of AD, thus representing a potential biomarker for early diagnosis and may potentially represent a neurophysiological biomarker of AD.

KEY WORDS

Electroencephalography, Brain Connectivity, Alzheimer's Disease, Subjective Cognitive Decline, Mild Cognitive Impairment, Elders, Resting State, Network Analysis

ΠΕΡΙΛΗΨΗ

Θέμα: Η υποκειμενική νοητική διαταραχή (ΥΝΔ) είναι μια άγνωστη κατάσταση που αποτελεί ένα προκλινικό στάδιο της νόσου του Alzheimer (ΝΑ) πριν από την ήπια νοητική διαταραχή (ΗΝΔ). Ωστόσο, η μελέτη του δικτύου του εγκεφάλου σε όλα τα στάδια είναι ελάχιστα διερευνημένη. Προκειμένου να διερευνηθούν οι νευροφυσιολογικές διαφορές σε άτομα που ανήκουν στο φάσμα της ΝΑ, ερευνήσαμε συγκεκριμένες ιδιότητες δικτύων εγκεφάλου ατόμων με ΥΝΔ, ΗΝΔ και ΝΑ συγκριτικά με υγιείς ηλικιωμένους.

Μέθοδος: Χρησιμοποιήσαμε ηλεκτροεγκεφαλογραφικές (ΗΕΓ) καταγραφές υψηλής ευκρίνειας σε κατάσταση ηρεμίας για τον υπολογισμό του συντελεστή Συσταδοποίησης και την ισχύ δικτύου σε ολόκληρο τον εγκέφαλο αλλά και σε τοπικό επίπεδο από συγκεκριμένα ηλεκτρόδια του βρεγματικού λοβού. Τα μέτρα δικτύων συγκρίθηκαν μεταξύ των ομάδων. Συμμετείχαν 70 ασθενείς (20 ΥΝΔ, 30 ΗΝΔ και 20 ΝΑ) και 22 υγιείς μάρτυρες (ΥΜ). Όλοι οι συμμετέχοντες υποβλήθηκαν σε λεπτομερή νευροψυχολογική αξιολόγηση και 10 λεπτά ανάπαυσης HD-EEG (EGI GES 300) με 256 κανάλια.

Αποτελέσματα: Η ομάδα των ασθενών με ΥΝΔ παρουσίασε στατιστικά σημαντικά μειωμένο συντελεστή Συσταδοποίησης και ισχύ τοπικά στη περιοχή του βρεγματικού λοβού, αλλά δεν παρουσίασε καμία διαφορά στο δίκτυο όλου του εγκεφάλου σε σχέση με τους ΥΜ. Ωστόσο εμφάνισε παρόμοιες αλλά μικρότερες αλλαγές ως προς το συντελεστή Συσταδοποίησης και την ισχύ, παρουσιάζοντας μεταβολές παρόμοιες με εκείνες που έδειξε η ΗΝΔ. Επίσης, οι ασθενείς με ΗΝΔ και ΝΑ παρουσίασαν πολύ μειωμένες τιμές στις συγκεκριμένες ιδιότητες δικτύου σε σχέση με τους υγιείς. Πιο συγκεκριμένα, οι ασθενείς με ΥΝΔ παρουσιάζουν σημαντική διαταραχή των δικτύων του εγκεφάλου σε τοπικό επίπεδο (βρεγματικός λοβός), παρουσιάζοντας ενδιάμεσες τιμές μεταξύ της ομάδας των υγιών και των ΗΝΔ. Τα αποτελέσματα αυτά υπογραμμίζουν τη συνάφεια των ανησυχιών σε σχέση με τη μνήμη και υποδεικνύουν ότι η αποδιοργάνωση του δικτύου στη ΝΑ θα μπορούσε να ξεκινήσει στα προκλινικά στάδια πριν από την εμφάνιση των μετρήσιμων νοητικών ελλειμμάτων.

Συμπεράσματα: Αυτά τα ευρήματα αποκαλύπτουν ένα διαταραγμένο μοτίβο του δικτύου στη ΝΑ που ξεκινά στις βρεγματικές περιοχές, όταν οι ασθενείς παρουσιάζουν υποκειμενικές ανησυχίες για τη μνήμη τους. Τα αποτελέσματα αυτά αποδεικνύουν ότι οι διαταραχές των εγκεφαλικών δικτύων στις βρεγματικές περιοχές του εγκεφάλου αποτελούν βασικό παράγοντα στην πρόοδο της ΝΑ που μπορεί να αντικατοπτρίζει δυναμικά την εξέλιξη της ΝΑ και έτσι να αντιπροσωπεύει έναν πιθανό νευροφυσιολογικό βιοδείκτη για την έγκαιρη διάγνωση της ΝΑ.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ

Ηλεκτροεγκεφαλογράφημα, Άνοια Τύπου Alzheimer, Υποκειμενική Νοητική διαταραχή, Ήπια Νοητική Διαταραχή, Δίκτυα εγκεφάλου

Στον πατέρα μου που μου έμαθε
να μην τα παρατάω ποτέ στα δύσκολα
και να αγωνίζομαι πάντα για το καλύτερο…

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ΣΥΝΟΨΗ ΣΤΑ ΕΛΛΗΝΙΚΑ

Η νόσος Alzheimer (ΝΑ) είναι μια νευροεκφυλιστική πάθηση η οποία έχει βρεθεί ότι αλλάζει τη δομή και τη λειτουργία του εγκεφάλου αρκετά χρόνια πριν από την εμφάνιση των κλινικών και νευροψυχολογικών συμπτωμάτων [1]. Επομένως, ο έγκαιρος εντοπισμός των μηχανισμών του εγκεφάλου σε άτομα που είναι πιθανό να αναπτύξουν Νόσο Alzheimer (ΝΑ) είναι από τις μεγαλύτερες προκλήσεις της τρέχουσας έρευνας στον τομέα της άνοιας [2].

Στόχος Μελέτης

Από όσο γνωρίζουμε, η παρούσα έρευνα αποτελεί την πρώτη μελέτη μέχρι σήμερα με τη χρήση μετρήσεων από υψηλής ευκρίνειας ηλεκτροεγκεφαλογράφημα που κατασκευάστηκαν από νευροφυσιολογικά δεδομένα με τη χρήση του EGI GES 300, για να χαρακτηρίσουν την εξέλιξη της δυναμικής του δικτύου σε όλα τα προκλινικά στάδια της ΝΑ, συμπεριλαμβανομένων υγιεινών ηλικιωμένων χωρίς νοητικές ανησυχίες, ασθενείς με Υποκειμενικής Νοητικής Διαταραχής (ΥΝΔ), Ήπιας Νοητικής Διαταραχής (ΗΝΔ) και ΝΑ. Για το σκοπό αυτό, χρησιμοποιήσαμε δεδομένα συμμετεχόντων σε κατάσταση ηρεμίας που καταγράφηκε με το υψηλής ευκρίνειας ηλεκτροεγκεφαλογράφημα (ΗΕΓ) ενώ στη πορεία δημιουργήθηκαν πίνακες διασυσχέτισης μεταξύ των ηλεκτροδίων εκ των οποίων κατασκευάστηκαν δίκτυα με βάρη για την ακριβή ανίχνευση των ιδιοτήτων του δικτύου σε όλο το φάσμα ΝΑ και σύγκριση των αποτελεσμάτων τους με τις νευροψυχολογικές εξετάσεις. Τα νευροφυσιολογικά μέτρα συγχρονισμού που προέρχονται από το EEG, το fMRI και το MEG έχουν αποδειχθεί χρήσιμα στην ανίχνευση διαφορετικών παθολογιών [105], [121], [122] και συγκεκριμένα σε ΝΑ [109], [110], [113], [119], [123] - [125]. Με βάση τις προηγούμενες μελέτες απεικόνισης, αναμενόταν η ανίχνευση διαφορών ως προς τις ιδιότητες του δικτύου σε ασθενείς με ΥΝΔ σε σχέση με την ομάδα των υγιών. Υποθέσαμε ότι οι συμμετέχοντες με ΥΝΔ θα παρουσιάσουν μεταβολές προς την ίδια κατεύθυνση με αυτές που εκδηλώθηκαν από ασθενείς με ΗΝΔ, αν και σε μικρότερο βαθμό, παρουσιάζοντας έτσι ενδιάμεσες τιμές μεταξύ αυτών των ΗΝΔ και υγιών ηλικιωμένων. Σε αυτή τη μελέτη, στοχεύσαμε να εξετάσουμε αυτή την εικασία αξιολογώντας την πιθανή κλινική ευαισθησία του συντελεστή συσταδοποίησης (ΣΣ) και της ισχύος τόσο σε σφαιρικό όσο και σε τοπικό επίπεδο σε όλο το φάσμα ΝΑ σε δείγμα ασθενών με ΝΑ, ασθενών με ΗΝΔ και ασθενών με ΥΝΔ. Από όσο γνωρίζουμε, καμία προηγούμενη μελέτη δεν έχει αξιολογήσει τις συγκεκριμένες ιδιότητες δικτύου σε κατάσταση ηρεμίας με τη χρήση του ΗΕΓ σε άτομα με ΥΝΔ μέχρι σήμερα. Με βάση τις καθιερωμένες γνώσεις σχετικά με την ανατομική κατανομή της παθοφυσιολογίας και των μεταβολών του ΗΕΓ σε κατάσταση ηρεμίας κατά τη διάρκεια της νόσου, διερευνήσαμε αλλοιώσεις του εγκεφάλου σε όλο τον εγκέφαλο όσο και σε συγκεκριμένες περιοχές του εγκεφάλου που εμπλέκουν τις δομές του βρεγματικού λοβού, αντανακλώντας ένα διαβαθμισμένο πρότυπο διαφορών που αντιστοιχούν στη σοβαρότητα της νόσου.

Νόσος Alzheimer και Υποκειμενική Νοητική Διαταραχή

Ενώ οι άνθρωποι γερνούν, πολλοί είναι εκείνοι που παρουσιάζουν διαταραχή στις νοητικές τους λειτουργίες που εκτείνεται πέρα από αυτό που θεωρείται υγιής γήρανση, χωρίς όμως να υπάρχει απαραίτητα η διάγνωση της άνοιας. Αυτή η μεταβατική νοητική κατάσταση χαρακτηρίστηκε ως ΗΝΔ [3]. Ωστόσο, μια υποκειμενική ανησυχία της

απώλειας μνήμης από τους ηλικιωμένους απουσία οποιασδήποτε οργανικής ή αναγνωρίσιμης κατάστασης από νευροψυχολογική εξέταση ονομάζεται ΥΝΔ [4]. Αυτή η κατάσταση είναι γνωστό ότι προκαλεί διαταραχή της μνήμης και έχει μεγάλη αξία ως προστάδιο της ΗΝΔ [5] με πιθανή εξέλιξη στο μετέπειτα στάδιο της ΝΑ [6]. Η προσπάθεια να ανιχνευθούν τα πολύ πρώιμα σημάδια άνοιας με τη δυνατότητα ανάπτυξης παρεμβάσεων για να επιβραδυνθεί η εξέλιξή τους, έδωσε την ώθηση για αυξημένο ενδιαφέρον για τη ΥΝΔ. Τι γνωρίζουμε για τη λειτουργία του εγκεφάλου και τις ιδιότητες του δικτύου ανθρώπων με ΥΝΔ; Τι αλλαγές παρατηρούνται στη συνδεσιμότητα των εγκεφαλικών περιοχών των ανθρώπων που μόλις άρχισαν να ανησυχούν για την απώλεια μνήμης; Αυτά ήταν τα ερωτήματα που πυροδότησαν το ερευνητικό μας ενδιαφέρον και αυτή η μελέτη έρχεται να παρουσιάσει μερικά προκαταρκτικά αποτελέσματα σχετικά με τα άτομα με ΥΝΔ και τη λειτουργικότητα του εγκεφάλου τους.

Ιδιότητες δικτύου και μελέτες νευροαπεικόνισης για ΥΝΔ

Συγκεκριμένα, οι μεταβολές στην τοπολογία των γραφημάτων και οι αντίστοιχες μετρήσεις επιτρέπουν την εξέταση των εξελισσόμενων αλληλεπιδράσεων μεταξύ πολλαπλών εγκεφαλικών περιοχών και περιοχών σε νοσήματα που σχετίζονται με τη νοητική λειτουργία, όπως η ΝΑ. Αρκετές μελέτες νευροαπεικόνισης έχουν διερευνήσει πολλαπλές ιδιότητες δικτύων ατόμων με μεγάλη ποικιλία ψυχικών διαταραχών [37] και ΝΑ [38] ειδικότερα. Αναλυτικά, την τελευταία δεκαετία όλο και περισσότερες μελέτες υποδεικνύουν ότι ο ανθρώπινος εγκέφαλος μπορεί να μοντελοποιηθεί ως δίκτυο, δείχνοντας την συνδεσιμότητα του εγκεφάλου, που αναφέρεται ως εγκεφαλική σύνδεση (brain connectome) [39]. Το Brain connectome παρέχει μια πιο ολιστική άποψη αξιολογώντας και μοντελοποιώντας ολόκληρο τον ανθρώπινο εγκέφαλο ως σύνολο διαφόρων δικτύων και αξιολογώντας την εγκεφαλική οργάνωση, τις εκτεταμένες αλλαγές ή τις διαταραχές ως οντότητα [40] - [42]. Υπάρχουν ενδείξεις ότι οι αλλαγές στα δίκτυα του εγκεφάλου εμφανίζονται τόσο σε πρώιμα στάδια, όπως η ΥΝΔ και η ΗΝΔ, καθώς και σε μεταγενέστερες ασθένειες όπως η νόσος του Alzheimer [43] - [65]. Συγκεκριμένα, έχει προταθεί ότι οι μεταβολές της λειτουργικής συνδεσιμότητας (Functional Connectivity - FC) σε άτομα που κινδυνεύουν από πιο προχωρημένα στάδια γνωστικής δυσλειτουργίας μετά από κάποιο χρονικό διάστημα, μπορεί να συμβούν πριν από εκτεταμένες διαρθρωτικές εγκεφαλικές βλάβες και γνωστικά ελλείμματα που εντοπίζονται από τη νευροψυχολογική εκτίμηση [29], [38] [41], [45], [66] - [68]. Πιο συγκεκριμένα, υπάρχουν όλο και περισσότερα στοιχεία που υποδηλώνουν ότι το στάδιο της ΥΝΔ συνδέεται με την παρουσία εγκεφαλικών αλλαγών και την αποδιοργάνωση της πρώιμης νοητικής έκπτωσης που σχετίζεται με την ΝΑ [86] - [89]. Παρά το γεγονός ότι τα άτομα με ΥΝΔ θα μπορούσαν να αντιπροσωπεύουν ένα προστάδιο της ΗΝΔ, παραμένει ασαφές ποιο από τα άτομα με ΥΝΔ θα μεταπηδήσει στο στάδιο της ΗΝΔ ή της ΝΑ και πότε [91], [94]. Παρόλα αυτά, τα άτομα με ΥΝΔ εμφανίζουν νευροεκφυλιστικές μεταβολές στον εγκέφαλό τους [89], [95] - [97] παρόμοιες με ανθρώπους σε πιο προχωρημένα στάδια του φάσματος της άνοιας [30], [33] , [64]. Διάφορες μελέτες έχουν αξιολογήσει τα χαρακτηριστικά της εγκεφαλικής δραστηριότητας μεταξύ των ατόμων ΥΝΔ [22], [49], [96], [98], ενώ άλλα έχουν ρίξει φως στη συνδεσιμότητα μεταξύ των εγκεφαλικών περιοχών ατόμων με ΥΝΔ [45] , [53], [60], [63] με διερεύνηση των ιδιοτήτων του εγκεφάλου και του δικτύου [48] - [50], [55], [63], [64].

Γενικά, η θεωρία των γραφημάτων στην έρευνα του εγκεφάλου περιγράφει ένα δίκτυο ως ένα σύνολο κόμβων, τα οποία αποτελούν τα συστατικά ενός συστήματος (που αντιπροσωπεύεται στην προοπτική του εγκεφαλικού δικτύου ως περιοχή ενδιαφέροντος - ROI και μια σειρά ακμών που αντιπροσωπεύουν τη σύνδεση των κόμβων. Ποικίλες νευροαπεικονιστικές μέθοδοι έχουν χρησιμοποιηθεί εκτεταμένα για να εξάγουν τις διαφορετικές ιδιότητες του δικτύου του εγκεφάλου. Η μειωμένη ικανότητα συγχρονισμού μεταξύ δύο κόμβων θα μπορούσε να υποδείξει τις δυσκολίες επιτυχούς σύζευξης μεταξύ των περιοχών του εγκεφάλου και να μειώσει την πιθανότητα αποτελεσματικής μετάδοσης πληροφοριών [101] που οδηγεί στις επακόλουθες δυσκολίες μνήμης. Την τελευταία δεκαετία όλο και περισσότερες μελέτες υποδηλώνουν ότι ο ανθρώπινος εγκέφαλος μπορεί να μοντελοποιηθεί ως δίκτυο, δείχνοντας τη συνδεσιμότητα του εγκεφάλου, που αναφέρεται ως εγκεφαλική σύνδεση [39]. Το Brain connectome παρέχει μια πιο ολιστική άποψη αξιολογώντας και μοντελοποιώντας ολόκληρο τον ανθρώπινο εγκέφαλο ως σύνολο διαφόρων δικτύων και αξιολογώντας την εγκεφαλική οργάνωση, τις εκτεταμένες αλλαγές ή τις διαταραχές ως οντότητα [40] - [42]. Υπάρχουν ενδείξεις ότι οι αλλαγές στα δίκτυα του εγκεφάλου εμφανίζονται τόσο σε πρώιμα στάδια, όπως αυτό της ΥΝΔ και της ΗΝΔ, όσο και σε αργότερα όπως η ΝΑ [43], [44], [55], [59] - [64]. Η διερεύνηση των αλλαγών στα προκλινικά στάδια της ΝΑ, μπορεί να οδηγήσει σε νέες υποθέσεις σχετικά με την επικείμενη παθοφυσιολογία, οι οποίες δεν μπορούν να εξακριβωθούν χρησιμοποιώντας πληροφορίες από την τρέχουσα νευροψυχολογική και κλινική αξιολόγηση ή από απομονωμένες περιοχές του εγκεφάλου [102] - [104].

Ως εκ τούτου, οι αλλαγές στο δίκτυο εγκεφάλου που σχετίζονται με την ΥΝΔ, θα μπορούσαν να βοηθήσουν στον προσδιορισμό της διάγνωσης και του προγραμματισμού της θεραπείας και μπορεί να παράσχουν περαιτέρω πληροφορίες σχετικά με το αν η ομοιότητα των εγκεφαλικών συνδέσεων και των μεταβολών της λειτουργικής συνδεσιμότητας (Functional Connectivity – FC) της ΥΝΔ σε σχέση με τους ΗΝΔ, ΝΑ και υγιών μπορεί να προετοιμάσει το δρόμο για την εξέλιξη της ΥΝΔ στο στάδιο της ΝΑ. Παρόλο που τρεις συστηματικές ανασκοπήσεις έχουν διερευνήσει μεταβολές FC στο φάσμα της ΝΑ και εγκεφαλικής συνδεσιμότητας [37], [38], [105], κανένα από αυτά δεν έχει χρησιμοποιήσει τον όρο "ΥΝΔ (SCD)" στα ερευνητικά τους κριτήρια. Πιο συγκεκριμένα, εκτός από τη μη χρήση της λέξης-κλειδιού "ΥΝΔ" στα ερευνητικά τους κριτήρια, οι συγγραφείς αναζητούσαν μόνο μελέτες fMRI σε άτομα με ΝΑ ή ΗΝΔ και υγιείς συμμετέχοντες, ή αλλαγές στις ιδιότητες δικτύου όπως έχουν διερευνηθεί με άλλα εργαλεία νευροαπεικόνισης, όπως το ΜΕΓ [38]. Σε μια άλλη συστηματική ανασκόπηση [37], οι συγγραφείς δεν αναζητούν μελέτες σχετικές με την ΥΝΔ, δεδομένου ότι η συστηματική ανασκόπηση πραγματοποιήθηκε το 2009, ενώ η πρώτη μελέτη που εξέτασε τις ιδιότητες του εγκεφαλικού δικτύου σε πληθυσμό με ΥΝΔ δημοσιεύθηκε το 2012 [53] διεξήγαγαν μια ακριβή και επαρκή αναζήτηση βιβλιογραφίας αποκλειστικά για δυσλειτουργία του Δικτύου Αυτόματης Λειτουργίας (ΔΑΛ -Default Mode Network – DMN) σε μια ευρεία ποικιλία ψυχικών διαταραχών. Σε μια άλλη ανασκόπηση [105] που διεξήχθη το 2010, οι συγγραφείς εκτός από το ότι δεν συμπεριελάμβαναν οποιαδήποτε μελέτη εγκεφαλικού δικτύου σε πληθυσμό με ΥΝΔ, ανέφεραν διάφορες μελέτες νευροαπεικόνισης, οι οποίες διερεύνησαν την FC μεταξύ των περιοχών του εγκεφάλου με τη χρήση νέων μεθόδων. Αυτή η συγκεκριμένη ανασκόπηση δεν διερεύνησε τα πιθανά ευρήματα της συνδεσιμότητας του εγκεφάλου άλλων μελετών που παρατηρούσαν

αλλοιώσεις του εγκεφαλικού δικτύου με άλλα εργαλεία νευροαπεικόνισης, όπως το MEG. Ως εκ τούτου, οι υπάρχουσες ανασκοπήσεις αποτελούνται κυρίως από μελέτες που εστιάζουν στη σύγκριση νοητικά υγιεινών ηλικιωμένων και ατόμων σε πιο προχωρημένα στάδια, όπως ΗΝΔ ή / και ΝΑ ή διάφορες νευρολογικές διαταραχές ή μελέτες που διερευνούν ιδιότητες ενός συγκεκριμένου δικτύου (δηλ. χρησιμοποιώντας ένα συγκεκριμένο εργαλείο νευροαπεικόνισης (π.χ. fMRI). Ως εκ τούτου, η γνώση σχετικά με την πορεία των μεταβολών της FC στα άτομα με ΥΝΔ είναι πραγματικά περιορισμένη και δεν υπάρχει μελέτη ανασκόπησης που να συνοψίζει και να διερευνά τα ευρήματα όλων των μελετών στον τομέα του εγκεφαλικού συνδέσμου στον πληθυσμό με ΥΝΔ. Ωστόσο, μέχρι σήμερα, αρκετές μελέτες έχουν αναφέρει διαταραχές του εγκεφαλικού δικτύου και τις φαινομενικές συνδέσεις στους ανθρώπους στα αρχικά στάδια της ΝΑ, όπως αυτό της ΥΝΔ.

Μελέτες νευροαπεικόνισης και δικτύου σχετικά με την ΥΝΔ

Πολλές μελέτες υποστηρίζουν την ιδέα ότι οι δείκτες που προέρχονται από την ανάλυση ηλεκτροεγκεφαλογραφημάτων, όπως η ισχύς του δικτύου του εγκεφάλου, το χαρακτηριστικό μονοπάτι και ο συντελεστής συσταδοποίησης και άλλα ποσοτικά χαρακτηριστικά, διαφέρουν μεταξύ των φυσιολογικών ατόμων της τρίτης ηλικίας, ΗΝΔ και ΝΑ, τουλάχιστον σε επίπεδο ομάδας [108] - [111] ενώ σε προχωρημένα στάδια έχει βρεθεί μειωμένο χαρακτηριστικό μονοπάτι σε άλφα και βήτα κύματα με σχετικώς διατηρούμενο (ή ελαφρώς αυξανόμενο) ΣΣ, υποδηλώνοντας ότι στη ΝΑ το δίκτυο γίνεται πιο τυχαίο όταν μελετάται στις υψηλότερες συχνότητες [101]. Συγκεκριμένα, πρόσφατες νευροφυσιολογικές μελέτες με ΗΕΓ έχουν αναφέρει ενδιαφέροντα αποτελέσματα σχετικά με τη πιθανή χρήση ανάλυσης ιδιοτήτων δικτύων και γραφημάτων σε δίκτυα εγκεφάλου σε στάδια πριν από την εμφάνιση της ΝΑ όπως ΗΝΔ καθώς και πιο προχωρημένα όπως η ΝΑ [43], [109] - [115]. Αυτές οι μελέτες ανέφεραν αλλοιωμένες ιδιότητες δικτύου σε σφαιρικό (όλο τον εγκέφαλο) και τοπικό επίπεδο σε πρώιμα στάδια ΝΑ, υποστηρίζοντας την πιθανή κλινική σημασία αυτών των μελετών. Πιο συγκεκριμένα, καθώς η νόσος εξελίσσεται, φαίνεται ότι έχει διαταραχθεί η ακεραιότητα των νευρικών κυκλωμάτων σε δομικά και λειτουργικά συστήματα που σχετίζονται με νοητικές λειτουργίες υψηλού επιπέδου σε ασθενείς με ΝΑ, που ερμηνεύονται κυρίως ως απώλεια των ιδιοτήτων μικροκόσμου (small world properties) που παρατηρείται στην εγκεφαλική συνδεσιμότητα και που τελικά μπορεί να εξηγήσει νοητικές ελλείψεις στους ασθενείς. Από την άλλη πλευρά αρκετές μελέτες έχουν συγκρίνει γραφήματα των ατόμων με ΗΝΔ και ΝΑ και υγιών και έχουν προτείνει ότι οι τιμές των ασθενών με ΗΝΔ είναι ενδιάμεσες αυτών των υγιών και των ΝΑ [109], [116], [117], γεγονός που υποδηλώνει ότι στο στάδιο ΗΝΔ, οι συνδεσιμότητα του εγκεφάλου είναι περιορισμένη όταν συγκρίνονται οι ασθενείς με ΗΝΔ με υγιή ηλικιωμένα άτομα. Επιπλέον, μελέτες με βάση το ΗΕΓ και το ΜΕΓ αποκάλυψαν ότι τα άτομα με ΗΝΔ εμφάνισαν σημαντική μείωση της ισχύος των συχνοτήτων στην «άλφα» μπάντα με εμφανή επιβράδυνση του ΗΕΓ, μειωμένη πολυπλοκότητα των σημάτων ΗΕΓ και διαταραχές στον συγχρονισμό ΗΕΓ σε σύγκριση με τους φυσιολογικούς ηλικιωμένους [118] [120]. Επομένως, η διερεύνηση της διάδοσης των διαταραγμένων δικτύων και των εγκεφαλικών αλλαγών σε προκλινικά στάδια σχετιζόμενα με τη ΝΑ, μπορεί να οδηγήσει σε νέες υποθέσεις σχετικά με την ΥΝΔ που δεν μπορούν να

εξακριβωθούν χρησιμοποιώντας πληροφορίες από την τρέχουσα νευροψυχολογική και κλινική αξιολόγηση ή από απομονωμένες περιοχές του εγκεφάλου [102] - [104].

Υλικά και μέθοδοι

Από την 1η Σεπτεμβρίου 2015 έως τις 30 Αυγούστου 2016, οι συμμετέχοντες επιλέχθηκαν από την κλινική μνήμης και άνοιας της 3ης Νευρολογικής Κλινικής του Αριστοτελείου Πανεπιστημίου Θεσσαλονίκης και από τα Κέντρα Ημέρας της Ελληνικής Εταιρεία Alzheimer και Συναφών Διαταραχών (GAADRD). Οι ασθενείς με ΝΑ διαγνώστηκαν από ειδικό νευρολόγο-ψυχίατρο (ΜΤ) σύμφωνα με το ιστορικό, τη νευρολογική εξέταση, τις νευροψυχολογικές εξετάσεις, τη μαγνητική τομογραφία (MRI) και άλλες απαραίτητες εργαστηριακές εξετάσεις. Η μελέτη διεξήχθη σύμφωνα με τη Διακήρυξη του Ελσίνκι και εγκρίθηκε από την επιστημονική και ηθική επιτροπή της GAADRD (27/11/2016). Συνολικά, 112 συμμετέχοντες συμμετείχαν στη μελέτη. Από αυτά είκοσι άτομα δημιούργησαν δεδομένα που περιείχαν αρκετό θόρυβο και παράσιτα κίνησης κεφαλής ή ματιών και επομένως αποκλείονταν από την επακόλουθη ανάλυση των δεδομένων, αφήνοντας 92 συμμετέχοντες να συμπεριληφθούν εν τέλει στη μελέτη. Η ομάδα των ατόμων με ΥΝΔ αποτελούταν από 20 συμμετέχοντες (μέσος όρος ± ΤΑ: ηλικία = 64,9 ± 7,92), η ομάδα των ΗΝΔ αποτελούταν από 30 συμμετέχοντες (μέση τιμή ± ΤΑ: ηλικία = 70,40 ± 5,96), ενώ η ομάδα των ΝΑ αποτελούταν από 20 συμμετέχοντες ± ΤΑ: ηλικία = 73,20 ± 8,17). Μια επιπλέον ομάδα υγιών ηλικιωμένων 22 (HC) συμμετείχαν με ένα παρόμοιο εύρος ηλικιών (μέσος όρος ± ΤΑ: ηλικία = 67,22 ± 4,03). Οι συμμετέχοντες με ΝΑπληρούσαν τα κριτήρια για την άνοια τύπου Alzheimer της APA, (1994), του Εθνικού Ινστιτούτου Νευρολογικών Διαταραχών και συμπτωμάτων εγκεφαλικού επεισοδίου / ΝΑκαι των συσχετιζόμενων διαταραχών (NINCDS-ADRDA) και τα κριτήρια του διαγνωστικού και στατιστικού εγχειρίδιου ψυχικών διαταραχών (DSM-V) για πιθανά κριτήρια ΝΑ [126], χρησιμοποιήθηκαν τα κριτήρια Petersen για τη διάγνωση της ΗΝΔ [127] και οι πρόσφατες κατευθυντήριες γραμμές NIH-AA-IWG1 [128] και IWG-2 [129] καθώς και οι τελευταίες προτάσεις της ομάδας SCD-I WG για τον καθορισμό της ΥΝΔ. Συγκεκριμένα, η ομάδα ελέγχου και η ΥΝΔ ήταν νοητικά και σωματικά υγιή άτομα και είχαν παρόμοια ηλικία και εκπαιδευτικό υπόβαθρο. Η συγκατάθεση με έγγραφη ενημέρωση αποκτήθηκε από όλους τους συμμετέχοντες πριν από τη συμμετοχή τους στη μελέτη.

Επιπλέον, ο προσδιορισμός των συμμετεχόντων στα άτομα με ΥΝΔ περιλάμβανε περαιτέρω επιδείνωση της μνήμης σε σχέση με άλλες νοητικές λειτουργίες και σε σχέση με άλλα άτομα της ίδιας ηλικίας που εμφανίστηκαν τα τελευταία πέντε χρόνια, όπως καθορίστηκε από το ιατρικό ιστορικό των ατόμων (ισχαιμικές βλάβες στη μαγνητική τομογραφία, εξέταση αίματος), ψυχιατρική (συνέντευξη, κλίμακα κατάθλιψης, ψυχοδραστικές ουσίες κτλ.) ή άλλες μορφές διαταραχής της μνήμης. συστηματική αιτιολογία με προσεκτική αξιολόγηση εργαστηριακών αποτελεσμάτων συμπεριλαμβανομένων δειγμάτων αίματος, δομικής μαγνητικής τομογραφίας, ιατρικού ιστορικού ασθενούς και συμπληρωματικών ερωτηματολογίων σύμφωνα με τα κριτήρια που έχουν οριστεί από την Ευρωπαϊκή ομάδα SCD- I WGI [130]. Επιπλέον, ήπια κλινική κατάθλιψη (σύμφωνα με την παθοφυσιολογία, συχνά συνυπάρχουσα πάθηση) θεωρήθηκε ως κριτήριο αποκλεισμού για όλους τους ασθενείς με ΥΝΔ, ΗΝΔ και ΝΑ με την προϋπόθεση ότι μπορεί να είναι η κύρια αιτία των νοητικών ελλειμμάτων. Τα

καταθλιπτικά συμπτώματα αξιολογήθηκαν με την κλίμακα αξιολόγησης της κλίμακας της γηριατρικής κατάθλιψης (GDS) χρησιμοποιώντας βαθμολογία αποκλεισμού <5 κατά τη διάρκεια της επίσκεψης. Αντίστοιχα, χρησιμοποιήσαμε την Κλίμακα Αντίληψης Άγχους (PSS) [133] και τη Νευροψυχιατρική Κλίμακα (NPI) [134] για την αξιολόγηση της διάθεσης και της συναισθηματικής κατάστασης, αφού αποτελεί κρίσιμο στοιχείο για την αξιολόγηση των ασθενών με ΥΝΔ και ΗΝΔ καθώς η συναισθηματική δυσφορία μπορεί να προκαλέσει ή να επιδεινώσει τη νοητική κατάσταση. Για να διασφαλιστεί η συμμόρφωση με τα κριτήρια και η ακριβής κατηγοριοποίηση των τριών ομάδων, εξετάστηκαν προσεκτικά όλα τα διαθέσιμα δεδομένα κάθε ατόμου, συμπεριλαμβανομένων των εργαστηριακών αποτελεσμάτων, των δεδομένων της νευροαπεικόνισης, του ιατρικού ιστορικού των ασθενών και των συμπληρωματικών ερωτηματολογίων. Κατά συνέπεια, οι συμμετέχοντες με δομικές ανωμαλίες, περιλαμβανομένων τυχαίων ευρημάτων όπως κύστες ή αγγειακά εγκεφαλικά που μπορεί να οδηγήσουν σε ΥΝΔ λόγω αγγειακών ή ΥΝΔ λόγω ψυχιατρικών προβλημάτων, εξαιρέθηκαν επίσης από την παρούσα μελέτη. Έτσι, λαμβάνοντας όλα τα προαναφερθέντα μέτρα, ελαχιστοποιήσαμε τον κίνδυνο να συμμετέχουν άτομα με ΥΝΔ εξαιτίας άλλων παραγόντων εκτός της ΝΑ.

Οι συμμετέχοντες που συμμετείχαν στη μελέτη υποβλήθηκαν σε 10 λεπτη καταγραφή του σήματος του εγκεφάλου σε κατάσταση ηρεμίας. Κατά τη διάρκεια της καταγραφής, οι συμμετέχοντες έλαβαν οδηγίες να παραμείνουν χαλαροί με ελαφρώς τα μάτια κλειστά. Επίσης δόθηκε η εντολή να προσπαθήσουν να μην κουνιούνται και να μην σφίγγουν το στόμα τους. Οι συμμετέχοντες ενημερώθηκαν ότι, σε περίπτωση υπερβολικής κίνησης των ματιών, ο βοηθός της έρευνας θα τους υπενθυμίσει να στερεώσουν το βλέμμα τους στη μαύρη οθόνη. Το ΗΕΓ καταγράφηκε σε συνθήκες ηρεμίας κλειστών (EC) και ανοιχτών (EO) ματιών, για τουλάχιστον 2 λεπτά για κάθε περίοδο. Τα άτομα κλήθηκαν να παραμείνουν ακίνητα, είχαν οδηγίες να μην ανοιγοκλείνουν τα μάτια τους και να αφήνουν το μυαλό τους να περιπλανηθεί. Για τη προεπεξεργασία των σημάτων, χρησιμοποιήθηκε το λογισμικό NetStation 4.3.

Εξαγωγή Δεδομένων και Κατασκευή Δικτύων

Τα άτομα εξετάστηκαν σε ένα ελαφρώς φωτισμένο, ήχο-εξασθενημένο δωμάτιο. Μετά τη φάση προετοιμασίας, οι συμμετέχοντες ενημερώθηκαν για τη παρούσα μελέτη. Τα δεδομένα HD-EEG συλλέχθηκαν με το EGI 300 Geodesic EEG σύστημα (GES 300) με 256 ηλεκτρόδια Geodeic Sensor Net Net (HCGSN) και ρυθμό δειγματοληψίας 250Hz (EGI Eugene, OR). Τα ηλεκτρόδια τοποθετήθηκαν σύμφωνα με το σύστημα μονταρίσματος «256 HCGSN ενηλίκων 1.0». Τα σήματα HD-EEG καταγράφηκαν σε σχέση με το κεντρικό ηλεκτρόδιο αναφοράς (Cz) και με το AFz ως ηλεκτρόδιο γείωσης. Η αντίσταση όλων των ηλεκτροδίων διατηρήθηκε κάτω από 50 kΩ όπως συνιστάται (NetAmps 300, Electrical Geodesics, Inc. (EGI), Eugene, OR, ΗΠΑ). Τα δεδομένα HD-EEG αναλύθηκαν χρησιμοποιώντας το λογισμικό Net Station 4.3 (EGI).

Σύγκριση ιδιοτήτων δικτύου μεταξύ συμμετεχόντων

Μεταξύ των ιδιοτήτων του δικτύου (ΣΣ και ισχύς του δικτύου), οι μέσες τιμές για την ομάδα των υγιών ήταν υψηλότερες σε σύγκριση με τις υπόλοιπες ομάδες. Τα αποτελέσματα έδειξαν στατιστικά σημαντική διαφορά μεταξύ των ομάδων μετά από

έλεγχο t-test για ανεξάρτητα δείγματα και One-way ANOVA τόσο ως προς το συντελεστή συσταδοποίησης ως και προς την ισχύς του τοπικού δικτύου (βρεγματικά ηλεκτρόδια). Οι μέσες τιμές τόσο των μετρήσεων του σφαιρικού όσο και του τοπικού δικτύου παρουσιάζονται επίσης για κάθε ομάδα. Ο έλεγχος μεταξύ των 4 ομάδων διεξήχθη για να συγκρίνει το αποτέλεσμα της διάγνωσης και στις δύο μετρήσεις δικτύου (ΣΣ και ισχύς) σε τοπικό και σφαιρικό επίπεδο. Υπήρξε μια σημαντική επίδραση της διάγνωσης σε κάθε ιδιότητα του δικτύου σε τοπικό επίπεδο (βρεγματικά ηλεκτρόδια) στο επίπεδο p <.05 μεταξύ των τεσσάρων ομάδων στο ΣΣ: [F (3, 88) = 4.76, p = 0.004] και στην ισχύ [F (3,88) = 4,69, ρ = 0,004]. Εντούτοις, δεν βρέθηκε στατιστική σημαντική διαφορά σε σφαιρικό επίπεδο μεταξύ των τεσσάρων ομάδων Συντελεστής Συσταδοποίησης: [F (3, 86) = 0.50, p = 0.681] και Ισχύς: [F (3, 86) = 0.67, p = 0.569]. Ωστόσο ο έλεγχος t-test για ανεξάρτητα δείγματα ανά δύο έδειξε ότι:

Ο Σφαιρικός και Τοπικός συντελεστής συσταδοποίησης: Σύμφωνα με το t-test ανεξάρτητου δείγματος ήταν υψηλότερος για την ομάδα των υγιών (M = 0,79, SD = 0,07) σε σύγκριση με την ομάδα της ΥΝΔ (M = 0,72, SD = 0,09). t (40) = 2,39, ρ = 0,02, την ομάδα της ΗΝΔ (M = 0,71, SD = 0,09). t (50) = 0,41, ρ = 0,004 και της ομάδας των ατόμων με ΝΑ (M = 0,68, SD = 0,11). t (40) = 3.62, ρ = 0.001 αντίστοιχα. Από την άλλη πλευρά, όσον αφορά τον συντελεστή συσταδοποίησης σε σφαιρικό επίπεδο, οι συγκρίσεις μεταξύ των ομάδων δεν έδειξαν κάποια στατιστικά σημαντική διαφορά. Παρόλο που η ομάδα των υγιών (M = 0,31, SD = 0,07) έδειξε μεγαλύτερες τιμές όσον αφορά τον σφαιρικό συντελεστή συσταδοποίησης, σε σύγκριση με την ομάδα των ΥΝΔ (M = 22,30, SD = 3,35). t (40) = 0,13, ρ = 0,897, ΗΝΔ (M = 0,29, SD = 0,07). t (48) = 0,94, ρ = 0,351 και ΝΑ (M = 0,68, SD = 0,11). t (40) = 0,97, p = 0,337, δεν βρέθηκε στατιστικά σημαντική διαφορά.

Η Σφαιρική και τοπική ισχύς: Σύμφωνα με το t-test ανεξάρτητων δειγμάτων, η τοπική ισχύς στα βρεγματικά ηλεκτρόδια έδειξε υψηλότερες τιμές για τους υγιείς (M = 22,56, SD = 1,65) σε σύγκριση με τους ΥΝΔ (M = 21,11, SD = 2,10). t (40) = 2.50, ρ = 0.01, MOI (M = 20.83, SD = 2.25). t (50) = 3,01, ρ = 0,004 και την ομάδα ΝΑ (M = 20,12, SD = 2,66). t (40) = 3,48, ρ = 0,001. Από την άλλη πλευρά, όσον αφορά την παγκόσμια ισχύ, μεταξύ των ομάδων δεν φάνηκε καμία στατιστικά σημαντική διαφορά. Παρόλο που η ομάδα των υγιών (M = 99.24, SD = 18.08) είχε μεγαλύτερες τιμές σε σύγκριση με την ομάδα των ΥΝΔ (M = 97.70, SD = 20.18). t (40) = 0,26, ρ = 0,795, ΗΝΔ (M = 94,01, SD = 16,20). t (48) = 1,07, ρ = 0,287 και ΝΑ (M = 91,88, SD = 21,91). t (40) = 1,18, p = 0,245, δεν βρέθηκε στατιστική σημαντική διαφορά ούτε μεταξύ τους.

Συζήτηση

Έχει προταθεί ότι η ΥΝΔ μπορεί να προηγείται της ΗΝΔ, η οποία με τη σειρά της συχνά συνδέεται με την εξέλιξη της σε ΝΑ [36], [87]. Επομένως, η αναζήτηση μιας εύλογης σχέσης μεταξύ των παθολογικών νοητικών ελλειμμάτων και της διαταραχής της εγκεφαλικής συνδεσιμότητας (brain connectome) στην ΥΝΔ χρειάζεται περαιτέρω διερεύνηση. Η παρούσα εργασία μας συνοψίζει τα ευρήματα της κύριας μελέτης στην εγκεφαλική συνδεσιμότητα και την ΥΝΔ χρησιμοποιώντας ένα υψηλής ευκρίνειας ΗΕΓ, υπογραμμίζοντας την προστιθέμενη αξία των ιδιοτήτων δικτύου που βασίζονται στη θεωρία των γραφημάτων για να εξαχθούν συμπεράσματα σχετικά με την πρόοδο του

σταδίου της ΥΝΔ σε πιο προχωρημένα στάδια της ΝΑ. Η μελέτη μας επιβεβαιώνει και υπογραμμίζει την αλλαγή ως προς την τοπολογική οργάνωση και συνδεσιμότητα του εγκεφάλου σε άτομα με ΥΝΔ και παρέχει τη δυνατότητα χρήσης των ιδιοτήτων δικτύων ως μελλοντικών βιοδεικτών. Επιπλέον, προτείνεται ότι η διαταραγμένη λειτουργία του εγκεφάλου, που χαρακτηρίζεται από μειωμένο συντελεστή Συσταδοποίησης και μειωμένη ισχύ σε συγκεκριμένους κόμβους, μπορεί να σχετίζεται με την ΥΝΔ. Αυτό σημαίνει ότι η ΥΝΔ βρίσκεται σε μια κάπως ενδιάμεση κατάσταση μεταξύ των δύο συνθηκών, της υγιούς γήρανσης και της ΗΝΔ. Δεδομένου ότι πρόκειται για την πρώτη μελέτη που ανέλυσε τις ιδιότητες του δικτύου σε άτομα με ΥΝΔ χρησιμοποιώντας το ΗΕΓ, συγκρίνουμε τα αποτελέσματά μας με άλλες κοινές προσεγγίσεις που χρησιμοποίησαν διαφορετικούς τρόπους (π.χ. ΜΕΓ, fMRI) ή με μελέτες ΗΕΓ οι οποίες διερεύνησαν πιθανές διαφορές μεταξύ υγιών ατόμων και ατόμων σε πιο προχωρημένα στάδια (π.χ. ΗΝΔ και ΝΑ).

Συγκεκριμένα, η πλειονότητα των μελετών που εξετάζει τη συνδεσιμότητα σε όλους τους κόμβους Δίκτυο αυτόματης Λειτουργίας (ΔΑΛ), παρουσιάζει διαταραγμένα μοτίβα και παρεκκλίνουσες συνδέσεις στο ΥΝΔ σε σύγκριση με τους υγιείς [51], [55], [59], [60]. Πιο συγκεκριμένα, η πλειοψηφία των αποτελεσμάτων των μελετών πρότεινε ότι η ΥΝΔ παρουσίασε σημαντικά μικρότερη συνδεσιμότητα μεταξύ των κόμβων που εντοπίζεται κυρίως στη περιοχή του ιπποκάμπου σε σύγκριση με την ομάδα των υγιών [60]. Συγκεκριμένα, βρέθηκε μειωμένη συνδεσιμότητα στις περιοχές όπως ο ραχιαίος προμετωπιαίος φλοιός, ο έσω βρεγματικός λοβός και ο οπίσθιος φλοιός του προσαγωγίου στην ομάδα των ασθενών με ΥΝΔ σε σχέση με τους υγιείς [51] (βρεγματικές και ινιακές περιοχές) [59]. Παρομοίως, στη μελέτη μας, τα άτομα με ΥΝΔ είχαν μικρότερη ισχύ και συντελεστή Συσταδοποίησης στη βρεγματική περιοχή σε σύγκριση με τους υγιείς αλλά μεγαλύτερες τιμές από αυτές των ΗΝΔ και ΝΑ. Παρόμοια αποτελέσματα μπορούν επίσης να βρεθούν σε μελέτες του δικτύου της λευκής ουσίας του εγκεφάλου, που αποδεικνύουν μειωμένη ισχύ στην βρεγματική περιοχή σε άτομα ΥΝΔ [61]. Επιπλέον, έχουν παρατηρηθεί μειωμένοι ρυθμοί μεταβολισμού της γλυκόζης στο κατώτερο βρεγματικό λοβό στα άτομα με ΥΝΔ και αυτό μπορεί να βοηθήσει στην εξήγηση αυτών των αλλαγών συνδεσιμότητας [147]. Ως εκ τούτου, η βρεγματική περιοχή, ως λειτουργικός πυρήνας του ΔΑΛ, παρουσιάζοντας ατροφία στη πορεία της νόσου, επηρεάζει την εγκεφαλική συνδεσιμότητα σε ασθενείς με ΝΑ [148] - [154]. Αυτό ανοίγει το δρόμο για περαιτέρω μελέτη της δραστηριότητας του εγκεφάλου και των ιδιοτήτων δικτύων σε κατάσταση ηρεμίας, και συγκεκριμένα των βρεγματικών περιοχών που εμπλέκονται στην ανάκτηση μνήμης [155], όπου επηρεάζονται ευρέως στο φάσμα της ΝΑ. Επιπλέον, μειωμένος συντελεστής Συσταδοποίησης καθώς και μειωμένη ισχύ σε σύγκριση με τους υγιείς βρέθηκε στη μελέτη μας επίσης και στην ομάδα των ασθενών με ΗΝΔ και ΝΑ. Αυτό σημαίνει ότι όλες οι συνδέσεις που επηρεάζονται στους ασθενείς με ΥΝΔ έχουν επίσης διαταραχθεί στο στάδιο της ΗΝΔ με παρόμοιο τρόπο και οι δύο ομάδες παρουσιάζουν παρόμοιο λειτουργικό μοτίβο σύζευξης, υποδηλώνοντας ότι οι ΥΝΔ έχουν ενδιάμεσες αλλαγές συνδεσιμότητας σε συγκεκριμένες περιοχές όπως οι αλλαγές που εντοπίζονται και στη σύγκριση μεταξύ ΗΝΔ και υγιών. Η περιοχή του προσφηνοειδούς λοβίου (precuneus) είναι το τμήμα του ανώτερου μέσου βρεγματικού λοβού του εγκεφάλου. Αυτό μπορεί να εξηγήσει επίσης τα συμπεράσματά μας που δείχνουν ότι οι διαταραχές των ιδιοτήτων δικτύων στο βρεγματικό λοβό παρατηρούνται ευρέως σε άτομα με ΥΝΔ σε σύγκριση με τους υγιείς, αλλά και σε μεταγενέστερα στάδια (ΗΝΔ και ΝΑ).

Συμπερασματικά, η μελέτη μας εντόπισε χαμηλότερες τιμές του συντελεστή Συσταδοποίησης και ισχύος μεταξύ των ομάδων ασθενών (ΥΝΔ, ΗΝΔ και ΝΑ) σε σύγκριση με τους υγιείς, γεγονός που υπογραμμίζει τη σημασία των μετρήσεων των ιδιοτήτων δικτύου για την πρόβλεψη πιθανής μελλοντικής μετατροπής του σταδίου της ΥΝΔ σε πιο προχωρημένα στάδια. Από όσο γνωρίζουμε, δεν υπάρχουν μελέτες που έχουν διερευνήσει τη συνδεσιμότητα εγκεφάλου χρησιμοποιώντας HD-EEG σε συμμετέχοντες με ΥΝΔ σε σύγκριση με ΝΑ, ΗΝΔ και υγιείς. Στη μελέτη μας, επίσης εξετάσαμε τις καμπύλες ROC για να καθορίσουμε το βαθμό ειδικότητας και ευαισθησίας κάθε δείκτη (συντελεστής συσταδοποίησης και ισχύος σε σφαιρικό και τοπικό επίπεδο). Με βάση τα ευρήματά μας, ο τοπικός συντελεστής συσταδοποίησης και η τοπική ισχύς μπορεί να θεωρηθούν ως δυνητικοί βιοδείκτες για την ανίχνευση της ΥΝΔ, καθώς διακρίνει την ΥΝΔ από τους υγιείς με ευαισθησία 75% και ειδικότητα 64% (AUC = 71%, σε καμπύλες ROC) (AUC = 73% και AUC = 79%, αντίστοιχα, σε καμπύλες ROC) και τους ΝΑ από τους υγιείς με ευαισθησία 65% και τους ΗΝΔ από τους υγιείς με ευαισθησία 80% και εξειδίκευση 64% και 82% (AUC = 79). Η μελέτη μας προσθέτει στην υπάρχουσα βιβλιογραφία ότι το στάδιο της ΥΝΔ μπορεί πράγματι να αντανακλά τις νευρωνικές αλλαγές σε επίπεδο δικτύου και υποδηλώνει ότι η συνδεσιμότητα του εγκεφάλου και ειδικότερα η εκτίμηση του συντελεστή Συσταδοποίησης και της ισχύος στις βρεγματικές περιοχές θα μπορούσε να χρησιμεύσει ως δυνητικός βιολογικός προγνωστικός δείκτης της επακόλουθης εξέλιξης σε ΝΑ. Ωστόσο, απαιτούνται περισσότερες προοπτικές έρευνες για την περαιτέρω αναπαραγωγή, επέκταση και διερεύνηση των πιθανών παθοφυσιολογικών μηχανισμών που σχετίζονται με αυτές τις μεταβολές του εγκεφαλικού δικτύου στο ΥΝΔ. Σε γενικές γραμμές, το στάδιο της ΥΝΔ παρουσίασε μικρότερο συντελεστή Συσταδοποίησης και ισχύος σε τοπικό δίκτυο, αλλά διατηρούσε ιδιότητες δικτύου σε σφαιρικό επίπεδο.

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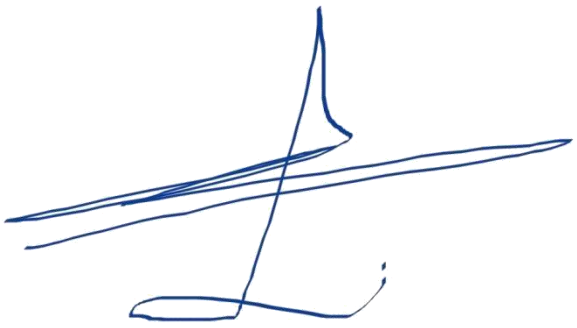
Ioulietta Lazarou



Title

Electrophysiological study of People with Cognitive Impairment related to Alzheimer's Disease by using a High- density EEG EGI GES 300

Mrs Ioulietta S. Lazarou

SUPERVISOR: Dimitrios Kugiumtzis, Professor, AUTH

Dr Ioannis Komaptsiaris, Researcher A, CERTH - ITI
Professor Magda Tsolaki, Medical School, AUTH

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder which has been found to change brain's structure and function several years before the onset of clinical manifestations [1]. In 2019 "ADI estimates that there are over 50 million people living with dementia globally, a figure set to increase to 152 million by 2050. Someone develops dementia every three seconds and the current annual cost of dementia is estimated at US $1trillion, a figure set to double by 2030" [3]. Therefore, the early identification of brain mechanisms in individuals that are likely to develop AD, such as people with Subjective Cognitive Decline (SCD) or Mild Cognitive Impairment (MCI) is among the greatest challenges of current research in the field of AD [2].

1.1 Importance and Significance of the Study

Recently, brain activity and brain network across several brain neurodegenerative diseases has been the focus of different researches [4,5]. Thus, the field of brain connectome has great promise for elucidating the complex relationships between SCD who will eventually develop AD and Functional Connectivity (FC) patterns.

1.2 Neuroimaging- Connectivity – Network – Metrics

1.2.1 Electroencephalography (EEG) – Time Series Resting State EEG Data

In particular, since time series data are gaining interest the last decades, novel network techniques by analyzing neuroimaging data (e.g., EEG) are being developed. More specifically, EEG is an electrophysiological monitoring method to record electrical activity of the brain. It is a noninvasive method to record brain activity, with the electrodes placed along the scalp. There are several EEG types with the number of the electrodes ranging from 15 – 256 electrodes. In general, EEG provides a temporally precise measure of neurophysiological function during different tasks (e.g., watching images, hearing a noise etc) and conditions (e.g., resting state condition – awake with closed eyes). The applications of this method are extremely wide-reaching, as they allow investigators to explore a nearly infinite number of domains where it is of interest to understand the relative timing of neural events (Figure 1). To collect EEG data, electrodes are placed on the scalp and face, and scrubbed with a conducting gel to facilitate measurement of the electrical activity of populations of neurons (scalp electrodes) and muscle activity (face electrodes). The recorded waveforms of the EEG reflect the cortical electrical activity, measured in microvolts (mV), while the main frequencies of the human EEG waves are: 1) Delta: 0.5 - 3 Hz, 2) Theta: 3.5 to 7.5 Hz, 3) Alpha: 7.5 - 13 Hz, 4) Beta: 14 -38 Hz. Finally, the brain is a highly complex system functioning based on interrelationships between multiple functional units simultaneously. Therefore, brain activity through EEG, can be seen as a time series, in particular, EEG can measure the activity of the brain over a specific time period (Figure 2).

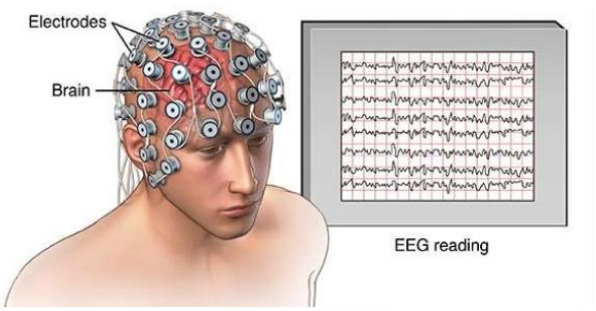


Figure 1 EEG

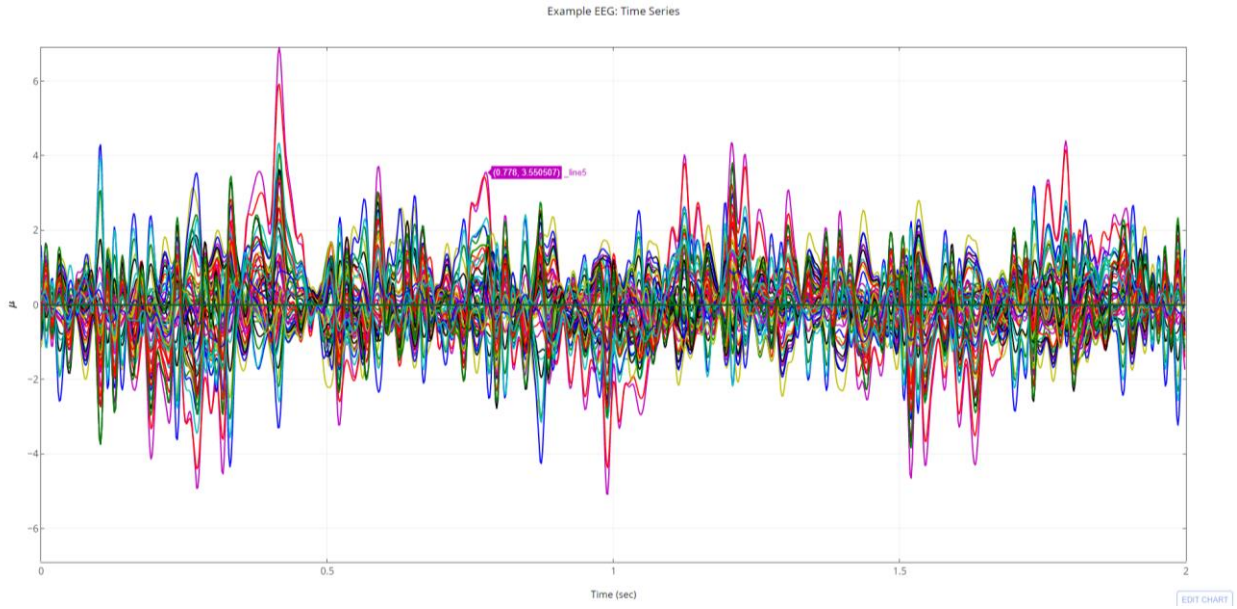


Figure 2: Example of EEG time series data (https://plot.ly/~samuelgthorpe/26/example-eeg-time-series.embed)

The use of EEG for the diagnosis of dementia is a viable option; it is widely available in neurological clinics, inexpensive, noninvasive, and potentially portable [6–9]. EEG has shown potential in identifying the earliest signs of brain dysfunction in subjects with SCD, MCI or dementia [10]. Among the diverse approaches of EEG, quantitative analysis of EEG rhythms in subjects who are awake and at rest (resting state EEG), which is the simplest method in terms of experimental design, is widely studied and is an easily accessible neurophysiological method for examining alterations and connectivity changes that commonly occur within the dementia spectrum [11–19].

Several studies support the idea that biomarkers derived from EEG rhythms, differ among normal elderly, MCI, and AD subjects, at least at group level [20–23]. In particular, recent neurophysiological EEG studies have reported interesting results on the use of complex networks and graph theory on brain networks in predementia stages such as MCI as well as more advanced like AD [21–25,25–28]. These studies have reported altered global and local metrics in early stages of AD, supporting the potential clinical relevance of this kind of studies.

1.2.2 Functional connectivity (FC) – Pearson Correlation Coefficient

Brain connectivity refers to how functionally specialized units of the brain interact with one another. Its analysis can be carried out with three different forms of connectivity, anatomical (AC), functional (FC) and effective (EC) [29]. AC, which is also called structural connectivity, forms the connectome through synaptic connections between neurons or fiber tracks connecting neuron pools at distant brain regions. FC [1] refers to statistical dependencies between distinct and distant brain regions or electrodes. This can be quantified with measures such as coherence, correlation. EC on the other hand refers to influence that one neural system exerts on the other. Of these FC finds important application in classifying subjects when using EEG. FC in EEG generally refers to the temporal correlations between time series data from 2 or more independent EEG

[1] https://www.sciencedirect.com/topics/medicine-and-dentistry/functional-connectivity

channels or sources. Network properties such as strength between regions of interest may be extracted from the data [30]. In many cases, EEG FC has been shown to reflect the underlying structural properties of the brain. For example, coherence between electrodes placed on each hemisphere is weakened in individuals with AD [31,32].

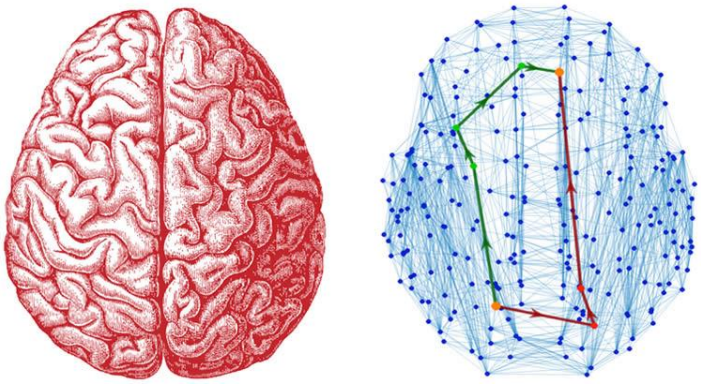


Figure 3 Illustration of the brain and the brain network

Quantification of FC is often performed using Spatial Covariance Matrix, Phase Locking Value (PLV), Phase Lag Index (PLI) or other similar approaches [33,34]. However, the most common one in EEG network studies is the Pearson's correlation coefficient (PCC) [35]. PCC measures the degree of co-activation of two brain regions or electrodes, that is, how well the time series from the two brain regions or electrodes are correlated. PCC is still the most widely used measure to quantify FC given its simple interpretability and wide acceptability [35]. Basically, time-series data analysis, such as EEG, select some regions of interest (ROI) as seeds and generate a connectivity map of the human brain by determining whether other regions are functionally connected to these seeds. A convenient method to define such a metric is based on PCC between the time courses of the seed region and any other brain region under consideration. Correlation is measured by the PCC r between variables X and Y is calculated by:

$$r_{XY} = \frac{\sum_{i=1}^{n}(X_i - \overline{X})(Y_i - \overline{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \overline{X})^2}\sqrt{\sum_{i=1}^{n}(Y_i - \overline{Y})^2}}$$

A correlation matrix is a table showing correlation coefficients between electrodes. Each cell in the table shows the correlation between two variables. A correlation matrix is used to summarize data, as an input into a more advanced analysis, and as a diagnostic for advanced analyses.

1.2.3 Brain Network

A network is a mathematical representation of a real-world complex system and is defined by a collection of nodes (vertices) and links (edges) between pairs of nodes. Several research approaches and research projects have tried to explore this very interesting territory of brain network/ brain connectome[2]. In general, graph theory in brain research describes a network as a set of nodes, which are the components of a system (represented in the brain network perspective as a region of interest – ROI), and a number of edges, representing the connection between each pair of nodes [36–38] (Figure

[2] http://www.humanconnectomeproject.org/about/

3). Several neuroimaging tools (e.g., MRI, EEG, etc) have been extensively used in order to extract different network properties. Brain connectome provides a more holistic view by assessing and modeling the entire human brain as a set of several networks and assessing whole-brain organization, widespread changes or disruptions as entity [39–41]. There is evidence that abnormalities in brain networks appear both in early stages such as SCD and MCI as well as in later ones such as AD [28,42–49]. Investigating changes in predementia stages of AD continuum, from a brain connectome perspective, may give rise to new hypotheses about underlying pathophysiology that cannot be ascertained using information from current neuropsychological and clinical assessment or from isolated brain regions [50–52]. More specifically, nodes in EEG brain networks usually represent specific electrodes, while links represent functional connections [53,54], depending on the dataset. The nature of nodes and links in individual brain networks is determined by combinations of brain mapping methods, anatomical parcellation schemes, and measures of connectivity. Many combinations occur in various experimental settings [55]. The choice of a given combination must be carefully motivated, as the nature of nodes and links largely determines the neurobiological interpretation of network topology [56]. Nodes should ideally represent brain regions or electrodes with coherent patterns of extrinsic anatomical or functional connections [30]. An individual network measure may characterize one or several aspects of global (whole brain network) and local brain connectivity (specific brain region). In addition to the type of networks, links are also differentiated on the basis of their weight and directionality. In detail, weighted links contain information about connection strengths. Weights in functional and effective networks may represent respective magnitudes of correlational or causal interactions [30].

More specifically, as the disease progresses, it appears that AD patients have disrupted neural circuits integrity in structural and functional systems related to high-level cognitive functions, mostly interpreted as an altered small-world capacity observed in neuronal connectivity and that may ultimately explain cognitive deficits in patients [36]. On the other hand several studies have compared MCI graphs with AD and healthy subjects have suggested that MCI topologies are intermediate [21,57,58], suggesting that in MCI stage, brain connectome changes are subtle when comparing MCI with healthy elderly subjects. Therefore, investigating brain changes in predementia stages of AD continuum, from a brain connectome perspective, may give rise to new hypotheses about underlying pathophysiology that cannot be ascertained using information from current neuropsychological and clinical assessment or from isolated brain regions [50–52].

1.2.4 Network Metrics

Network metrics are often represented in multiple ways. Thus, metrics of individual network elements (such as nodes or links) typically quantify connectivity profiles associated with these elements and hence reflect the way in which these elements are embedded in the network. Measurement values of all individual elements comprise a distribution, which provides a more global description of the network. In addition to these different representations, network measures also have binary and weighted, directed and undirected variants [30]. Connectivity metrics, which attempt to characterize the strength

of connectivity, are plentiful. In Table 1 we present some commonly studied in brain connectome studies.

Table 1 Commonly Studied Network Properties of Brain Connectome Studies

Network Properties	Meaning
Small World	The small-world measure is defined as the clustering coefficient divided by the path length, and a network is considered "small-world" if this measure is much larger than 1.
Rich Club	The extent to which central or well-connected nodes also interconnect to each other
Strength	The number of connections from the node of interest to other nodes of the network
Path Length	The minimum number of edges that must be traversed to reach from one node of interest to another
Clustering Coefficient	The number of connections between the nearest neighbors of a node proportional to the maximum number of connections
Transitivity	The transitivity is based on the relative number of triangles in the graph, compared to the total number of connected triples of nodes
Modularity	Modularity shows the strength of division of a network into modules (clusters)
Betweenness	The proportion of shortest paths between any two nodes that pass through this node
Global/ Local Efficiency	The average global efficiency of subgraphs for each node containing the neighbors of that node

1.2.4.1 Clustering Coefficient (CC)

The weighted clustering-coefficient $Ci^{weighted}$ of node *i* is expressing the likelihood that the neighbors of node *i* are interconnected, providing information on how strong node *i* and its direct neighbors are clustered, formally [30] (Figure 4):

$$C_i^{weighted} = \frac{\sum_{j,h \in N} (w_{ij} w_{ih} w_{jh})^{\frac{1}{3}}}{k_i(k_i - 1)},$$

where *wij, wih and wjh* indicate the weight between each pair of the three nodes of the network (i,h and j) is the edge weight between two nodes.

The overall clustering-coefficient *C* of a graph *(G)* was computed as the average of *Ci* over all voxels *i* in *G*:

$$C^{weighted} = \frac{1}{n} \sum_{i \in N} C_i^{weighted}.$$

By means of weighted network we refer to network where the ties among nodes have weights assigned to them

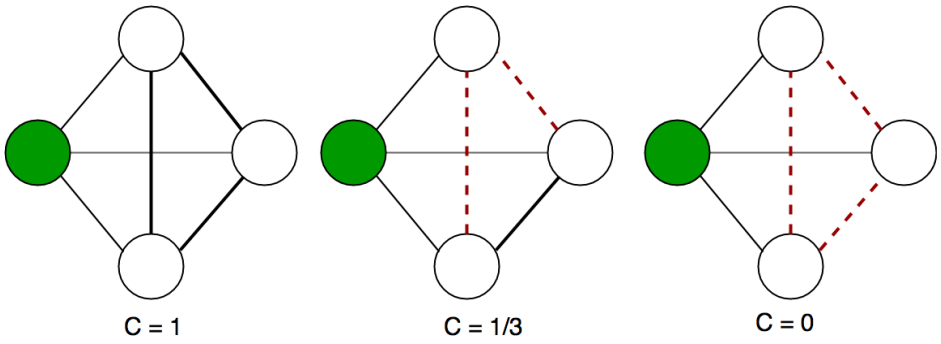


Figure 4 Example of calculating CC in three different networks

1.2.4.2 Strength (S)

Next, the connection strength *Si* of each node *i* in the network is computed as the sum of the weights of all the connections of node *i*, providing information on the total level of (weighted) connectivity of a node. The strength indicates how strongly the node is connected with its neighboring nodes, by summing all edge weights connected with the node. For Weighted Undirected graphs, strengths are calculated as sums over either rows or columns of the weighted correlation matrix. Strength equals to the sum of connectivity weights attached to a given node. The S is defined as:

$$S_i = \sum_{j \in N} w_{ij}.$$

In turn, the total connection strength *S* of the graph *G* is computed as the sum of *Si* for all nodes N in *G:*

$$S = \frac{1}{N} \sum_{i \in N} S_i.$$

1.3 Overview of Sections of the Master Thesis

In Section 2, we outline the importance of the network analysis and brain connectome in cognitive impairment due to AD. Moving forward, we outline and present our study aim in Section 3. Moreover, we conducted a review of the current literature to present every relevant study in brain connectome to SCD (Section 4). The following section (Section 5.1) presents the materials and methods of the cross-sectional study of the four groups of people with cognitive impairment within the dementia spectrum, ranging from SCD to AD compared to HC. The first subsection (Section 5.1.1) describes the setting of the study and the participants' characteristics, while the two following subsections (Section 5.1.2 & Section 5.1.3) present in detail the neuropsychological assessment of the participants and the EEG recording protocol. Also, the fourth subsection (5.1.4) presents the EEG network analysis, the connectivity measures (5.1.4.1) and network metrics (5.1.4.2) we used and presents in detail the EEG acquisition, while Section 5.1.5 presents the statistical analysis we have followed. Furthermore, the Section 5.2 presents an insightful description of the evaluation methods and data analysis between the groups. Section 6 highlights the main outcomes of the study and compares them with other similar approaches, while Section 7

underlines the main conclusion of the thesis and presents future research questions. Finally, Section 8 presents all the contributors of this thesis.

2 Clinical Validity of SCD in AD continuum

While people age, few people are those who experience decay on cognitive functions that extends beyond what is considered healthy ageing, yet not exhibiting dementia. This transitional cognitive state has been characterized as MCI [59]. However, a subjective awareness of memory loss by the elderly in the absence of any organic or identifiable condition by neuropsychological examination is called SCD [60]. This state is known to cause memory disturbance and has great value as a preliminary stage of MCI [61] and as a predictor of dementia [62]. The endeavor to detect the very early signs of dementia with the possibility of developing interventions to slow its progression has provided the impetus for increased interest in SCD. What do we know about the brain function and network properties and brain connectome of people with SCD? How is the FC of people who have just started to be aware of their memory loss? These were the questions that triggered our research interest and this study comes to present some preliminary pieces of evidence regarding people with SCD and their brain functionality.

Till today, the prognostic value of SCD condition is a controversial issue [63–65]. In population-based studies, including both cognitively normal subjects and those with probable cognitive impairment, the prevalence of SCD ranges from 10% to 81% [65,66]. Several longitudinal population-based studies of SCD in older adults without dementia have reported an association with future cognitive decline [67–69], dementia [70–75], AD [76,77], depression [78] and AD pathology at autopsy [79]. However, a variety of studies have demonstrated a relationship between SCD and putative AD biomarker evidence, such as gray matter volume loss [76,80], cerebral hypo metabolism [63], amyloid accumulation [81,82], brain activation on functional imaging [83,84], volume reduction of cortex [76], CSF biological markers [85] and genetic risk for AD [86]. Clinic-based studies of similar groups have reported that, compared to healthy controls, SCD exhibit smaller volume of left and right hippocampus [87], entorhinal cortex [76] and posterior callosal [71], reduced frontoparietal, parahippocampal, medial temporal and grey matter density [88], as well as reduced metabolism of parahippocampal region [89]. On the other hand, it has been suggested that SCD, at the stage of preclinical AD, may indicate initial cognitive declines that are otherwise undetectable with standardized objective tests of cognitive performance [90].

More specifically, there is a growing evidence to imply that the stage of SCD is associated with the presence of brain changes of early cognitive decline related to AD [91–94]. In detail, SCD is defined as a perceived self-reported decline of cognitive abilities without objective abnormal clinical and neuropsychological findings [80] and it has been recently characterized by a set of criteria suggested by SCD – International Working Group (SCD-IWG) [95]. People with SCD have been regarded with greater rates of incident MCI and subsequently AD compared to normal elders without cognitive concerns and its conversion rate per year to MCI and dementia is around 6.6% and 2.3% respectively [96]. In particular, there is 4.5 - 6.5 times greater risk for people with SCD to convert to MCI or AD than it is for people without cognitive complaints [60,74,97,98]. Despite the fact that SCD could represent a prodromal stage of MCI, at this point it remains unclear which of the individuals with SCD will convert in MCI and subsequently AD [96,99]. Nevertheless, people with SCD have been found to exhibit neurodegenerative

changes in their brain [94,100–102] in similar regional patterns with people in more advance stages of AD continuum [48,49,84,87]. Several studies have evaluated the spatial profiles of brain activity among SCD people [76,101,103,104], while others have shed light on connectivity between brain regions of people with SCD [45,48,105–107] by investigating brain connectome and network properties through graph theoretical approaches [43,48,49,103,108,109].

Consequently, since the stage of SCD related to AD pathophysiology is hardly distinguishable from healthy controls, it is important to seek and investigate the neurophysiological, psychological and cognitive decline of populations that are still considered to be in the expected cognitive level, based on their age and education. This will allow us to gain better knowledge about the dementia process and its potential correlation with changes or abnormalities in brain functionality. An illustration of all stages ranging from healthy ageing to AD is depicting in Figure 5.

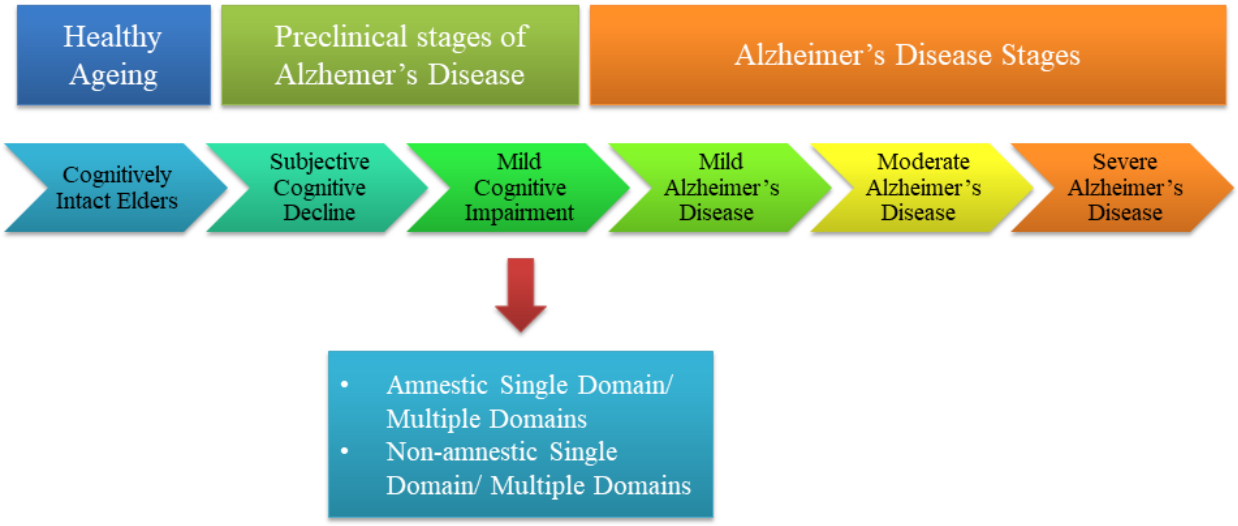


Figure 5 Stages from Healthy Ageing to Alzheimer's Disease

3 Study Aim

To the best of our knowledge, this is the first study to date employing graph metrics built from electrophysiological data form HD-EEG (EGI GES 300), to characterize the evolution of network dynamics throughout the preclinical stages of AD including healthy elders without cognitive concerns (HC), healthy elders with SCD, MCI and AD patients. To this aim, we employed resting state activity recorded with electroencephalography (EEG), we constructed correlation matrices and weighted undirected networks to precisely detect brain network properties across AD spectrum and compare their results with standard neuropsychological tests. Electrophysiological measures of synchrony derived from EEG, fMRI and MEG have been proven useful in the detection of different pathologies [4,110,111] and specifically in AD [21,22,25,27,112–115]. Based on previous imaging studies, we expected to detect altered network properties in SCD patients with respect to HC. More importantly, we hypothesized that SCD elders will show alterations in the same direction of those exhibited by MCI patients, although to a lower extent, thus exhibiting intermediate values between HC and MCI. In this study, we aim to test this conjecture by assessing the potential clinical sensitivity of clustering coefficient and strength both at global and local level across the AD spectrum in a sample of patients with AD, individuals with MCI, and those with SCD. To the best of our knowledge, no previous study has evaluated this type of network metrics in EEG resting state activity in an aging and neurodegeneration context of SCD population in particular. Based on established knowledge about the anatomical distribution of the pathophysiology and resting-state EEG alterations in AD, we investigated brain alterations both at the whole-brain level and at specific brain areas implicating parietal structures, reflecting a graded pattern of differences corresponding with disease severity.

4 Review of the Literature and network studies on SCD

In order to gain a better knowledge of the so far neuroimaging studies focusing on brain connectome in SCD population, we have conducted a review of studies exploring SCD characteristics with a focus on brain connectome studies which explored whether FC alterations of SCD with respect to MCI, AD and HC can help us make assumptions on the progression of SCD into more advanced stages of cognitive impairment related to AD pathology. Since a great body of literature suggests that cognitive decline in people with AD and MCI is not only caused by the damage of a single or local brain region but also results from changes in several brain areas and their connections, investigation of brain connectome of pre dementia stages could be insightful. Therefore, we present a number of studies, with the intention to provide a better understanding about the brain connectome of people with SCD and highlight its importance in early detection and its potential predictive value of this stage.

4.1 Searching Strategy

The following electronic databases have been searched for relevant studies: MEDLINE / PubMed, EMBASE, Scopus, IEEExplore, Research Gate and Google Scholar. The specific focus of our search was brain connectome and brain networks based on graph theory as measured by any neuroimaging tool (MRI, EEG and MEG) in people with SCD. Studies related to cognitive decline due to other medical reasons such as epilepsy, Parkinson's disease, Multiple Sclerosis, stroke etc, or studies with cognitively intact participants only were excluded from our review. Databases were searched using keyword combinations containing "subjective cognitive decline" or "SCD" or "subjective memory complaints" or "SMC" or "subjective cognitive complaints" or "SCC" or "cognitive complaints" or "cognitive impairment" or "elders" or "Alzheimer's Disease" or "AD" or "mild cognitive impairment" or "MCI" or "cognitive decline" or "dementia" or "subjective cognitive impairment" or "SCI" or "brain imaging" or "Magnetic Resonance Imaging" or "MRI" or "neurophysiology" or "neuroimaging" or "Magnetoencephalography" or "electroencephalography" "EEG" or "Diffusion Tensor Imaging" or "DTI" or "brain networks" or "network" or "default mode network" or "DMN" or "executive control network" or "salience network" or "sensorimotor network" or "auditory network" or "visual network" or "gray matter network" or "white matter network" or "functional connectivity" or "connectome" or "resting state networks" or "functionality" or "synchronization likelihood" and "connectivity", separately or combined. We included only English-language journal articles that directly analyzed network properties in participants with SCD. We conducted the systematic review with journal papers and conference articles up to 30 October, 2018 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [116].

4.2 Study Selection

The titles and abstracts of identified studies were screened for relevance to the topic. Those studies considered not to be relevant on the grounds of the topic have been excluded. Studies which were relevant to the topic, but probably not very relevant on the grounds of population or brain network analysis have been read carefully for consideration and then excluded or remained for the qualitative analysis. Only full

text/papers for all studies, which appear to meet the inclusion criteria, were selected for this review. The flow chart of Figure 6 was used to facilitate the selection process of our study.

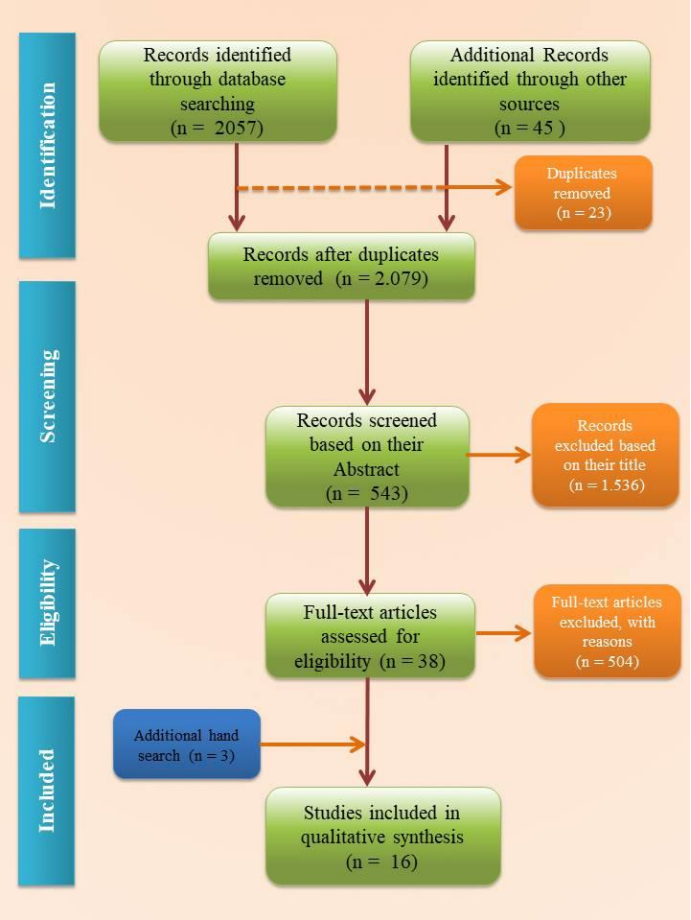


Figure 6 PRISMA flow diagram of the article screening and selection process. Article selection was conducted in accordance with PRISMA guidelines for reporting systematic reviews (Moher et al., 2009).

4.3 Data Extraction

Our search identified 2.102 potentially relevant papers. We further examined if there were any duplicates of the retrieved articles (23 duplicates identified and removed). Of the remaining 2.079 articles, 1.536 studies were removed after screening of their title. Five hundred forty three (543) articles were screened thoroughly, based on both title and abstract, to only include studies involving individuals with SCD related to AD and brain network analysis. Screening of titles, abstracts, and full texts yielded 38 publications that met the inclusion criteria. Further screening for studies focused on brain connectome, network analysis based on graph theory in the target population (SCD) reduced the sample to 16 articles (Figure 6) from 2012 to 2018. In the following sections, we appraise these articles with respect to the participants' characteristics, the neuroimaging tool used; the utilized network based analysis, the clinical findings and outcomes. From the 16 selected studies, only two investigated brain connectome including SCD group without other groups as comparators. One of which conducted a clinical trial with Ganglioside to SCD and the other examined the SCD cohort longitudinally. A total of 13 studies involved both HC and participants with SCD. The majority of studies included also participants with MCI (nine studies), while some included participants at different stages of AD (four

studies). Among the selected studies, seven used fMRI, four used MEG, three applied DTI method and two used structural MRI as neuroimaging tool. Although we screened and searched also for studies which used EEG to study brain connectome of SCD population, we did not find any published study which met our research criteria (e.g., EEG related studies included only MCI or AD). Also the majority of studies has examined the participants for general cognitive function and has reported their demographic characteristics.

4.4 Network Properties and Neuroimaging Studies of Subjective Cognitive Decline

Several neuroimaging studies have explored multiple network properties of people with a wide variety of mental disorders [117] and AD [118] in particular. More specifically, alterations in graph topology and its corresponding metrics allow the examination of the evolving interactions among multiple brain areas and regions both in cognitive-related diseases, such as AD. In detail, the last decade more and more studies suggest that the human brain can be modeled as a network, showing the brain connectivity, referred to as a brain connectome [119]. Brain connectome provides a more holistic view by assessing and modeling the entire human brain as a set of several networks and assessing whole-brain organization, widespread changes or disruptions as entity [39–41]. There is evidence that abnormalities in brain networks appear both in early stages such SCD and MCI as well as in later ones such as AD [28,42,105–109,120–124,43,125–127,44–49,103]. In particular, it has been suggested that FC changes in individuals at risk in sifting at more advanced stages of cognitive impairment after some time, may occur before extensive structural brain damage and objective cognitive decline [40,83,105,118,128–130] takes place. Many studies have reported that people with AD, from the pre dementia to dementia stages, have significant hub-concentrated lesion distributions [131,132]. Furthermore, alterations in the precuneus, which is the main component of the Default Mode Network (DMN)[3], have been suggested to begin almost 15 - 20 years before the manifestation of dementia-related symptoms [38,105,109,133,134]. There are also several studies which have demonstrated that the disruption of FC involves the areas of the posterior DMN, comprising largely the posterior cingulate cortex, a key hub of DMN and are evident in the earliest stages of AD and MCI [122,134–137], underlying decreased FC between parietal and occipital regions. Previous research has identified differences in brain activation of the cingulate cortex, precuneus, superior parietal lobule, and medial temporal lobe during encoding in patients with AD and amnestic MCI compared to healthy controls [138–140]. Therefore, network changes associated with SCD could help in determining the diagnosis and treatment planning and may provide further insights on whether the resemblance of brain connectome and FC alterations of SCD with respect to MCI, AD and HC can pave the way on the progression of SCD into more severe stages of AD. However, the knowledge about the course of FC alterations in SCD is really in its infancy.

[3] Default Mode Network (DMN): a large scale brain network of interacting brain regions known to have activity highly correlated with each other and distinct from other networks in the brain

Despite the fact that in the majority of the studies, brain connections were interrupted in SCD group compared to HC, small - world properties were widely preserved in SCD. This implies that the brain has not undergone such damage to demonstrate a randomized network. While still preserving some intact network properties, SCD elders exhibited disruptions (node degree, path length etc) at the network level compatible with those evidenced in MCI, although to a lower degree. Our literature search showed that several neuroimaging studies reinforces the idea of SCD as a preclinical asymptomatic stage of AD with potential future progression in more advanced stages. In other words, MCI and AD groups suffer severe disturbances in the connections of rich - club brain regions and present a more random brain network instead of small – world. On the other hand, SCD have relatively stable connections as far as small - world properties and rich - club is concerned compared to HC, but they exhibit lower values in between specific regions connections over posterior brain structures. These findings reinforce that disrupted nodal strength of posterior DMN nodes and temporal regions of the brain, and increases over anterior areas is evident among SCD as in MCI and AD respectively. This localized disconnection has been proposed also in previous works demonstrating that posterior DMN subsystem connectivity declines within the AD spectrum [141]. These results further add to the growing body of literature that SCD may indeed reflect neuronal changes at network level and suggests that brain connectome could serve as a potential biological predictor of subsequent cognitive decline associated with AD. For instance, neuroimaging studies have identified AD - related brain interruptions, that also occur in SCD before cognitive deficits are detected in neuropsychological assessment. However, more longitudinal research is required to further replicate, expand and investigate the potential pathophysiological mechanisms that are associated with these brain network changes in SCD. In general, SCD showed less network strength, global efficiency and local efficiency and a longer shortest - path length but preserved properties such as rich – club and small world.

5 MAIN PART

5.1 Materials and Methods

5.1.1 Settings and Participants

From 1 September 2015 to 30 August 2016, participants were recruited from the memory & dementia clinic of the 3rd Neurological Department of Aristotle University of Thessaloniki, Greece[4], and from the Day Centers of the Greek Association of Alzheimer's Disease and Related Disorders (GAADRD)[5]. Patients with AD were diagnosed by a neuropsychiatrist (MT) according to history, neurological examination, neuropsychological tests, structural magnetic resonance imaging (MRI), and other necessary laboratory examinations. The study was carried out in accordance with the Declaration of Helsinki, and was approved by the GAADRD scientific & ethic committee (27/11/2016). Overall, 112 participants took part in the study. Twenty individuals generated electroencephalographic (EEG) data that contained excessive head or eye movement artifacts, and hence were excluded from subsequent data analysis, leaving 92 participants to be included in the study. The SCD group consisted of 20 participants (mean ± SD: age = 64. 9 ± 7.92), the MCI group consisted of 30 participants (mean ± SD: age = 70.40 ± 5.96), while the AD group consisted of 20 participants (mean ± SD: age = 73.20 ± 8.17). An additional elderly group of 22 healthy controls participants (HC) was also formed, spanning a similar range of ages (mean ± SD: age = 67.22 ± 4.03). Participants fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for dementia of Alzheimer type (APA, 1994) and the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [142], Petersen criteria for MCI [143] and the recent NHI-AA-IWG1 [144] and IWG-2 Guidelines [145] as well as the latest SCD-I Working Group suggestions [146] for SCD. More specifically, HC and SCD were mentally and physically healthy who shared a similar age and educational background. Since there are some existing studies [147,148], which have shown that in discrimination tasks, the amplitude is greater, with smaller corresponding latencies, in left-handed participants versus right-handers, to avoid any confounding factor, we excluded people who were left-handed. Thus, all participants were right-handed, had normal or corrected-to-normal vision and audition (effective communication between patient and clinician), and had no other neurological, psychological or serious medical disorders. Written informed consent was obtained from all participants prior to their participation in the study.

Moreover, the identification of SCD participants further included self-perceived memory decline compared to other cognitive functions and in reference to others of the same age occurring during the past five years as determined by the individuals' medical history and an informant report, at an age cut-off of 60. We additionally strived to exclude participants where other etiologies could explain self-perceived memory deficits including vascular (examination of ischemic lesions of MRI, blood

[4] http://www.med.auth.gr/
[5] http://www.alzheimer-hellas.gr/index.php/el/

testing), psychiatric (interview, depression scale, psychoactive drugs etc), or other systematic etiologies by carefully evaluating laboratory results including blood samples, structural MRI, the patient's medical history, and additional questionnaires following the SCD-I Working Group criteria [146]. Our team of multi-disciplinary clinicians meticulously ensured the compliance of these criteria for every SCD, MCI or AD participant prior to classifying them as such. Moreover, a mild clinical depression (as per pathophysiology often a comorbid condition) was considered an exclusion criterion for all SCD, MCI and AD patients provided it may be the primary cause of the cognitive deficits. Depressive symptoms were assessed with the Geriatric Depression Scale (GDS) rating scale using a cut-off score of <5 at the time of the study visit. Equivalently, we have used the Perceived Stress Scale (PSS) [149] and Neuropsychiatric Inventory (NPI) [150] for the assessment of mood and emotional state, since it is a critical component for the evaluation of the SCD and MCI subjects, since emotional distress can cause or exacerbate cognitive problems. To ensure adherence to the inclusion criteria and accurate categorization of our three groups, all available data of each individual including laboratory results, neuroimaging data, the patients' medical history, and additional questionnaires were carefully reviewed. Consequently, participants with structural abnormalities, including incidental findings such as cysts or vascular infarcts which may lead to SCD due to vascular or SCD due to psychiatric problems were also excluded from the present study. Thus, by taking all aforementioned measures, we have minimized the risk of recruiting participants with SCD due to reasons other than AD.

Inclusion criteria: Subjects were aged 60 years or older (in Table 2 it is shown the average age with the standard deviation for each group of study). Additional inclusion criteria for the SCD and HC subjects were to have a normal general medical, neurological and neuropsychological examination without any chronic systemic illness, not receiving psychoactive drugs, and without a history of present or previous neurological or psychiatric disease. More specifically, criteria used for diagnosis of SCD were based on recent studies in the same direction [69,80,84]: "i) self-perceived memory deficit persistent and severe enough to seek advice from a healthcare professional; ii) memory complaint perceived as a clear decline from previous memory performance and not a lifelong or longstanding non-progressive deficit; iii) performance within normal limits for age and educational background on the neuropsychological tests; iv) absence of any physical or psychiatric illness that may be responsible for the perceived memory deficit; v) normal activities of daily living; vi) absence of MCI or dementia".

Exclusion criteria: included i) any severe physical illness, ii) current psychiatric or neurological disorder, history of drug or alcohol abuse and use of neuro modifying drugs other than Cholinesterase Inhibitors or Memantine in AD group, iii) having any somatic disorder that may have caused subjective or objective cognitive impairment such as a cerebrovascular accident, other neurodegenerative diseases, traumatic brain injury, brain tumor, alcohol abuse and depression or other psychiatric disorders, iv) left handedness, v) being under treatment at least for 90 days before the experiment. During the neuropsychological interview, particular attention was devoted

to rule out subjects reporting any symptom of severe memory problems or depressive symptoms.

5.1.2 Neuropsychological Assessment

All participants went through a standard neuropsychological assessment, which involved a psychiatric interview, mental state examination, medical history, physical and neurological examination, as well as a detailed cognitive assessment. All subjects were assessed for the magnitude of cognitive decline at baseline, using the Global Deterioration Scale (GDS) [151] for age-associated cognitive decline and primary degenerative dementia. Those with a GDS score of 2 were considered as potential study subjects of SCD. All subjects were assessed with a standardized neuropsychological test battery. Briefly, subjects at GDS stage 1 are free of subjective complaints or objective evidence of cognitive impairment. Subjects at GDS stage 2 have subjective complaints in the absence of objectively manifested deficits. Subjects at GDS stage 3 have mildly manifest deficits consistent with a diagnosis of MCI [15]. Subjects at GDS stage 4 or greater meet DSM-V criteria for dementia. Cognitive assessment was performed by means of a neuropsychological battery designed to comprehensively evaluate attention, working memory, memory, executive functioning, and language. We administered also Brief Cognitive Rating Scale (BCRS) [152], where participants with score at the scale of 2 were considered as SCD. The neuropsychological battery included the Greek version of Mini Mental State Examination (MMSE) [153] to assess the general cognitive function, RBMT-story Direct and delayed recall [154] for episodic memory, Rey Osterrieth Complex Figure Test copy and delay recall (ROCFT-copy and delayed recall) [155] which measures visuospatial long-term memory and executive functioning, Rey Auditory Verbal Learning Test (RAVLT) in order to measure the ability of learning and long-term memory, Trail Making Test part-B [156], to examine visuo-spatial ability, attention and executive functions, FAS for testing verbal fluency [157], Functional Rating Scale for Dementia (FRSSD) and Functional and Cognitive Assessment Test (FUCAS) [158] to assess daily functionality. Assessment of mood and emotional state is a critical component for the evaluation of the SCD and MCI subjects as emotional distress can cause or exacerbate cognitive problems. Therefore, the assessment of mood comprised of interview data and responses to brief self-report measures Perceived Stress Scale (PSS) [149] and Neuropsychiatric Inventory (NPI) [150]. Psychiatric disorder in SCD participants was excluded by a psychologist using the Structured Clinical Interview for DSM-IV Axis I Disorders Clinical Version (SCID-CV) [159]. Relevant physical illness was excluded by physical and neurological examination and appropriate investigations.

Table 2 The table presents mean±SD (standard deviation) of demographic characteristicsamong participants (HC = 22, SCD= 20, MCI= 30, AD=20)

	Groups			
	HC	**SCD**	**MCI**	**AD**
Age	67,22 (4,03)	64,90 (7,92)	70,40 (5,96)	73,20 (8,17)
Gender (M:F)	8:14	7:13	8:22	8:12
Education	13,16 (4,59)	13,75 (3,29)	11,45 (4,06)	9,77 (5,51)

5.1.3 Resting state EEG Recording

Participants resting EEG activity was recorded for 10 minutes. During recordings of resting-state EEG, participants were instructed to remain relaxed and close their eyes and minimize blinking or mouth movements, while a research assistant monitored for excessive blinking or horizontal eye movements by visual inspection of EEG during recording. EEG was recorded in eyes closed (EC) and eyes open (EO) resting conditions, for at least 2-3 min for every period. Subjects were asked to sit still, were instructed not to blink or move their eyes, and let their mind wander.

5.1.4 EEG Data Acquisition and Network Construction

HD-EEG data were collected with the EGI 300 Geodesic EEG system (GES 300) using a 256-channel HydroCel Geodesic Sensor Net (HCGSN) and a sampling rate of 250Hz (EGI Eugene, OR). Electrodes were positioned according to the '256 HCGSN adult 1.0' montage system. HD-EEG signals were recorded relative to a vertex reference electrode (Cz) and with AFz as the ground electrode. The impedance of all electrodes was kept below 50 kΩ as recommended [160] for the high-input impedance amplifier (NetAmps 300, Electrical Geodesics, Inc. (EGI), Eugene, OR, USA). The HD-EEG data were analysed offline for artifact-detection and pre-processing using the Net Station 4.3 software (EGI)[6]. Figure 7 illustrates the pipeline process for data acquisition and analysis of the resting state EEG.

HD-EEG data were initially filtered with 5th-order bandpass butterworth IIR filter of 0.3-75 Hz and then segmented using 500 samples. Artefact detection and bad channel replacement was performed. More specifically, after the segmentation, artefact detection was conducted with Net Station artefact detection tool, which automatically detects eye blinks and eye movements. Identification of "bad" segments was also performed, marking a segment as "bad" when the peak-to-peak amplitude was higher than 100μV. A channel was entirely marked as bad throughout recording, if it was marked bad for more than 10% of the segments. Signals from rejected (bad) electrodes were replaced using an interpolation processes provided by the 'bad channel replacement' algorithm (Net Station 4.3). Data were afterwards baseline-corrected using a 200msec pre-stimulus period using the Net Station 4.3 software (EGI) and average re-referenced to transform into reference-independent values. The brain network analysis was conducted in Matlab 2018b (The Mathworks, Natick, USA). Figure 7 outline the methodology of the EEG acquisition, construction of the weighted undirected networks and extraction of the metrics derived from Correlation Matrices.

[6] https://m.egi.com/clinical-division/clinical-division-clinical-products/ges-300

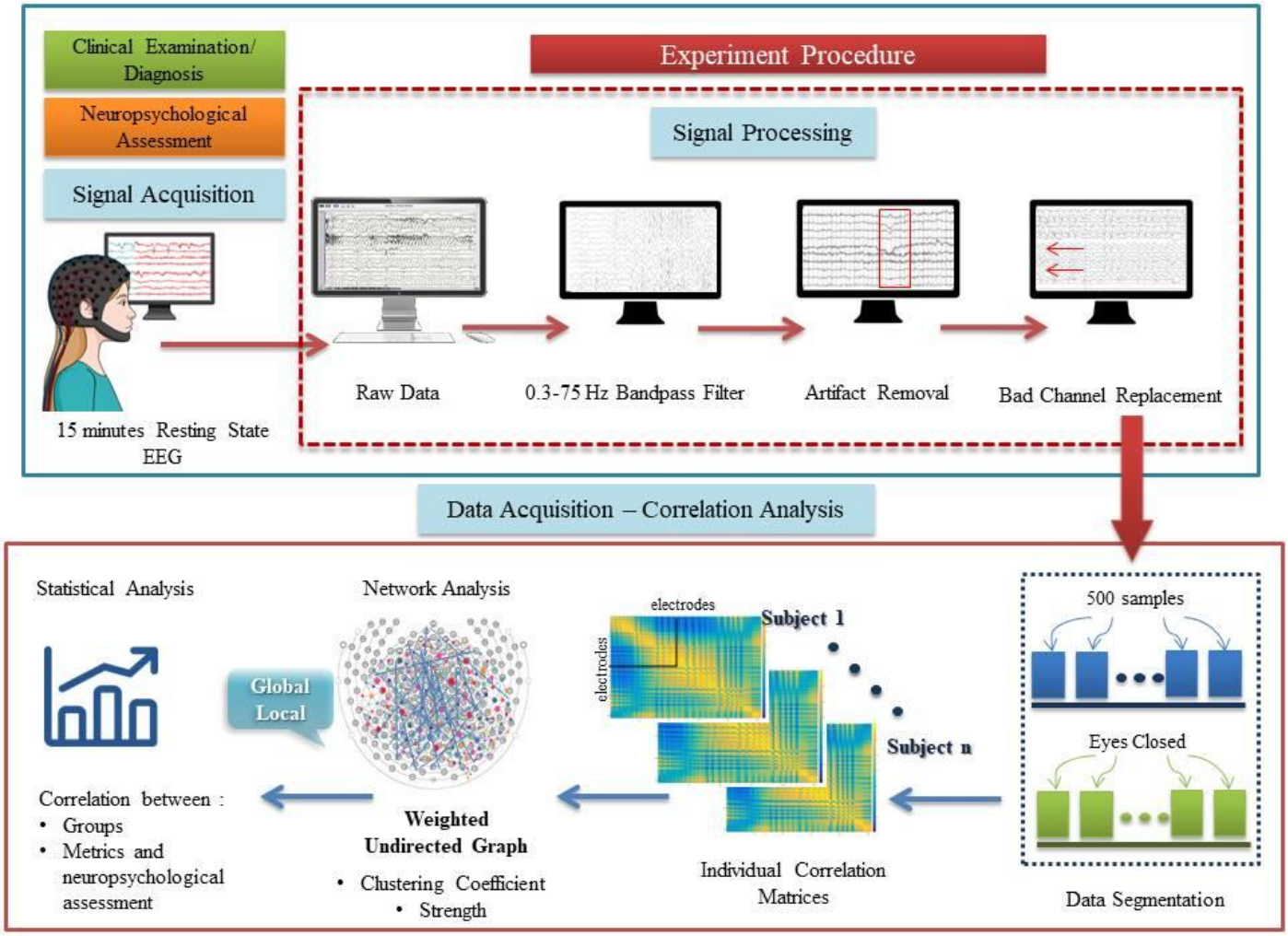


Figure 7 Outline of the methodology for extracting the network metrics derived from Correlation Matrices.

5.1.4.1 Connectivity – Correlation

The Pearson's Correlation Coefficient (PCC) was used to measure connectivity between all pairs of electrodes. PCC which is also referred to as Pearson's correlation (PC) is a measure of normalized covariance between two continuous variables. It can be calculated by dividing covariance of two variables from the product of their standard deviations. Weighted matrices were created (Figure 12 and Figure 13 as presented in Section 5.2.2) using the PCC between the time series of each pair of electrodes (all electrodes at global level, only selected parietal electrodes at local level). Negative values of the matrices were included to consider also the functional anti correlations.

5.1.4.2 Global brain and local network analysis

Global and local network characteristics were explored using the Brain Connectivity Toolbox (brain-connectivity-toolbox.net). Network metrics, including global and local clustering coefficient and network strength were assessed to characterize the global topologic organization of global brain and local parietal networks. In order to investigate the network characteristics in different areas of the brain, we collected information from the 256 electrodes. Moreover, the individual correlation matrices of the electrodes were constructed and used as weights of the network. Global and local metrics were compared between groups using ANOVA analysis. In detail we considered a local

network by selected specific electrodes (parietal region), which is the most studied and representative for resting state network examination [22,25,114,161–163]. Regarding the local parietal networks we chose the following electrodes “78, 88, 100, 101, 129, 142, 154, 77, 87, 99, 110, 119, 128, 141, 153, 163, 86, 98, 109, 118, 127, 140, 152, 162, 96, 97, 108, 170, 161”, which represent the respective parietal area (Figure 8).

In this work, graph analysis was adopted to explore any significant differences between the four groups (HC, SCD, MCI and AD) in the brain network. The nodes in the graph are represented by channels and the edges are defined as the correlation between two EEG nodes - electrodes recorded at the corresponding channels. Weighted graph was directly used to analyze the brain network to avoid choosing an arbitrary threshold for binary graph analysis. Graphs can be characterized by many measures. Two fundamental measures are the clustering coefficient and strength, both of which have been widely used to analyze the brain function network.

We compared brain network data (in terms of PCC) between groups at the level of significance p = 0.05. Exploratory correlation analysis tested the relationship of global and local network metrics with neuropsychological test scores of patients using the Pearson correlation (p = 0.05, uncorrected for multiple comparisons) in order to explore the potential relationship between cognitive performance and how this is interpreted in network metrics. In detail the metrics we measured were: Global and Local Clustering Coefficient (CC) and global and local strength (S) as described in Section 1.2.4.1 and 1.2.4.2 respectively.

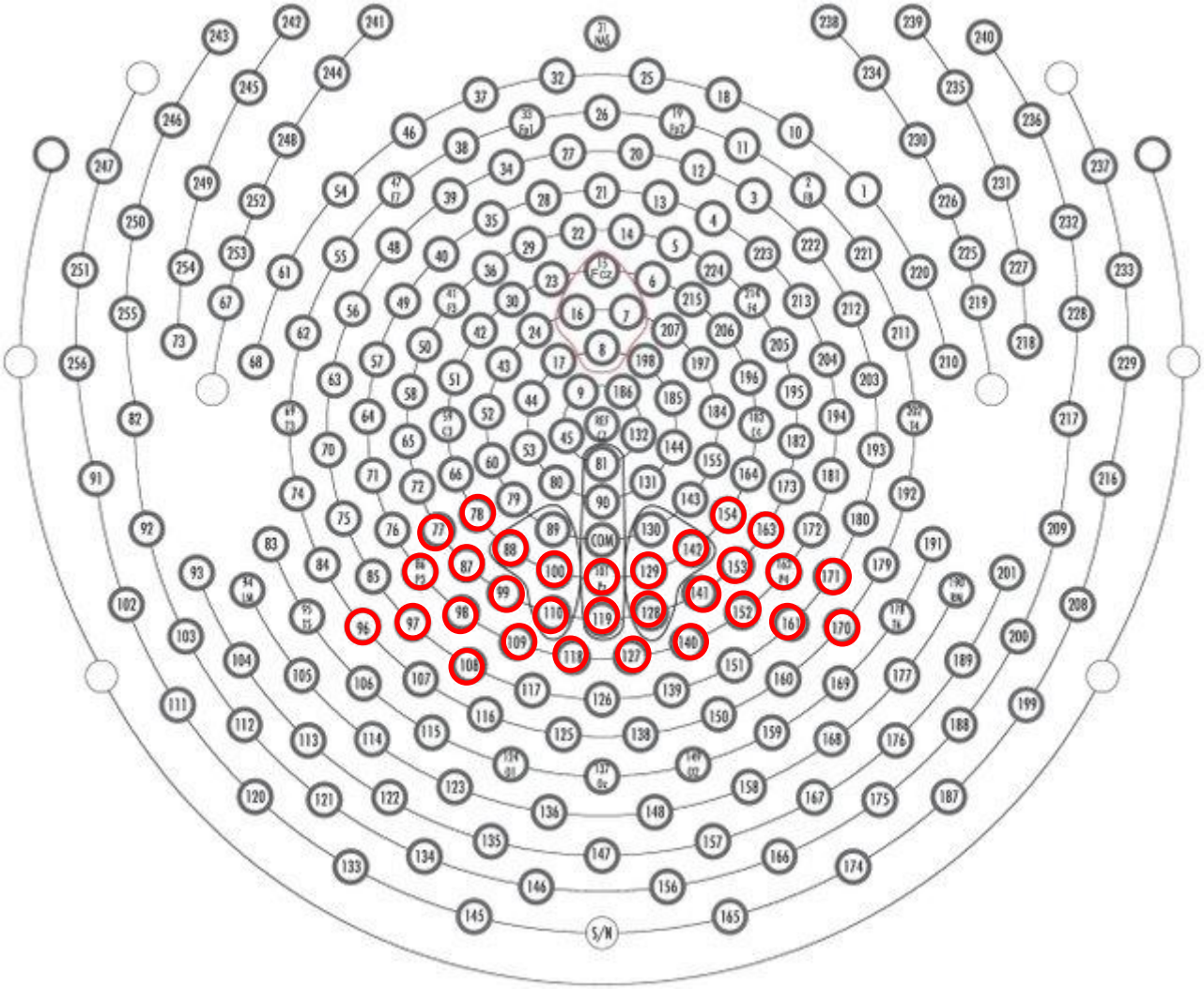


Figure 8 Selected parietal electrodes for local network analysis

5.1.5 Statistical Analysis

Statistical Analysis was performed using SPSS v25.0 for Windows (IBM Corporation, Armonk, NY, USA) and R Studio software. The Kolmogorov-Smirnov test was used to assess the normality assumption for continuous variables. The chi-squared test was used to test the independence between categorical variables. Comparisons between two independent groups were conducted using the t- test depending on the normality assumptions of the data (e.g. HC and SCD). Pearson Correlation test was used to compare neuropsychological tests and network parameters between groups. *P*-values less than 0.05 were considered statistically significant. T-test was used with respect to age and education and no statistical difference was found between the two groups, with $p = .615$ and $p = 0.253$ respectively. Chi-Square analysis was used to determine gender differences and we found that there were no significant difference between the two gender groups ($p = .522$). However, in each group more women were participating than men, which reflect also the prevalence of dementia and cognitive impairment among women. The t-test was also used to figure out if there was any statistical significant difference in neuropsychological tests. In this study, One-Way ANOVA was used to analyse the difference in the network metrics characteristics across the four groups. In cases, where graph measures showed statistical significance between groups, within group differences

were tested with t-test for independent samples. Associations between general cognitive state and network-derived measures were assessed with Pearson's linear correlations.

5.2 Results

5.2.1 Comparison of Neuropsychological performance between HC, SCD, MCI and AD participants

As shown in Table 3, among the set of cognitive tests, performance of all the HC and SCD subjects was within the normal range without any clue of cognitive deterioration. On the other hand, the MCI and AD group received significantly, as ANOVA test revealed, worse performance scores on all the items in MMSE, in the two daily functionality tests (FRSSD and FUCAS) and some of their subscales, in the three memory tests (Rey of Auditory Verbal Learning Test, Rey Osterrieth Complex Figure Test, Rivermead Behavioral Memory Test), and the language test FAS test. Superscripts indicate statistical significance between the groups after independent t-test. The neuropsychological performance is also illustrated in Figure 9, where the mean values of each group are presented.

In detail, the one-way between subjects ANOVA was conducted to compare the effect of the diagnosis in neuropsychological assessment. There was a significant effect of diagnosis on several neuropsychological tests at the $p<.05$ level among the four groups as follows MMSE: [$F(3, 88) = 42.35$, $p = 0.0001$], FRSSD-total score: [$F(3, 88) = 5.55$, $p = 0.002$], FUCAS-total score: [$F(3, 88) = 9.76$, $p = 0.0001$], TRAIL-B: [$F(3, 88) = 5.54$, $p = 0.002$], RBMT-immediate recall: [$F(3, 88) = 3.89$, $p = 0.015$], ROCFT-delayed recall: [$F(3, 88) = 11.71$, $p = 0.0001$], RAVLT- immediate recall: [$F(3, 88) = 3.14$, $p = 0.035$], RAVLT-total score: [$F(3, 88) = 7.07$, $p = 0.001$]. In order to further investigate the differences among each pair of groups, we conducted the Independent sample t-test which indicated that in:

Global Cognition: According to Independent Sample t-test, MMSE score was better for HC ($M = 29.13$, $SD = 0.99$) compared with MCI ($M = 27.13$, $SD = 2.55$); $t(50) = 3.48$, $p = 0.001$, and AD group ($M = 22.30$, $SD = 3.35$); $t(40) = 9.13$, $p < 0.0001$. In this common vein, SCD ($M = 29.25$, $SD = 1.06$) group also outperformed MCI ($M = 27.13$, $SD=2.55$); $t(48) = 3.49$, $p = 0.001$, and AD group ($M = 22.30$, $SD = 3.35$); $t(38) = 8.82$, $p < 0.0001$ in MMSE, while MCI demonstrated statistically significant better performance compared to AD $t(48) = 5.77$, $p < 0.0001$. Bonferroni corrected test revealed also statistical significant differences between the groups (HC vs MCI and AD, SCD vs MCI and AD, MCI vs AD) in global cognition as measured by neuropsychological tool, $P's < .008$.

Daily Functionality: Independent sample t-test revealed that the FRSSD total score was better for HC ($M = 1.58$, $SD = 2.50$) compared to MCI ($M = 4$, $SD = 1.51$); $t(32) = -3.52$, $p = 0.001$ and AD group ($M = 6.75$, $SD = 6.60$); $t(40) = -2.28$, $p = 0.03$. There was also a significant difference in the scores for FRSSD total score between HC ($M = 1.58$, $SD = 2.50$) and SCD ($M = 3.20$, $SD = 1.57$); $t(30) = -2.25$, $p = 0.032$, but both were within normal range. Moreover, HC group ($M = 42.0$, $SD = 0.00$) outperformed both MCI ($M = 44.77$, $SD = 3.41$); $t(32) = -2.79$, $p = 0.009$ and AD ($M = 50.37$, $SD = 8.99$); $t(38)$

= -3.27, p = 0.004 in FUCAS test. Moreover SCD group (M = 42.55, SD = 1.27) demonstrated better performance than MCI (M = 44.77, SD = 3.41); t (40) = -2.75, p = 0.009 and AD (M = 50.37, SD = 8.99); t (38) = -3.90, p = 0.001 in FUCAS total score. Finally, MCI group had greater scores than AD in FRSSD-total score t (48) = -1.87, p = 0.07 and FUCAS total score t (48) = -2.52, p = 0.01. Bonferroni corrected test revealed also statistical significant differences between the HC and MCI comparisons, as for daily functionality measurements, *P's*< .008, except the subcategory of FUCAS-memory and FRSSD-personal hygiene.

Memory and Executive Function: HC (M = 143, SD = 54.86) had better scores than MCI (M = 262.42, SD = 137.61); t (50) = -2.86, p = 0.007 in TRAIL-part B. Also, independent sample t-test revealed that the RBMT-immediate recall was better for HC (M = 17.4, SD = 2.70) compared to MCI (M = 12.71, SD = 4.04); t (50) = 2.44, p = 0.022 and AD (M = 10.30, SD = 2.49); t (40) = 4.32, p = 0.003 respectively. Additionally, HC showed better performance compared to AD (M = 9.50, SD = 3.31); t (40) = 3.37, p = 0.01 in RBMT- delayed recall as well. Also HC (M = 31, SD = 1.41) had better performance than MCI group (M = 13.54, SD = 5.76); t (50) = 4.18, p = 0.0001 and AD (M = 9.90, SD = 9.16); t (40) = 3.06, p = 0.02 in the ROCFT – delayed recall. In this common vein, SCD (M = 144.75, SD = 49.64) had better scores than MCI (M = 262.42, SD = 137.61); t (35) = -3.25, p = 0.003 in TRAIL-part B. Also SCD (M = 22.08, SD = 5.69) had better performance than MCI group (M = 13.54, SD = 5.76); t (35) = 4.48, p = 0.0001 and AD group (M = 9.90, SD = 9.16); t (38) = 3.61, p = 0.002 in the ROCFT – delayed recall respectively. Moreover, SCD had better performance in RBMT – immediate (M = 14.18, SD = 3.28) and RBMT- delayed recall (M = 13.09, SD = 3.23) as well as ROCFT- copy (M = 33.68, SD = 1.64) compared to AD group [RBMT – immediate recall: (M = 10.30, SD = 2.49) ; t (38) = 2.42, p = 0.02, RBMT – delayed recall: (M = 9.50, SD = 3.32) ; t (38) = 2.16, p = 0.04 and ROCFT – copy: (M = 22.80, SD = 13.43); t (38) = 3.35, p = 0.003]. Finally, MCI group (M = 30.23, SD = 5.05) also demonstrated significantly better performance with respect to AD group (M = 22.80, SD = 13.43); t (48) = 2.08, p = 0.004 in ROCFT copy test. Bonferroni corrected test revealed also statistical significant differences between groups of HC, SCD, MCI and AD in memory and executive function neuropsychological tests, *P's*< .008. However, Bonferroni correction did not reveal statistical significant difference between HC and MCI in TRAIL-part B and RBMT-delayed recall, P's >.008 and similar between SCD and MCI in ROCFT-delayed recall (P> .008), while as for AD and SCD comparison, Bonferroni corrected test revealed no statistical significant difference in RAVL-learning (P <.008).

Verbal Fluency-Learning: HC (M = 53.33, SD = 13.86) outperformed MCI (M = 33.38, SD = 16.09); t (31) = 2.09, p = 0.05 in RAVLT – total score. Also, independent sample t-test revealed that the FAS total score was better for HC (M = 14.3, SD = 3.20) compared to MCI (M = 9.49, SD = 3.75); t (31) = 2.09, p = 0.04. Moreover, SCD (M = 53.33, SD = 13.86) outperformed MCI (M = 33.38, SD = 16.09); t (36) = 4.29, p = 0.0001 in RAVLT – total score. In addition to that, SCD showed better performance in RAVLT -2 (M = 7.35, SD = 3.83) and RAVLT immediate recall (M = 7.23, SD = 2.75) compared to MCI (M = 5.33, SD = 2.19); t (36) = 2.03, p = 0.04 and (M = 5.19, SD = 2.08); t (36) = 2.60, p = 0.01 respectively. Moreover, SCD showed significant better performance in

RAVLT total score (M = 53.88, SD = 12.56) compared to AD (M = 34.0, SD = 16.85); t (38) = 2.88, p = 0.009. Also, independent sample t-test revealed that the FAS total score was better for SCD (M = 12.18, SD = 3.20) compared to MCI (M = 9.49, SD = 3.75); t (36) = 2.19, p = 0.03. Bonferroni corrected test revealed also statistical significant differences between groups of HC, SCD, MCI and AD in memory and executive function neuropsychological tests, *P's*< .008. However, as for AD and MCI comparison, Bonferroni corrected test revealed statistical significant differences except in RAVL-learning and RAVLT delayed recall (*P's* >.008).

Mood: Lower scores which indicate better performance for HC (M = 0.00, SD = 0.00) and SCD (M = 0.33, SD = 0.73) were found in NPI compared with AD group (M = 2.75, SD = 4.23); t (40) = -2.28, p = 0.03 and (M = 2.75, SD = 4.23); t (38) = -2.56, p = 0.01 respectively. Bonferroni corrected test revealed no statistical significant differences between the HC, SCD, MCI and AD comparisons, as for mood measurements, *P's*> .008. However, all groups had no clinical profile of any depressive or anxiety (mean scores of NPI and PSS below the cut-off scores).

Therefore, as statistical analysis revealed the four groups (HC, SCD, MCI and AD) differed statistically significant in several neuropsychological measurements (except HC with SCD), which shows that our participants are well-differentiated in all categories (Global Cognition, Daily functionality, Memory and Executive Function and Mood), as measured by well-established neuropsychological tests. Therefore the next step was to seek for any potential difference between the four groups on the grounds of brain connectome at resting state condition.

Table 3 The table shows mean±SD (standard deviation) of neuropsychological assessment of the participants (HC = 22, SCD= 20, MCI= 30, AD=20). The last column of the table shows the p-values resulting of the significant between groups ANOVA comparisons.

Diagnosis	HC		SCD		MCI		AD		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P value
MMSE	29,13	0,99	29,25	1,06	27,13**	2,55	22,30	3,35	**0,001**
NPI	0,00	0,00	0,30	0,73	2,81	6,08	2,75	4,23	0,092
FRSSD total score	1,58*	2,50	3,20	1,57	4,00**	1,51	6,75	6,60	**0,002**
FUCAS total score	42,00	0,00	42,55	1,27	44,77**	3,40	50,375	8,99	**0,001**
TRAIL-B	143,00	54,86	144,75	49,64	262,42**	137,61	147,00	149,18	**0,002**
RBMT-immediate recall	17,40	2,70	14,18	3,28	12,71**	4,04	10,30	2,48	**0,015**
RBMT-delayed recall	15,40	2,07	13,09	3,23	12,04	4,07	9,50	3,31	0,070
ROCFT - copy	33,50	2,12	33,68	1,65	30,23	5,05	22,80	13,43	**0,005**
ROCFT – delayed recall	31,00*	1,41	22,08	5,69	13,54**	5,76	9,90	9,16	**0,000**
RAVLT 1	7,33	3,05	7,23	2,75	5,19	2,08	4,60	2,07	0,035
RAVLT 2	5,00*	0	7,35	3,83	5,33	2,19	5,40	3,84	0,201
RAVLT total score	53,33	13,86	53,88	12,56	33,38	16,09	34,00	16,85	**0,001**
RAVLT 4	-1,33	0,57	1,23	6,20	-1,76	2,99	-2,20	4,6	0,208
FAS	14,3	3,20	12,18	3,69	9,49**	3,75	10,66	3,67	0,073

HC vs SCD - p-value <0.05

**HC vs MCI- p-value <0.01*

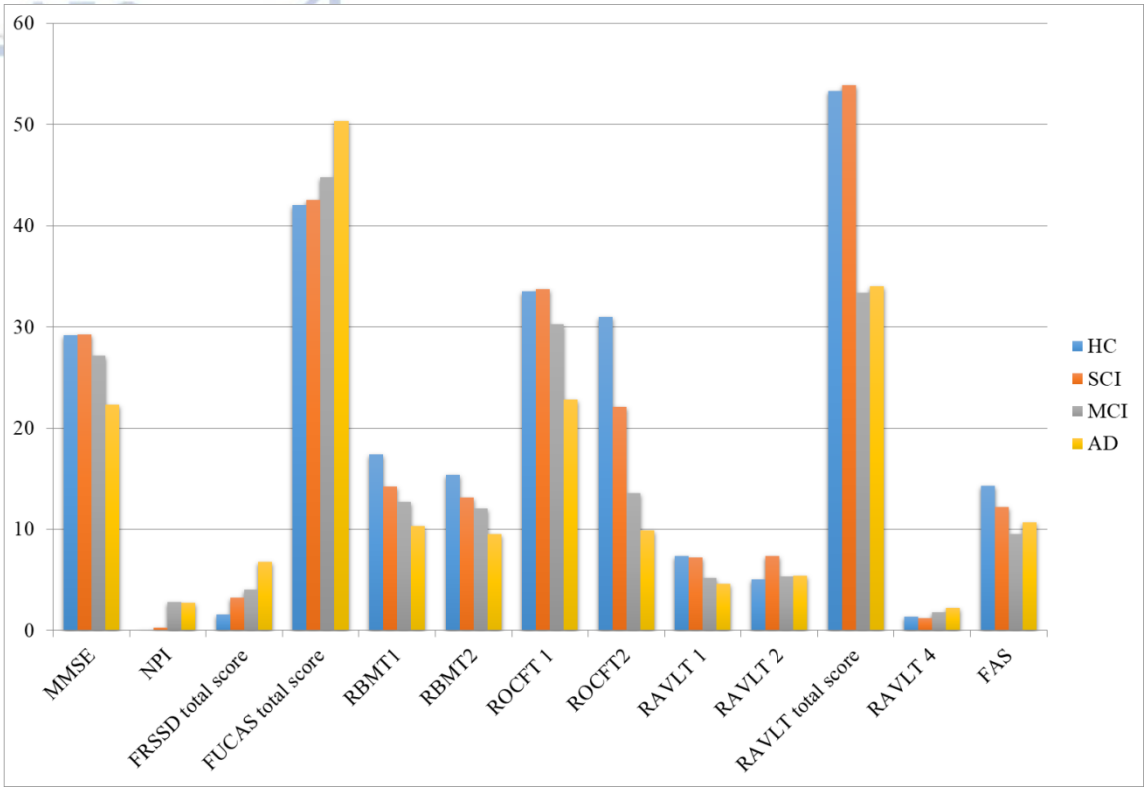


Figure 9 Mean values of neuropsychological performance across the four groups (HC, SCD, MCI and AD)

5.2.2 Comparison of Network Properties between HC, SCD, MCI and AD participants

As shown in Table 4 and Table 5, among the network properties measured (Clustering Coefficient and Strength), mean values of the HC were higher compared to the rest groups. Superscripts indicate statistical significance between the groups after independent t-test. Moreover, Figure 12 and Figure 13 illustrate the correlation matrices at local and global level respectively, from which the network was constructed in order to estimate the network metrics. From the matrices of local network as depicted in Figure 12, we constructed the weighted undirected networks for each group of participants as depicted in Figure 14 - Figure 17. From the matrices of global network as depicted in Figure 13, we constructed the weighted undirected networks for each group of participants as depicted in Figure 18 - Figure 21. We kept only the PCC values higher than 0.65. Moreover, the mean values of both global and local network metrics of each group are also illustrated in Figure 10 and Figure 11. A one-way ANOVA was conducted to compare the effect of the diagnosis in both network properties at local and global level. There was a significant effect of diagnosis on every network property at local level (parietal electrodes) at a 0.05 level among the four groups in Clustering Coefficient: [F (3, 88) = 4.76, p = 0.004], Strength: [F (3, 88) = 4.69, p = 0.004]. However, no statistical significant difference was found at global level between the four groups Global Clustering Coefficient: [F (3, 86) = 0.50, p = 0.681], Global Strength: [F (3, 86) = 0.67, p

= 0.569]. Independent sample t-test indicated that in significant differences were found in network metrics as presented below and especially at local level.

Global and Local Clustering Coefficient: According to Independent Sample t-test, local clustering coefficient was higher for HC (M = 0.79, SD = 0.07) compared with SCD (M = 0.72, SD = 0.09); t (40) = 2.39, p = 0.02, MCI group (M = 0.71, SD = 0.09); t (50) = 0.41, p = 0.004 and AD group (M = 0.68, SD = 0.11); t (40) = 3.62, p = 0.001 as well. On the other hand, with regards to global clustering coefficient, comparisons between SCD and MCI, SCD and AD and MCI versus AD revealed no statistical significant difference. Despite that HC (M = 0.31, SD = 0.07) showed greater values with regards to global clustering coefficient, compared to SCD (M = 22.30, SD = 3.35); t (40) = 0.13, p = 0.897, MCI (M = 0.29, SD = 0.07); t (48) = 0.94, p = 0.351 and AD (M = 0.68, SD = 0.11); t (40) = 0.97, p = 0.337, no statistical significant difference was found.

Global and Local Strength: According to Independent Sample t-test [t(n-2)], local strength at parietal electrodes showed higher values for HC (M = 22.56, SD = 1.65) compared to SCD (M = 21.11, SD = 2.10); t (40) = 2.50, p = 0.01, MCI (M = 20.83, SD = 2.25); t (50) = 3.01, p = 0.004 and AD group (M = 20.12, SD = 2.66); t (40) = 3.48, p = 0.001. On the other hand, with regards to global strength, comparisons between SCD and MCI, SCD and AD and MCI versus AD revealed no statistical significant difference. Although HC (M = 99.24, SD = 18.08) showed greater values with regards to global strength, compared to SCD (M = 97.70, SD = 20.18); t (40) = 0.26, p = 0.795, MCI (M = 94.01, SD = 16.20); t (48) = 1.07, p = 0.287 and AD (M = 91.88, SD = 21.91); t (40) = 1.18, p = 0.245, no statistical significant difference was found neither between SCD vs MCI and AD or MCI vs AD.

Table 4 The table shows mean±SD (standard deviation) of network properties at local level (parietal electrodes) of the participants (HC = 22, SCD= 20, MCI= 30, AD=20). The last column of the table shows the p-values between groups ANOVA. Superscripts indicate the statistical significance between groups after independent sample t-test.

	HC		SCD		MCI		AD		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Clustering Coefficient	0,79	0,07	0,73*	0,09	0,72**	0,09	0,68***	0,11	**0,004**
Strength	22,56	1,65	21,11*	2,10	20,83**	2,25	20,12***	2,67	**0,004**

**HC vs SCD - p-value <0.05*
***HC vs MCI- p-value <0.01*
**** HC vs AD- p-value <0.001*

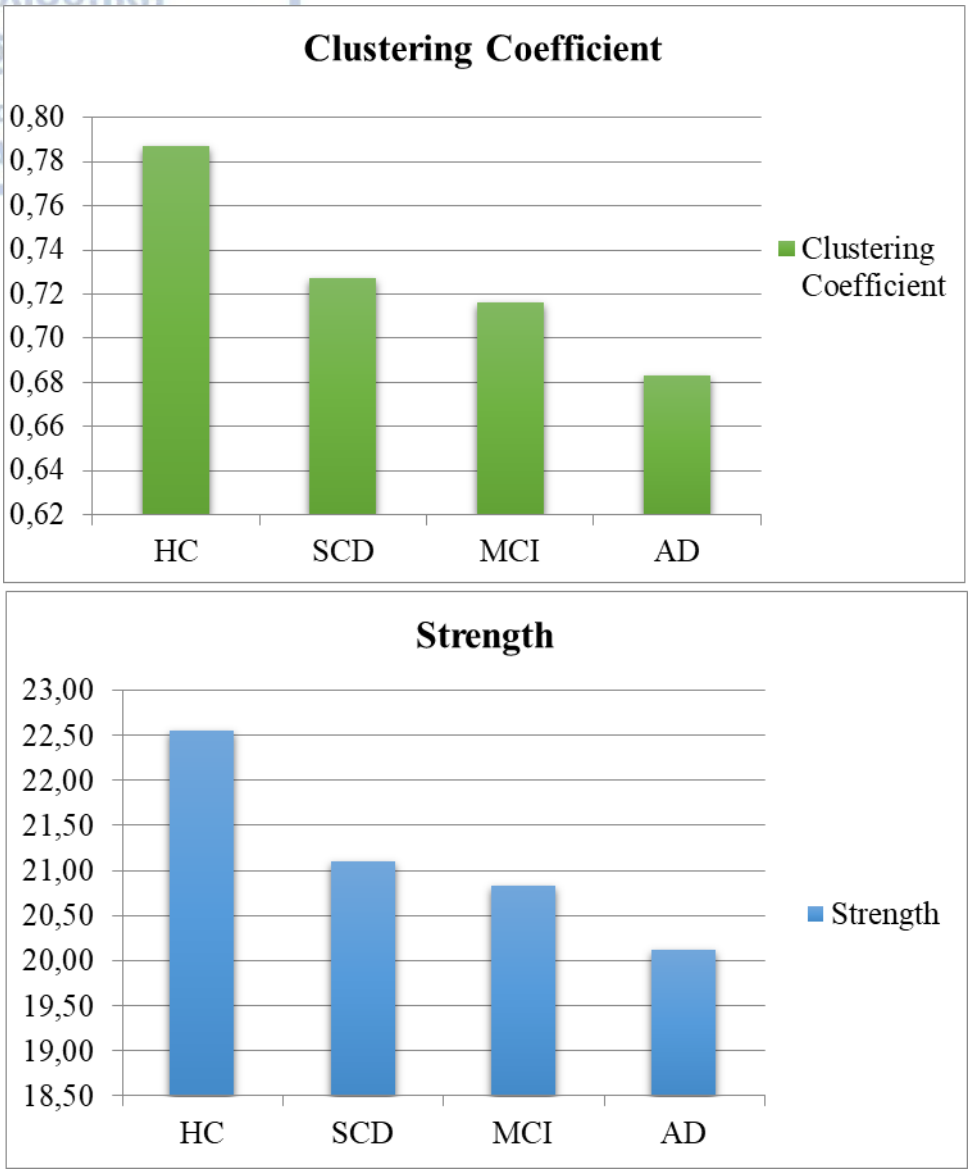


Figure 10 Mean values of local clustering coefficient (upper) and local strength (lower) of parietal electrodes of the four groups

Table 5 The table shows mean±SD (standard deviation) of network properties at global level of the participants (HC = 22, SCD= 20, MCI= 30, AD=20). The last column of the table shows the p-values resulting of the between groups ANOVA

	HC		SCD		MCI		AD		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Clustering Coefficient	0,311	0,079	0,308	0,088	0,291	0,072	0,285	0,091	**0,681**
Strength	99,24	18,08	97,70	20,19	94,01	16,20	91,88	21,92	**0569**

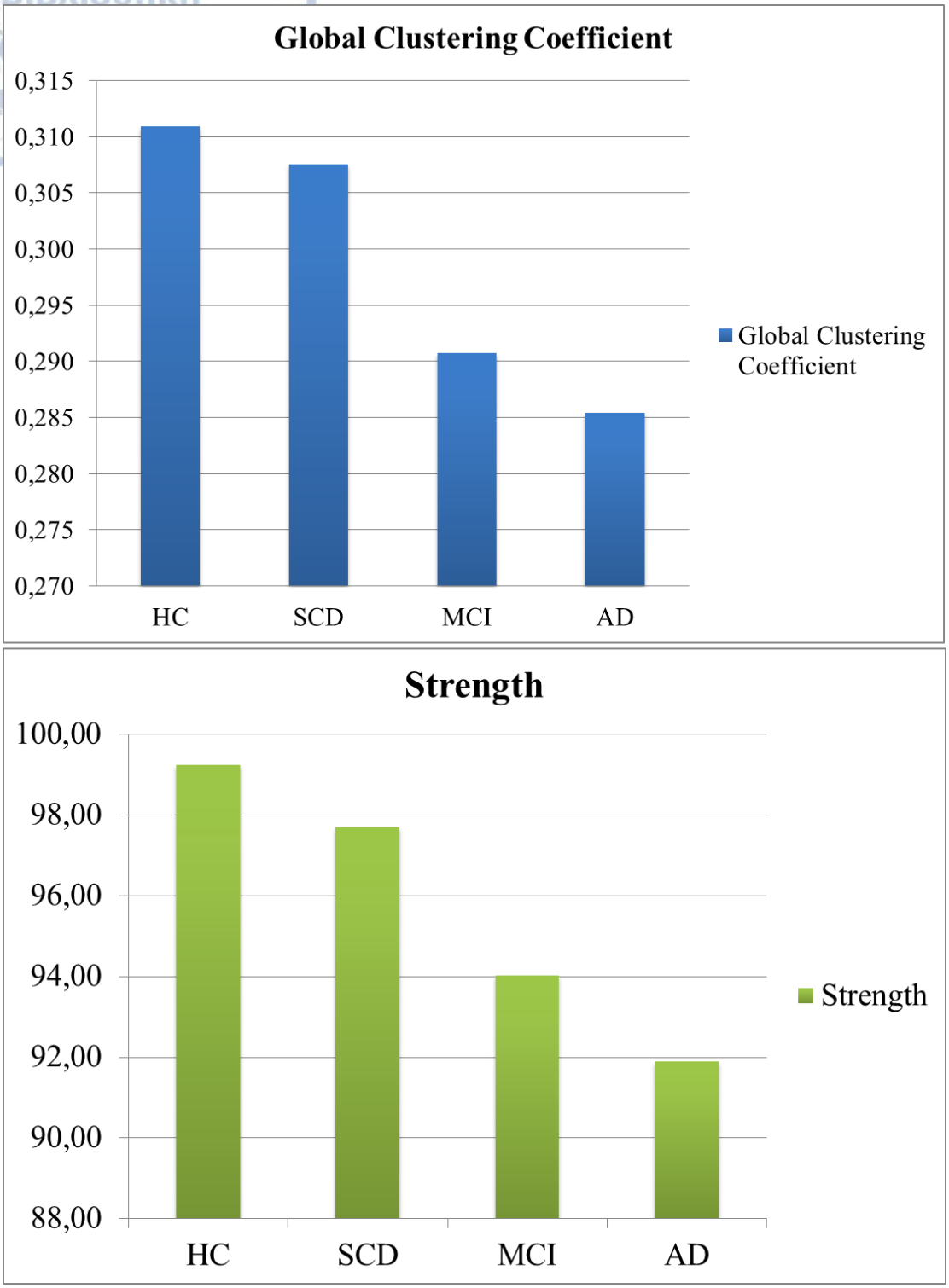


Figure 11 Mean values of global clustering coefficient (upper) and global strength (lower) of all electrodes of the four groups

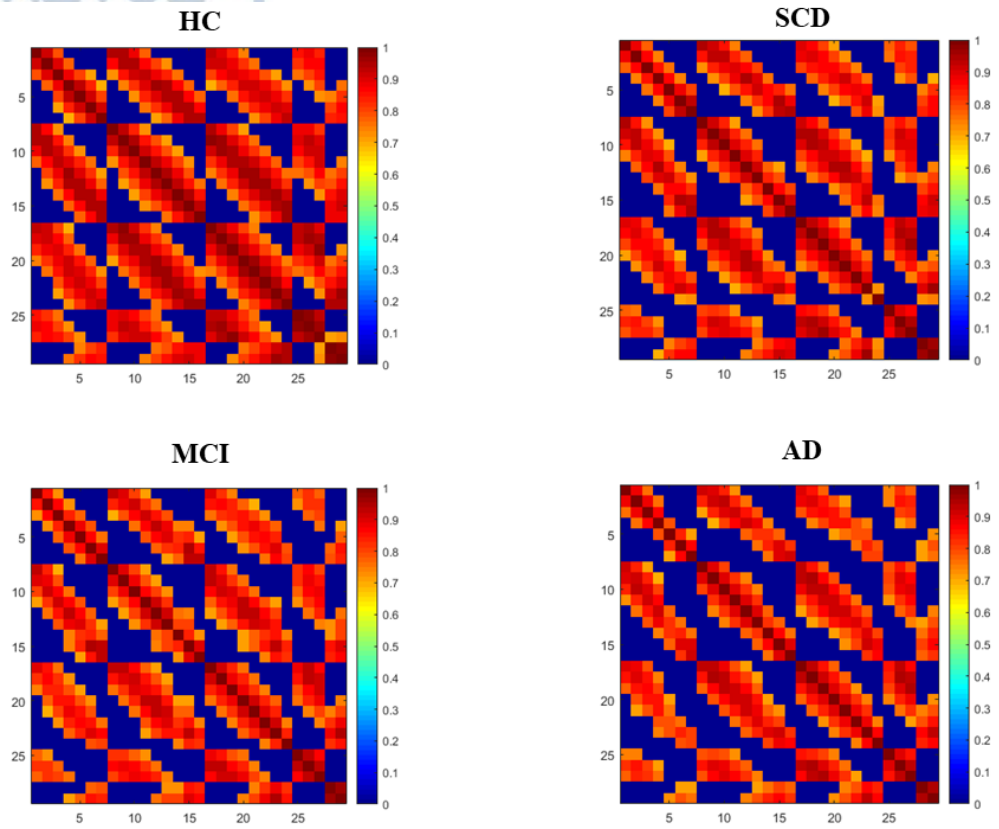


Figure 12 Corellation Matrices of Parietal electrodes at local level of the four groups

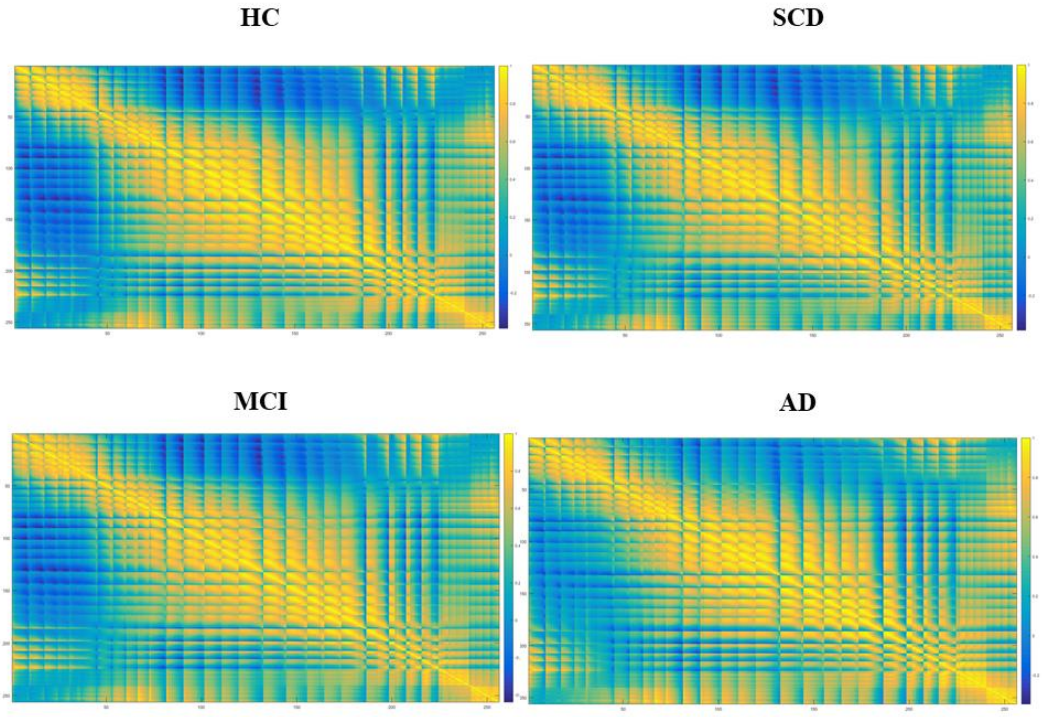


Figure 13 Corellation Matrices of all electrodes at global level of the four groups

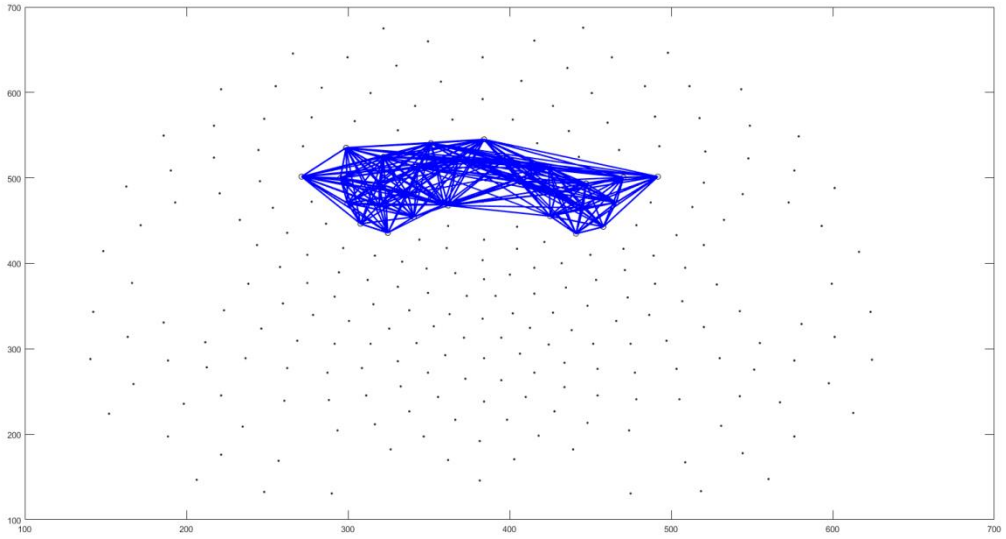


Figure 14 Brain Network from Correlation Matrices for HC at local network (parietal electrodes)

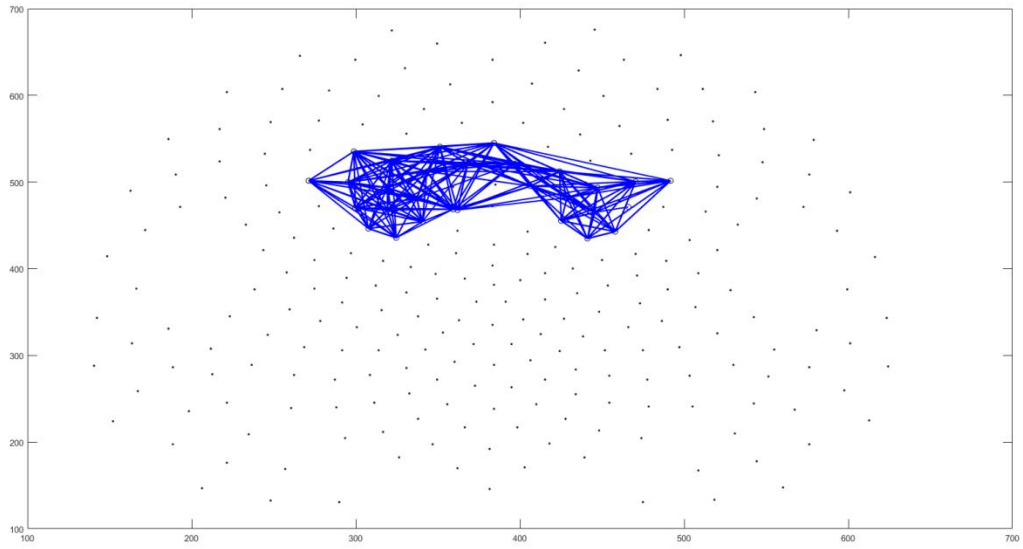


Figure 15 Brain Network from Correlation Matrices for SCD at local network (parietal electrodes)

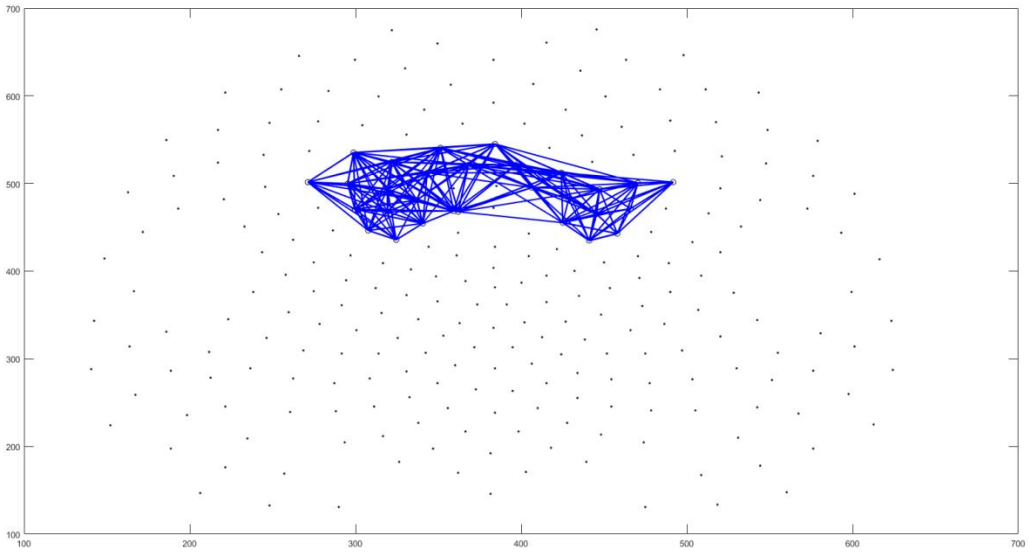


Figure 16 Brain Network from Correlation Matrices for MCI at local network (parietal electrodes)

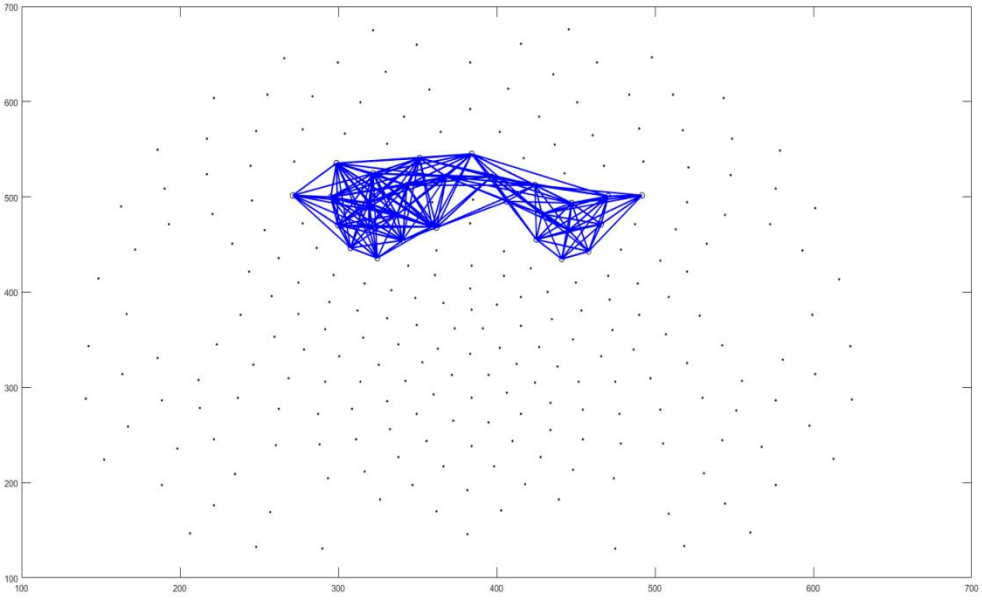


Figure 17 Brain Network from Correlation Matrices for AD at local network (parietal electrodes)

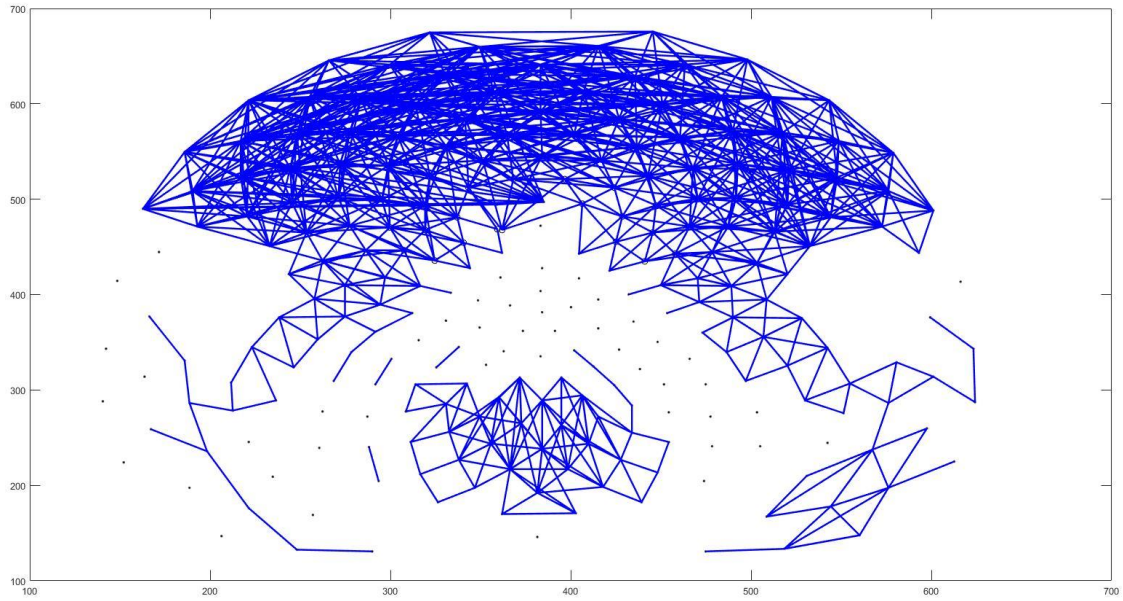


Figure 18 Brain Network from Correlation Matrices for HC at global network (all 256 electrodes)

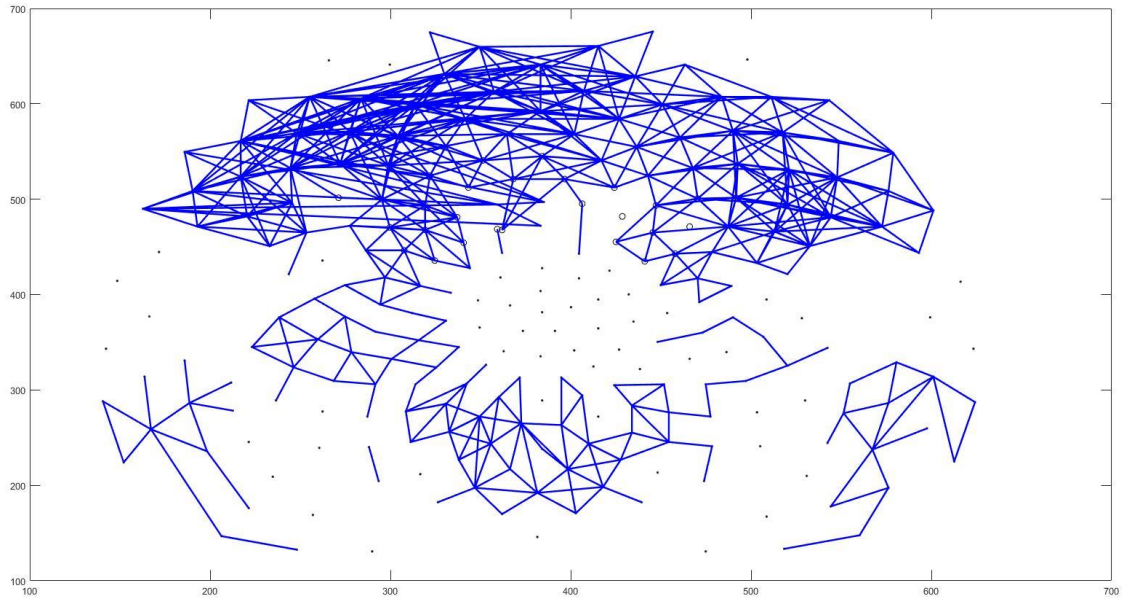


Figure 19 Brain Network from Correlation Matrices for SCI at global network (all 256 electrodes)

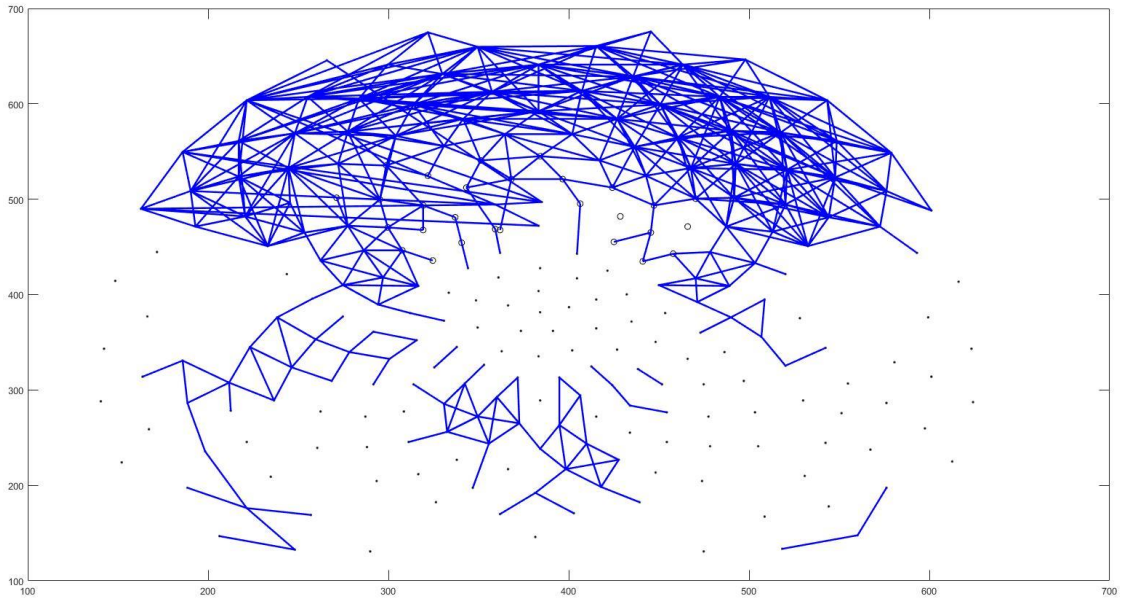


Figure 20 Brain Network from Correlation Matrices for MCI at global network (all 256 electrodes)

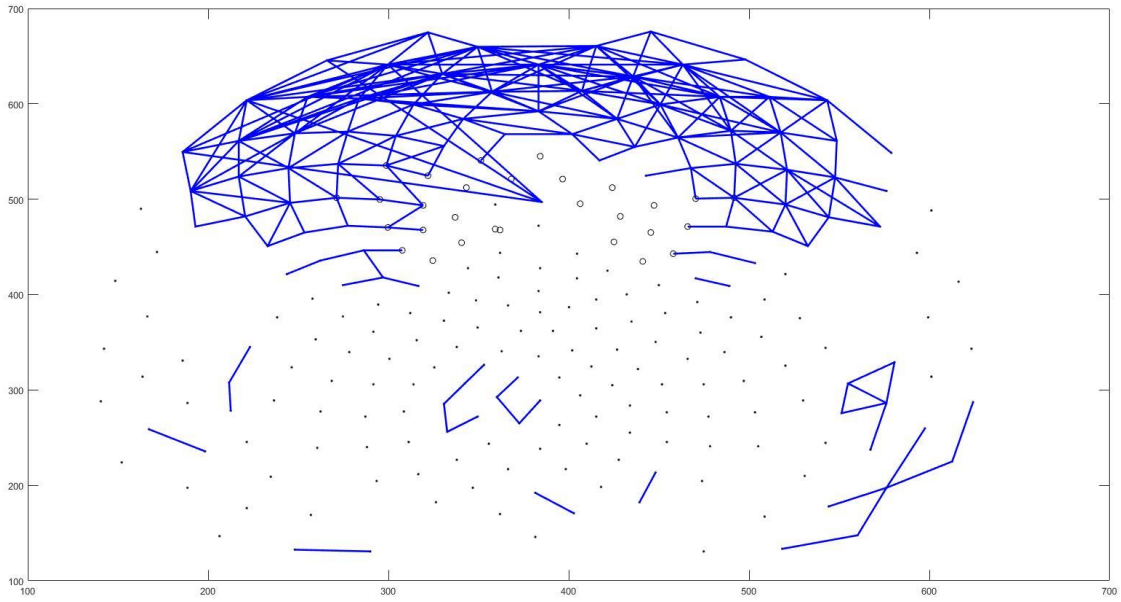


Figure 21 Brain Network from Correlation Matrices for AD at global network (all 256 electrodes)

As we can see for Figures 11 - 14, HC present a denser network with more connections between nodes at local area (parietal electrodes). As the disease progresses we can see less connections between nodes. Even in the case of SCD (Figure 12) there is an obvious difference compared to HC (Figure 11), while in MCI (Figure 13) and AD (Figure 14) the connections of networks in these patient groups are much more apparent.

5.2.3 Sensitivity and Specificity of the Groups – ROC Curves

In the previous section we have compared the network properties among SCD, MCI, AD and HC participants with the intention to verify whether the different groups can be distinguished based on the statistical properties of the clustering coefficient and strength both at local network (parietal electrodes only) and global network (all 256 channels). In this section we move one step further towards simulating the usage of the abovementioned network properties as a biomarker of the patient's condition (SCD, MCI and AD) or HC by testing sensitivity and specificity among the groups. More specifically, we examined the Area under the Curve (AUC) as well as Sensitivity and Specificity values of six bilateral combinations in a pairwise mode "one vs one" mode, as well as four cases in an "one vs other" mode. These results can essentially simulate the use of local or global clustering coefficient and strength as a biomarker that would indicate the condition of an "unseen" subject as being SCD (and not MCI, AD or HC), being MCI (and not SCD, AD or HC), etc. Given that SCD is still a condition that is not identifiable through neuropsychological examination we consider these classifiers to be of particular clinical interest, since they can verify the SCD condition of a certain subject with sufficient reliability. Thus, by positioning this subject at the earliest stages of AD we can help introduce a set of interventions that could potentially prolong the progression of the disease.

Specificity and sensitivity rates were computed with the help of SPSS v25.0. More specifically, in using SPSS, we constructed corresponding ROC curves and identified the best threshold (i.e. the threshold that maximizes the sum of sensitivity and specificity) of the local and global clustering coefficient and strength values to differentiate our four groups. A ROC curve provides the sensitivity and the specificity over a range of possible threshold values; an area under the curve (AUC) of 100% corresponds to a perfect prediction whereas a value of 50% to a useless model (Figure 22 - Figure 25). A minimum value of 65% for both sensitivity and specificity can be considered as acceptable, based on a recent neurophysiological study [164,165]. The sensitivity and specificity scores corresponding to the cutoff thresholds (as defined above) together with the AUC are presented in Table 6 and Table 8 at local network while Table 7 and Table 9 present in detail the results of the AUC, Sensitivity and Specificity at global network.

For the clustering coefficient and strength network property at local level as recorded from the parietal electrodes, eight ROC curves reached the minimum threshold value of 65% (Table 6 and Table 8) of sensitivity and specificity both for clustering coefficient and strength: (1) for discriminating HC participants from the SCD, MCI and AD groups the sensitivity was 64% and the specificity 78-79%; (2) for discriminating HC from SCD the values were 75% (sensitivity) and 64% (specificity); (3) for discriminating of HC from MCI the values were 80% (sensitivity) and 64% (specificity); (4) for discriminating of HC from AD the values were 65% (sensitivity) and 82% (specificity) both for clustering coefficient and strength (Figure 22 and Figure 24).

In general, five AUC reached the 65% threshold both for clustering coefficient and strength: (1) for discriminating the HC from the SCD, MCI and AD, this was 74%; (2) for discriminating the AD from the HC, SCD and MCI, this was 66%, (3) for discriminating the SCD from the HC, this was 71%, (4) for discriminating the MCI from the HC, the

AUC was 73% for clustering coefficient and 79% for strength; while (5) for discriminating the AD from the HC, the AUC was 79% (Table 6 and Table 8).

On the other hand, at global level, neither clustering coefficient ROC nor strength ROC reached 65% of sensitivity and specificity for discriminations (Figure 23 and Figure 25). Moreover, none of the AUC found to discriminate our groups (Table 7 and Table 9).

These results are very promising but there is still work to do for reaching an acceptable level for discriminating each pair of groups.

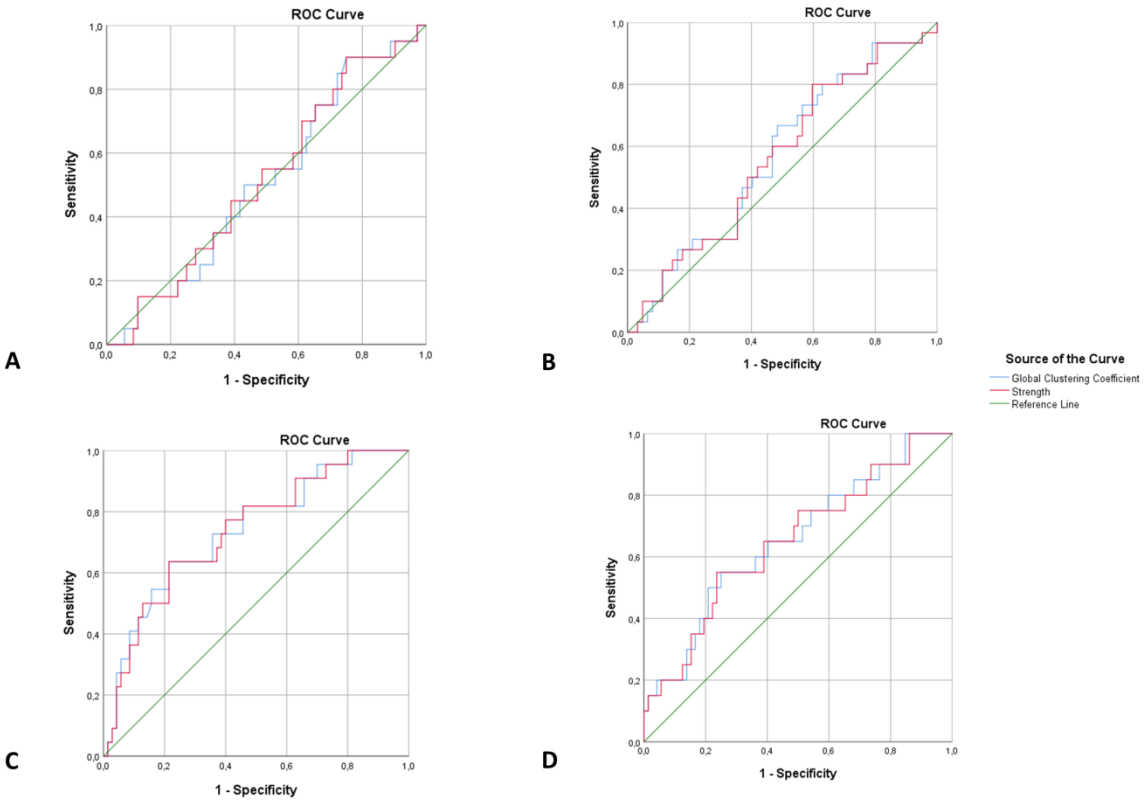


Figure 22 ROC Curves presenting for the Clustering Coefficient and Strength at Local level for discrimination between: A) SCD vs HC,MCI,AD, B) MCI vs SCD,HC,AD, C) HC vs SCD, MCI and AD and, D) AD vs SCD, MCI and HC

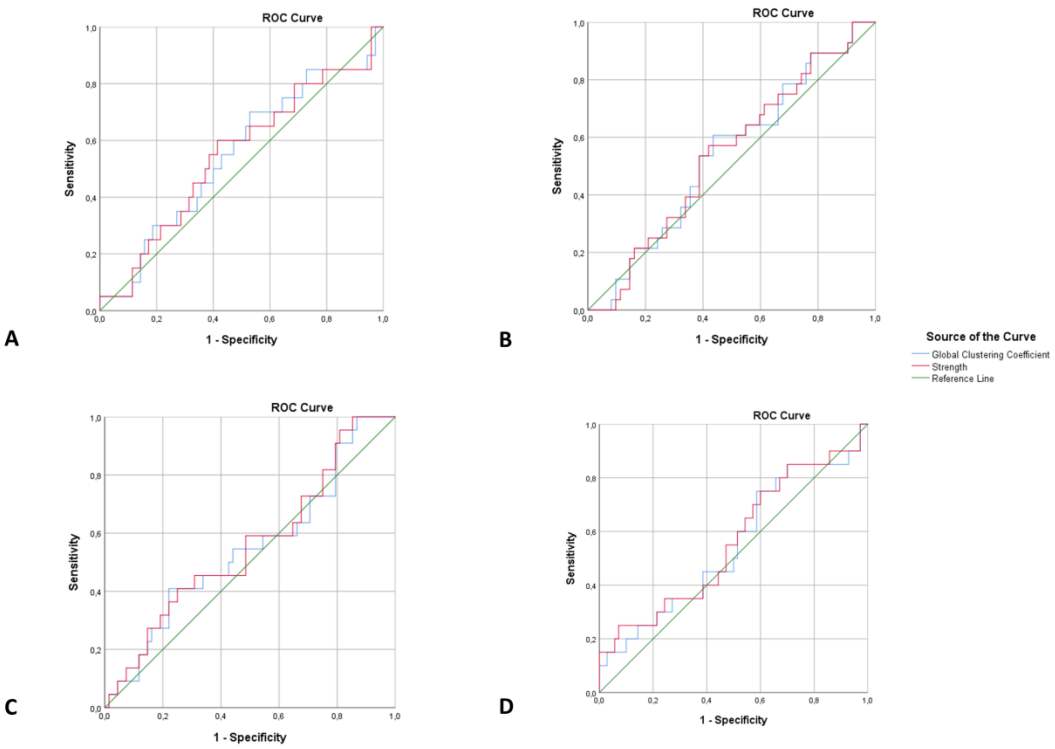


Figure 23 ROC Curves presenting for the Clustering Coefficient and Strength at global level for discrimination between: A) SCD vs HC,MCI,AD, B) MCI vs SCD,HC,AD, C) HC vs SCD,MCI and AD and, D) AD vs SCD, MCI and HC

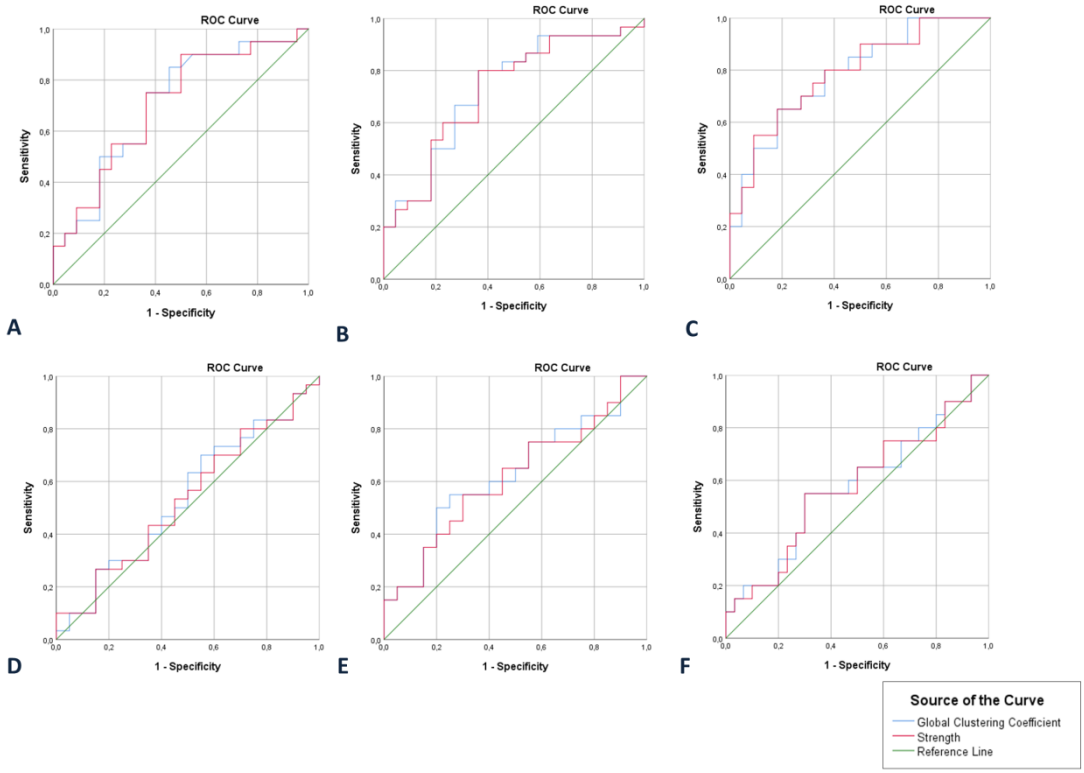


Figure 24 ROC Curves presenting for the Clustering Coefficient and Strength at Local level for discrimination between: A) SCD and HC, B) MCI and HC, C) AD and HC, D) MCI and SCD, E) SCD and AD, F) MCI and AD

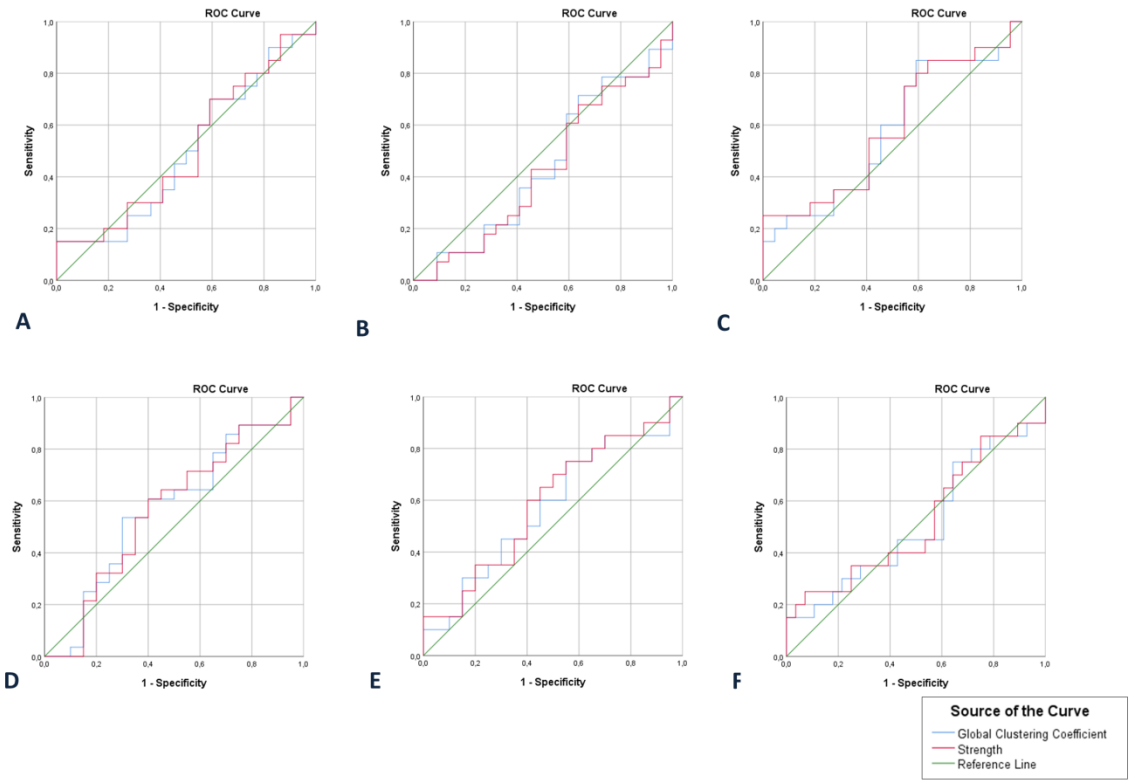


Figure 25 ROC Curves presenting for the Clustering Coefficient and Strength at global level for discrimination between: A) SCD and HC, B) MCI and HC, C) AD and HC, D) MCI and SCD, E) SCD and AD, F) MCI and AD

Table 6 Sensitivity and specificity of clustering Coefficient and Strength at local level for each group of participants compared with the rest groups

Groups	Network Property	AUC (%)	Threshold Value	Sensitivity (%)	Specificity (%)
HC vs SCD, MCI and AD	Clustering Coefficient	**74**	0,78	**64**	**78**
	Strength	**74**	22,38	**64**	**79**
SCD vs HC, MCI and AD	Clustering Coefficient	51	0,79	**90**	25
	Strength	52	22,85	**90**	25
MCI vs SCD, HC and AD	Clustering Coefficient	57	0,75	67	**52**
	Strength	57	22,14	**77**	40
AD vs HC, SCD and MCI	Clustering Coefficient	**66**	0,70	55	**75**
	Strength	**65**	20,37	55	**76**

Table 7 Sensitivity and specificity of clustering Coefficient and Strength at global level for each group of participants compared with the rest groups

Groups	Network Property	AUC (%)	Threshold Value	Sensitivity (%)	Specificity (%)
HC vs SCD, MCI and AD	Clustering Coefficient	55	0,5	41	**78**
	Strength	56	106,65	41	**75**
SCD vs HC, MCI and AD	Clustering Coefficient	55	0,28	**70**	44
	Strength	55	97,11	60	58
MCI vs SCD, HC and AD	Clustering Coefficient	54	0,30	61	**57**
	Strength	**54**	94,48	**57**	58
AD vs HC, SCD and MCI	Clustering Coefficient	**55**	0,32	**75**	41
	Strength	56	72,31	25	**93**

Table 8 Sensitivity and specificity of clustering Coefficient and Strength at local level for each type of diagnosis

Groups	Network Property	AUC	Threshold Value	Sensitivity (%)	Specificity (%)
HC vs SCD	**Clustering Coefficient**	**71**	0,78	**75**	**64**
	Strength	**71**	22,34	**75**	**64**
HC vs MCI	**Clustering Coefficient**	**73**	0,78	**80**	**64**
	Strength	**79**	22,31	**80**	**64**
HC vs AD	**Clustering Coefficient**	**79**	0,73	**65**	**82**
	Strength	**79**	21,16	**65**	**82**
SCD vs MCI	**Clustering Coefficient**	54	0,76	**70**	45
	Strength	53	19,80	27	**85**
SCD vs AD	**Clustering Coefficient**	63	0,69	50	**80**
	Strength	62	20,41	55	**70**
MCI vs AD	**Clustering Coefficient**	58	0,70	55	**70**
	Strength	58	20,50	55	**70**

Table 9 Sensitivity and specificity of clustering Coefficient and Strength at global level for each type of diagnosis

Groups	Network Property	AUC	Threshold Value	Sensitivity (%)	Specificity (%)
HC vs SCD	**Clustering Coefficient**	49	0,185	15	**100**
	Strength	51	69,829	15	**100**
HC vs MCI	**Clustering Coefficient**	44	0,259	**74**	36
	Strength	43	86,773	**68**	36
HC vs AD	**Clustering Coefficient**	58	0,351	**85**	41
	Strength	59	107,412	**85**	36
SCD vs MCI	**Clustering Coefficient**	57	0,285	54	**70**
	Strength	56	93,358	54	**65**
SCD vs AD	**Clustering Coefficient**	57	0,317	**75**	45
	Strength	59	97,879	**65**	55
MCI vs AD	**Clustering Coefficient**	51	0,241	30	**79**
	Strength	52	70,799	20	**96**

5.2.4 Correlation between Neuropsychological Assessment and Network Properties

One of the purposes of our study was to further evaluate cognitive impairment in SCD, MCI and AD participants by using extensive neuropsychological tests and seek for any potential correlation with the global and local clustering coefficient and strength. To verify possible correlations between the neuropsychological performance and the network metrics, Pearson's correlation was used, and it was observed that in almost none of the tests, was a strong correlation ($p < .05$, $p < .01$) between different cognitive functions and network properties (Table 10). More specifically, we can see that values of sleep as measured from the FRSSD test, were highly negative correlated with the values of local clustering coefficient at parietal electrodes generated during the resting state EEG. The local clustering coefficient captures how strongly a brain region is connected with its neighboring brain regions; a larger value indicates that a brain region strongly affects its neighboring brain regions. The local clustering coefficient of the parietal is negatively statistically significant correlated with the FRSSD sleep score ($r = -0.286$, $p = 0.034$).

Table 10 Spearman Correlation between neuropsychological tests and network properties of all participants at local level.

Domain	Neuropsychological Tests	Clustering Coefficient	Strength
Global Cognition	**MMSE**	0,158	0,141
Mood	**NPI**	-0,082	-0,083
Memory and Executive Function	**RBMT- immediate recall**	0,167	0,146
	RBMT- delayed recall	0,205	0,186
	ROCFT- copy	0,119	0,085
	ROCFT- recall	0,169	0,149
Learning	**RAVLT- learning**	0,018	0,014
	RAVLT- recall	0,152	0,144
Daily Functionality	**FRSSD- total score**	-0,070	-0,053
	FUCAS- total score	-0,053	-0,028
	FRSSD- Sleep	**-0,286***	-0.280

** Correlation is significant at the 0.05 level (2-tailed).*
No superscripts indicate no statistical significant difference

6 Discussion and Comparison with other studies

It has been proposed that SCD may precedes MCI, which in turn often progresses to AD [90,92]. Therefore, seeking a plausible relationship between the pathologic interruptions and the brain connectome disruption in the SCD warrants further investigation. Our present study summarizes the main study findings in brain connectome and SCD using a HD-EEG, while underlying the added value of connectome-based metrics to draw conclusions on the progression of SCD into more advanced stages of AD. Our study confirms and underlines the disrupted topologic organization of brain connectome in people with SCD and provides the potential of future connectome - based biomarkers for the early detection of subsequent future cognitive impairment related to AD. Additionally, it suggests that disordered brain function, characterized by decreased coherence in specific nodes, may be related to SCD. This implies that SCD is situated in a somewhat intermediate state between the two conditions, healthy ageing and MCI. Since this is the first ever reported study which explored network properties in people with SCD by using EEG, we compare our results with other common approaches which deployed different modalities (e.g., MEG, fMRI) or with EEG studies which explored potential differences between HC and people of more advanced stages (e.g., MCI and AD).

Despite that the majority of the resting state studies examine exclusively the connectivity across DMN nodes consistently, showed disrupted patterns and aberrant connections in SCD compared to HC [43–45,122], there were some with conflicting results, showing increased FC in SCD compared to HC [105,109]. To be more precise, the majority of studies' results proposed that SCD demonstrated significantly less DMN connectivity in the right hippocampus compared to the HC [45]. In detail, decrease of functional coupling of the vmPFC to the IPL and left-sided PCC was found in SCD [122] as well as decreased FC with respect to the HC group in connections between posterior cortical brain areas (medial structures, parietal and occipital areas) [44]. Similarly, in our study SCD had less strength and clustering coefficient at parietal area compared to HC. Similar results can also be found in similar brain network studies, demonstrating decreased nodal strength in the parietal region in SCD individuals [46]. Moreover, early suffering from decreased glucose metabolic rates in the inferior parietal lobe in SMC individuals may help explain these connectivity abnormalities [166]. Therefore, parietal region, as a functional core of the resting state network, is vulnerable to functional connectivity breakdown in AD patients [167–173]. Therefore, we proposed that the parietal region is the primary target of functional decrease in SCD individuals which may further lead to cognition decline. This paves the way to suggest that interdependent activity of resting state networks, such as DMN and parietal regions, are involved in memory retrieval [174], are widely interrupted in AD. Thus, these findings suggest that strong connections between brain regions in the frontoparietal network and in the resting state condition such as DMN are important for better memory and general cognitive performance. Moreover, less strength and clustering coefficient compared to HC was found in our study also in MCI and AD as well. Additionally, in the majority of the existing studies, SCD and MCI exhibited higher FC compared to HC over anterior regions such as left Inferior Temporal Gyrus, left Paracingulate and left Anterior Cingulate. This implies that all the links affected in the SCD were also disrupted in the MCI in a similar way and both groups present a similar functional coupling pattern, suggesting that SCD

have intermediate changes of DMN connectivity over specific posterior regions between MCI and HC. More specifically, the Posterior Cingulate Cortex (PCC)/Retrosplenial Cortex (RSC), the hippocampus, a structure crucial for memory formation and anatomically connected to the RSC, as well as the precuneus, found to consistently display pathological changes in the SCD [45,122]. Albeit, in the few studies where increased FC of SCD with respect to HC was found, was basically located over precuneus (PUN) [105,109], a key region of DMN located at parietal brain area, which has been found to demonstrate interrupted connections as the disease progresses [136,171,175]. The precuneus is the portion of the superior parietal lobule on the medial surface of each brain hemisphere. That can explain also our findings showing that parietal network disruptions both at strength and at clustering coefficient are widely observed in SCD compared to HC, but also in later stages as well (MCI and AD). However, these inconsistencies between studies' findings may result from the heterogeneity of the disease stages of SCD participants and the inclusion criteria the authors applied during recruitment. The selection of the SCD participants has been conducted without taking into account the latest proposed SCD-I WG criteria, since SCD group had MMSE total score *M* (SD)= 27.2 (0.4), including participants even with 26.8, which is a total score of global cognitive function more suitable for MCI [105]. Additionally, participants younger than 60 (range 55 – 77) were also recruited for the study of [109], a selection criterion which also falls apart according to SCD – I WG guidelines [146]. Albeit in our study we used the SCD-I WG criteria, and were recruited from memory clinic which increases the risk of developing AD [176]. Both selection criteria support that this particular group was well-diagnosed and our findings can be generalized.

Based on the previous studies, disruptions of FC in SCD were observed not only in DMN but also in other tested networks. Moreover, network properties such as shortest path length of Grey Matter Network (GMN) originate in the PUN, one of the brain areas involved in the early amyloid deposition [177] and from which later network alterations may spread to the fronto-temporo-occipital cortices, found to have lower values in SCD [108]. Additionally, lower clustering coefficient values in SCD indicated a more randomly organized GMN showing faster decline in global cognition and language [108]. In particular, lower values of clustering coefficient and path length have been related with longitudinal decline in language, which is often impaired in AD [39,178,179]. In this common line, our study found lower values of clustering coefficient between patient groups (SCD, MCI and AD) compared to HC, which highlights the importance of this particular network metric to predict potential future conversion of SCD to more advanced stages.

Also in MEG studies, SCD found to have a general hypo-synchronization compared to HC [106]. These results suggest that the subjective feeling of cognitive dysfunction without any objective cognitive dysfunction could be an early sign of pathological brain function related to future progression to AD. When FC alterations were compared between SCD and HC, the HC found to have higher synchronization values, while a posterior disconnection over lateral inferior parietal, medial temporal and occipital areas was observed in SCD with an anterior hyper-synchronization affecting the exact same regions with MCI [44]. Thus, SCD elders exhibited disruptions at the brain connectome in a

similar manner with those observed in MCI. Regarding nodal clustering changes, it is worth noting that differences were found only between HC and MCI, whereas SCD local clustering was different neither from HC nor from MCI, while MCI exhibited widespread clustering decreases, which indicate local disconnection of those nodes [48]. In contrast with the abovementioned findings our study found statistical significant differences between SCD and HC with respect to local clustering coefficient. However, we failed to show any statistical significant difference between HC and SCD with regards to global clustering coefficient.

The impaired capacity of information transfer due to the early White Matter Network (WMN) degeneration in SCD has been observed also in several reported studies [46,107,125,127]. More specifically, disrupted connectivity and nodal efficiency of WMN observed widely in the bilateral frontal, temporal, parietal, and occipital regions, including bilateral orbital frontal cortex as well as bilateral orbital part of middle frontal gyrus and superior frontal gyrus, left thalamus, left temporal pole of superior temporal gyrus, left and right anterior cingulate and paracingulate gyrus, PCUN, PUT, the left temporal pole of superior temporal gyrus, the left superior occipital gyrus, the right cuneus, calcarine fissure and surrounding cortex (CAL), and several occipital regions [46,49,107]. In addition, despite the fact that rich - club regions (CAU.R) of WMN were widely preserved in SCD and were disrupted gradually in later stages, as the disease progresses (MCI and AD), the peripheral regions (CAU.L and ORBmid.L) were more likely to show aberrant connections in predementia stages, before obvious symptoms appear in neuropsychological assessment [107]. In sum, SCD have shown significantly lower strength of the rich - club, feeder, global and local efficiency of brain networks connections of WMN compared to HC, which suggests that there is brain interruption of both functional integration and segregation. In all abovementioned studies which investigated WMN, SCD had values intermediate to MCI and HC, suggesting a similar damage pattern of structure network in SCD but milder than MCI. In this common vein, our study showed that strength values were significantly lower in SCD, MCI and AD compared to HC at local level but not at global level, suggesting that in EEG also can be found intermediate values of the SCD between HC and MCI.

Another study has found that individuals with, compared to without, SCD showed lower subsequent memory effects in the occipital lobe, superior parietal lobe, and posterior cingulate cortex, despite of a lack of difference in task performance and other cognitive measures [103]. First, they found disrupted functional coupling between frontal and parietal areas in prodromal AD suggesting a reduction of anterior-posterior coupling; positive cognitive–functional dynamic correlations, which suggests that the coupling between the left vmPFC and the left PCC might be able to differentiate prodromal AD patients with relatively preserved memory performance from those with memory decline. In support of the disconnection hypothesis, they found functional decoupling between the vmPFC and posterior parietal regions, which is further supported by the different network hierarchies they found in prodromal AD compared to SCD and HC. In prodromal AD the PCC, IPL, and RSC form a main cluster. The role of these three parietal regions indicating a prodromal AD-related assembly of posterior parietal regions is well established in AD[180–182]. This suggests that these regions segregate from remaining

DMN nodes in prodromal AD, potentially resulting from the high metabolic activity and accumulation of amyloid plaques [183–185]. Importantly, we did not find a significant difference in global brain network properties (clustering coefficient and strength) between HC and SCD neither between SCD and the rest groups (MCI and AD), which could indicate that not all SCD participants are characterized by an underlying AD-pathology or that these changes are yet too subtle to be detected at the whole brain. The characterization of SCD individuals being at risk for AD is current work in progress [186]. For the definition of our SCD group, we followed the recently developed framework proposed by Jessen et al. [80]. It has been found that in the prodromal phase of the disease, parietal region is associated with worse cognition in prodromal AD patients. Therefore, reduced parietal activity may be used as a clinical tool for early identification of individuals at risk to manifestation of AD. These results may furthermore serve as groundwork for future intervention studies using non-invasive brain stimulation techniques focusing on altering the functional coupling between several regions to induce compensatory changes in SCD thereby delaying memory decline [122].

Despite the fact that in the majority of the studies, brain connections were interrupted in SCD group compared to HC, small - world properties were widely preserved in SCD. This could also partially explain our results regarding the preserved global network metrics in this population. This implies that the brain has not undergone such damage to demonstrate a randomized network. While still preserving some intact network properties, SCD elders exhibited disruptions (node degree, local clustering coefficient, path length etc) at the local network level compatible with those evidenced in MCI, although to a lower degree. Also, our recent systematic review [31] of several neuroimaging studies reinforces the idea of SCD as a preclinical asymptomatic stage of AD with potential future progression in more advanced stages. In other words, MCI and AD groups suffer severe disturbances in the connections of brain regions and present a more random brain network instead of small – world. On the other hand, SCD have relatively stable connections as far as network properties at global network is concerned compared to HC, but they exhibit lower values in between specific regions connections over posterior brain structures. Compatible with the findings of the abovementioned studies, our results reinforce that disrupted nodal strength of posterior areas - parietal channels of the brain is evident among SCD as in MCI and AD respectively with respect to HC. This localized disconnection has been proposed also in previous works demonstrating that posterior DMN subsystem connectivity declines within the AD spectrum [141].

Also a recent EEG study showed that the network properties showed significant differences between the MCI and HC groups. Specifically, the MCI group showed the decreased clustering coefficient and increased shortest path length compared to the HC in alpha band [25]. These results demonstrated that MCI have less efficiency in processing both local and global information, which could account for cognition problems such as the memory impairment that is usually encountered by aMCI patients [187,188]. In this common vein, another EEG study revealed that the brain network of aMCI patients displayed a disconnection syndrome and a loss of small-world architecture [24]. The correlation between cognitive states and network characteristics suggested that the more

in deterioration of the patients' cognitive state, the less optimal the network organization becomes. Hence, both in the abovementioned studies as well as in ours, the complex network-derived biomarkers based on EEG could be employed to track cognitive function of people at preclinical stages of AD and provide a new diagnosis tool for both SCD and MCI. Furthermore, findings in the MCI patients are quite contradictory among studies, since some of them report no significant changes of brain network in MCI whereas others show decreased or increased "small-worldness." Specifically, Seo et al. reported that local clustering of networks was lower in MCI compared to normal cognitive subjects [189], whereas Vecchio et al. found a significant increment of the clustering coefficient for MCI group [190]. Besides, both the above two studies did not observe obvious difference in path length between two groups, whereas Xu et al. found that the MCI group had increased path length; using this network feature allows to distinguish the two groups with 90% accuracy [28]. Hence, it is still uncertain that whether MCI individuals would exhibit a disrupted small-world property similar to those of dementia patients, and more work is needed to make clear this problem, especially for the preclinical stages of AD, such as MCI patient. Moreover, in a similar approach, the authors concluded that functional connectivity disruptions between certain brain regions, as measured with lagged phase synchronization, may potentially represent a neurophysiological biomarker of AD [191].

7 Conclusion and Future Research

To the best of our knowledge, there are no studies which have investigated the brain connectivity using HD-EEG in SCD participants compared to AD, MCI and HC. In our study, we proceed to ROC curves analysis in order to define the cut-off scores and the specificity and the sensitivity of every variable (clustering coefficient and strength at global and local level). Based on our findings, the local clustering coefficient and local strength may be considered as a potential biomarker for the detection of SCD, discriminating SCD from the HC with 75% sensitivity and 64% specificity (AUC= 71%, in ROC curves) in case of clustering coefficient and strength, MCI from HC with 80% sensitivity and 64% specificity in case of clustering coefficient and strength (AUC=73% and AUC=79% respectively, in ROC curves), and AD from HC with 65% sensitivity and 82% specificity in case of clustering coefficient and strength (AUC=79 in ROC curves).

Our study further adds to the growing body of literature that SCD may indeed reflect neuronal changes at network level and suggests that brain connectome and more specifically estimation of clustering coefficient and strength at parietal areas, could serve as a potential biological predictor of subsequent cognitive decline associated with AD. However, more longitudinal research is required to further replicate, expand and investigate the potential pathophysiological mechanisms that are associated with these brain network changes in SCD. In general, SCD showed less local network strength and clustering coefficient but preserved network properties at global level. Finally, the field of brain connectome has great promise for elucidating the complex relationships between SCD who will eventually develop AD and FC patterns but a more consistent analytic procedure should be adopted across research groups in order to integrate the findings of several studies.

8 Abbreviations

Abbreviations of Brain Areas	
Alzheimer's Disease (AD)	Medial Temporal Memory system (MTMS)
Anterior Cingulate Cortex (ACC)	Medial Visual Network (MVN)
Anterior Ventral DMN (avDMN)	Mild Cognitive Impairment (MCI)
Caudate nucleus (CAU)	Posterior Cingulate Cortex (PCC)
Cuneus (CUN)	Posterior Default Mode Network (pDMN)
Default Mode Network (DMN)	Precuneus (PUN)
Dorsal Attention Network (DAN)	Putamen (PUT)
Functional Connectivity (FC)	Region of Interest (ROI)
Gray Matter Networks (GMN)	Retrosplenial Cortex (RSC)
Healthy Controls (HC)	Subjective Cognitive Decline (SCD)
Hippocampus (HP)	Supplementary Motor Area (SMA)
Inferior Parietal Cortex (IPC)	Synchronization Likelihood (SL)
Inferior Parietal Gyrus (IPG)	Thalamus (THA)
Inferior Parietal Lobule (IPL)	Ventral Medial Prefrontal Cortex (vmPFC)
Medial Prefrontal Cortex (mPFC)	White Matter Network (WMN)
Medial Temporal Lobe (MTL)	

9 Contributions

Mrs Ioulietta Lazarou is the correspondence author of the present master thesis. She was written, formatted the text. She has conducted the literature search as described in Section 1, 2 and 4. Moreover, she has examined all the participants using validated and standardized neuropsychological tests as described in Section 5.1.2. In addition she has appointed the participants and has conducted the resting state EEG recordings as described in 5.1.3.Finally, she has made the preprocessing analysis of EEG recording using NetStation 4.3 and has collected and contributed in the data collection and network construction and analysis of the network metrics as described in 5.1.4 and 5.2.2, using MATLAB by guidance of prof Kugiumtzis and valuable contribution and help of Mr Kostas Georgiadis. Finally she has done the statistical analysis of the results (Section 5.2) using SPSS and RStudio.

Prof Dimitris Kugiumtzis is the supervisor of the thesis and has provided all the algorithms and functions necessary for the network construction and analysis in the MATLAB as described in Section 1.2.4 and Section 5.1.4. Also, he has given instructions for the statistical analysis as described in Section 5.1.5. I detail, he has written formatted and corrected several parts of the thesis and has significantly contributed towards the final construction of the contents of the master thesis (Section 1.3). He has provided valuable instructions on how to conduct the analysis as described in Appendices. He was the responsible for the aim of the study (Section 3) and has supervised the process and the analysis of the results step-by-step as described in Section 5.2.

Mr Kostas Georgiadis has significantly contributed in EEG recordings as described in Section 5.1.3 by using the EGI GES 300. Moreover, due to his expertise he had a main role in network analysis as described in Section 5.1.4 and 5.2.2 using MATLAB.

Dr Spiros Nikolopoulos has supervised the EEG recordings as described in Section 5.1.3 using EGI GES 300 and NetStation 4.3. Also, he has provided scientific input in Section 4 and he has contributed towards the data acquisition as presented in Section 5.1.4. Finally he has act as the second reader of this thesis, and he has provided very valuable comments on this thesis.

Dr Ioannis Kompatsiaris has provided access to the EEG infrastructure (EGI GES 300) which is part of the MKLab (CERTH-ITI). He has provided valuable input during the literature search as described in Section 4 and has written, formatted and corrected several parts of the thesis by providing insightful comments.

Prof Magda Tsolaki is the responsible clinical principal investigator of the current study. She has examined all the participants through neurological and clinical examination (laboratory examination and MRI) as described in Section 5.1.1 and Section 5.1.2 and has set the final diagnosis and categorization of each participant. She has also supervised and corrected specific parts of the manuscript (Sec 1, 2, 4 and 6) by providing valuable input and corrections.

10 APPENDICES

Στον παρακάτω σύνδεσμο βρίσκονται τα scripts που χρησιμοποιήθηκαν για τις αναλύσεις:

https://drive.google.com/drive/folders/1fRRIytwU7GeAs_9eVGSWq3cRqpSCI3tA?usp=sharing

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