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Editorial
Άρθρο σύνταξης

Gut microbiome and adaptive immunity in schizophrenia

Psychiatriki 2019, 30:189–190

Over the past few years, immunopathogenesis has emerged as one of the most compelling aetiopathological models of schizophrenia (SCZ), suggesting a chronic, immune-based, low-grade inflammatory background of this devastating disorder.[1,2] Mounting evidence points towards a prominent role of the adaptive immune system in SCZ, suggesting alterations in defense mechanisms, such as altered T-cell function and a shift towards B-cell immunity.[3] Immune cells have the ability to infiltrate the brain and mediate a neuroimmune cross-talk through activation of microglia, production of pro-inflammatory cytokines and reactive oxygen species, leading to neuroinflammation, as mediator of neuroprogressive and neurodegenerative changes in SCZ.[4] Antipsychotic drugs, commonly used to treat SCZ, are also known to affect the adaptive immune system, interfering with the differentiation and function of immune cells, towards their normalization in response to treatment.

Adaptive immunity is principally founded on T-cell and B-cell populations, but also includes the host microbiome. The gastrointestinal microbiota is a complex ecosystem with a great organism diversity and refined genomic structure that resides in the intestinal tract and has a central position in human health and disease.[5] Neuroimmune dysregulation, relying of the highly sensitive and fine-tuned equilibrium between microbiome and adaptive immunity, can tip the scales towards neuroinflammation and disruption of higher-order brain networks.[4,6,7]

During the last decade, the human microbiome and the microbiota-gut-brain (MGB)-axis have become a novel epicentre in mental health research as a potentially vital new determinant in the field of neuroimmunoregulation, brain development, emotions, cognition and behaviour.[7] The MGB-axis represents a bidirectional, key communication pathway between the immune system and the brain, thus partly also mediating the regulation of cognitive and emotional processing. An imbalanced human microbiome might greatly influence proper neuroimmune reactions and neurodevelopment with long-lasting effects and could thus play a pivotal role in the susceptibility and aetiology of psychiatric illness.

Recent research offers first evidence that patients with SCZ show marked disturbances of gut bacterial taxa composition with a decreased microbiome diversity index, party associated with specific SCZ phenotype, symptom severity and treatment response.[8,9] As the elegant education of the adaptive immune compartment depends on the colonization niche, antigen type and metabolic property of different gut microbes, T-cell differentiation as well as a continuous diversification of B-cell repertoire is expressed through microbiome-related, antigen-specific receptors that define a unique clonotype.[10] However, there is only sparse evidence on the precise role of the microbiome on the programming of T- and B-cells in the underlying neurobiological pathways of SCZ and even less findings on the association of molecular T- and B-cell receptor repertoire signature and microbiome clonal landscape with specific phenotypical features of the disease.[11]

The latest conceptual advances in immunology urge an integrative re-evaluation of previous immunological findings in SCZ through modern approaches. High-throughput, next-generation sequencing (NGS) represents a powerful single-cell transcriptomic tool to profile the whole clonal landscape of T and B cells and human microbiome. NGS thus offers a unique opportunity for in-depth characterization of cellular and molecular signatures of adaptive immune receptor repertoires and microbiome taxonomy in SCZ and investigation of their intersection as a relevant pathway of disease progression and phenotype differentiation. SCZ patients are likely to show a diverging host-microbiome immune ho-

meostasis with disease-specific clonotypes of adaptive immune receptor repertoires associated with altered microbiome taxonomy and molecular signature differences, which, in turn, may be related to distinct symptomatic phenotypes and neurocognitive patterns.

Such sophisticated immuno-bioinformatic analyses may transform our understanding of SCZ by identification of novel neuroimmune pathways, offering us clinically accessible symptomatic and diagnostic biomarkers important for personalized medicine implications.[12] An increased understanding and better characterization of immuno-phenotypes in SCZ will better guide the development of novel immune-based treatments in this severe disease and pave the way for possible prevention options through implementation of antibody engineering, vaccine design, and cellular immunotherapy.

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Άρθρο σύνταξης
Editorial

Εντερικό μικροβίωμα και προσαρμοστική ανοσία στη σχιζοφρένεια

Ψυχιατρική 2019, 30:191–192

Η ανοσολογική θεωρία της σχιζοφρένειας (ΣΧΖ) αποτελεί ένα ενδιαφέρον βιολογικό μοντέλο, το οποίο εμπλέκει ένα χρόνιο ανοσολογικό υπόβαθρο με χαμηλού βαθμού φλεγμονή στην παθοφυσιολογία αυτής της τόσο σοβαρής διαταραχής.[1,2] Ένας αυξανόμενος αριθμός δεδομένων υποδεικνύει έναν προεξέρχοντα ρόλο της προσαρμοστικής επίκτητης ανοσολογικής απάντησης του οργανισμού στη ΣΧΖ, με μεταβολές στη λειτουργία των αμυντικών μηχανισμών των Τ και Β λεμφοκυττάρων.[3] Τα ανοσοκύτταρα έχουν τη δυνατότητα να διεισδύουν στο κεντρικό νευρικό σύστημα (ΚΝΣ) και να προκαλούν διαφοροποίηση της νευροανοσολογικής ισορροπίας μέσω ενεργοποίησης της μικρογλοίας καθώς και της παραγωγής προ-φλεγμονωδών κυτοκινών και δραστικών ειδών οξυγόνου, οδηγώντας έτσι σε φλεγμονή, που με τη σειρά της προκαλεί προοδευτικές και εκφυλιστικές αλλαγές στον εγκέφαλο που σχετίζονται με τη ΣΧΖ.[4] Είναι, επίσης, γνωστό πως τα αντιψυχωτικά φάρμακα επηρεάζουν και το προσαρμοστικό ανοσοποιητικό σύστημα επεμβαίνοντας στη διαφοροποίηση και στη λειτουργία των ανοσοκυττάρων, με αποτέλεσμα την ομαλοποίηση της ανοσοαπάντησης του οργανισμού κατά τη διάρκεια της θεραπείας.

Η προσαρμοστική ανοσία βασίζεται κυρίως στους πληθυσμούς των Τ και Β λεμφοκυττάρων, αλλά περιλαμβάνει επίσης και το εντερικό μικροβίωμα. Η μικροχλωρίδα αυτή είναι ένα σύνθετο οικοσύστημα με μεγάλη βιοποικιλότητα και ιδιαίτερη δομή γονιδιώματος, βρίσκεται στην εντερική οδό και έχει κεντρική θέση στη διατήρηση της ανθρώπινης υγείας αλλά και στην αιτιοπαθογένεια πολλών ασθενειών.[5] Μία ανατροπή της σωστής νευροανοσολογικής λειτουργίας, που βασίζεται στην ιδιαίτερα ευαίσθητη και καλά συντονισμένη ισορροπία μεταξύ αυτού του εντερικού μικροβιώματος και του προσαρμοστικού ανοσολογικού συστήματος, μπορεί να οδηγήσει σε φλεγμονή του εγκεφάλου και διαταραχή των ανώτερων εγκεφαλικών νευρικών δικτύων.[4,6,7]

Κατά τη διάρκεια της τελευταίας δεκαετίας, το ανθρώπινο μικροβίωμα και ο άξονας μικροβιώματος-εντέρου-εγκεφάλου έχει αποτελέσει επίκεντρο στην ψυχιατρική έρευνα, ως ένας πιθανός νέος και καθοριστικός παράγοντας στη νευροανοσολογική ρύθμιση, στην ανάπτυξη του εγκεφάλου, στα συναισθήματα, στη γνωστική λειτουργία και στη συμπεριφορά.[7] Ο άξονας μικροβιώματος-εντέρου-εγκεφάλου αποτελεί μια αμφίδρομη και βασική οδό επικοινωνίας μεταξύ του ανοσοποιητικού συστήματος και του εγκεφάλου, εν μέρει διαμεσολαβώντας τη ρύθμιση της γνωστικής και συναισθηματικής επεξεργασίας. Ένα μη ισορροπημένο ανθρώπινο μικροβίωμα μπορεί να επηρεάσει σε μεγάλο βαθμό την καταλληλόλητα της νευροανοσολογικής απάντησης και της νευροανάπτυξης με μακροχρόνιες συνέπειες, παίζοντας, με αυτόν τον τρόπο, έναν καθοριστικό ρόλο στην ευαλωτότητα και αιτιολογία των ψυχιατρικών νοσημάτων.

Πρόσφατες έρευνες υποδεικνύουν τα πρώτα στοιχεία αναφορικά με σημαντικές ταξινομικές διαταραχές του μικροβιώματος και μειωμένο δείκτη μικροβιακής ποικιλομορφίας σε ασθενείς με ΣΧΖ, ευρήματα τα οποία σχετίζονται και μερικώς με συγκεκριμένους φαινότυπους της ασθένειας, τη σοβαρότητα των συμπτωμάτων αλλά και την ανταπόκριση στη θεραπεία.[8,9] Δεδομένου ότι η «εκπαίδευση» του προσαρμοστικού ανοσολογικού διαμερίσματος εξαρτάται από τον ιδιαίτερο αποικισμό και το αντιγονικό ρεπερτόριο των διαφόρων εντερικών μικροβίων, η διαφοροποίηση των Τ και Β λεμφοκυττάρων εκφράζεται μέσω σχετιζόμενων με το μικροβίωμα υποδοχέων αντιγόνων που ορίζουν έναν μοναδικό κλωνότυπο.[10] Ωστόσο, υπάρχουν ελάχιστα μόνο στοιχεία σχετικά με τον ακριβή ρόλο του μικροβιώματος στον προγραμματισμό των

Τ και Β λεμφοκυττάρων στη ΣΧΖ και ακόμη λιγότερα ευρήματα σχετικά με τη συσχέτιση της μοριακής υπογραφής των υποδοχέων των Τ και Β λεμφοκυττάρων και του μικροβιώματος με συγκεκριμένα φαινοτυπικά χαρακτηριστικά της νόσου.[11]

Οι τελευταίες ερευνητικές εξελίξεις στην ανοσολογία απαιτούν μια ολοκληρωμένη επανεκτίμηση των μέχρι τώρα ανοσολογικών ευρημάτων στη ΣΧΖ μέσω σύγχρονων τεχνολογικών προσεγγίσεων. Η υψηλής απόδοσης αλληλούχηση νέας γενεάς (next-generation sequencing, NGS) αντιπροσωπεύει ένα ισχυρό βιοπληροφορικό εργαλείο κυτταρικής μεταγραφωματικής ανάλυσης του συνόλου του κλωνικού ρεπερτορίου των Τ και Β λεμφοκυττάρων και του εντερικού μικροβιώματος. Η NGS προσφέρει έτσι μια μοναδική ευκαιρία για τον εις βάθος μοριακό ανοσογενετικό χαρακτηρισμό κυτταρικών υποδοχέων προσαρμοστικής ανοσίας και ταξονομικής ποικιλομορφίας του μικροβιώματος στη ΣΧΖ και την περαιτέρω διερεύνησή τους της αντιγονικής εμπλοκής στην παθογένεση, στην εξέλιξη και στη φαινοτυπική διαφοροποίηση της νόσου. Οι ασθενείς με ΣΧΖ είναι πιθανό να εμφανίζουν διαταραγμένη ανοσολογική ισορροπία μεταξύ προσαρμοστικού ανοσοποιητικού συστήματος και μικροβιώματος με συγκεκριμένα για τη νόσο κλωνικά ανοσογενετικά χαρακτηριστικά, που με τη σειρά τους πιθανώς να σχετίζονται με διαφορετικά προφίλ συμπτωματικών εκδηλώσεων και νευρογνωστικών ελλειμμάτων.

Τέτοιου είδους εκλεπτυσμένες ανοσο-βιοπληροφορικές αναλύσεις μπορούν να οδηγήσουν στην αναγνώριση νέων νευροανοσολογικών οδών στη ΣΧΖ και να αλλάξουν την κατανόησή μας για την παθοφυσιολογία της νόσου, προσφέροντάς μας κλινικά προσβάσιμους, συμπτωματικούς και διαγνωστικούς βιοδείκτες σημαντικούς για εξατομικευμένες ιατρικές παρεμβάσεις.[12] Η αυξανόμενη κατανόηση και ο καλύτερος βιομοριακός χαρακτηρισμός διαφορετικών ανοσοφαινοτύπων στη ΣΧΖ θα ήταν επίσης σε θέση να καθοδηγήσει την ανάπτυξη νέων ανοσολογικών θεραπειών και να ανοίξει τον δρόμο για πιθανές μελλοντικές προληπτικές θεραπευτικές επιλογές, για παράδειγμα μέσω μηχανικής τροποποίησης αντισωμάτων, σχεδιασμού εμβολίου και κυτταρικής ανοσοθεραπείας.

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Research article
Ερευνητική εργασία

Differential effects of earthquakes on patients with bipolar disorder versus schizophrenia: Findings from Crete, Greece, 2008–2010

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Electromagnetic radiation influences in many ways humans and animals, while earthquakes are known to be related with electromagnetic phenomena. We recently showed that large earthquakes reduced admissions of psychiatric patients, whereas small earthquakes were associated with increased number of admissions. Our aim was to examine the effect of seismic-related electromagnetic activity on two chronic and severe psychiatric disorders varying in terms of etiology and treatment, i.e. bipolar disorder and schizophrenia. Retrospective data concerning monthly admission rates of patients diagnosed with schizophrenia or bipolar disorder in the Psychiatric Unit of the University Hospital of Heraklion, Crete, Greece between 2008 and 2010 were analyzed in relation to the number of earthquakes with small (≥2) or larger magnitude in the Crete region in Greece. Results showed a marked reduction of acute admissions during a storm of large earthquakes, which was greater in patients with bipolar disorder (91.2%) than schizophrenia patients (52.4%). In addition there was a significant increase of admissions during a period of frequent small earthquakes, primarily among patients with bipolar disorder. The results suggest that electrostatic fields that accompany large earthquakes may have a protective effect on psychiatric disorders, particularly on bipolar disorder. These findings are consistent with the ameliorating effect of electromagnetic fields used in Electroconvulsive therapy (ECT) and Transcranial Magnetic Stimulation (TMS) in patients with bipolar disorder. Future studies focusing on the underlying mechanisms may lead to more specific treatments of psychiatric disorders.

Key words: Psychosis, mood disorders, relapses, electromagnetic fields, earthquakes, hospital admissions.

Introduction

The pathophysiology of severe mental disorders such as schizophrenia and bipolar disorder is largely unknown despite extensive research and is considered to be multifactorial. Among the factors believed to relate with adverse effects of mental disorders, excessive occupational or environmental exposure to electromagnetic radiation[1–3] and geomagnetic disturbances and storms[4–6] have been examined with promising results. A variety of naturally occurring environmental electromagnetic phenomena (Ultra Low Frequency radiation, electron precipitation, geoelectric and geomagnetic field anomalous variations, etc.) have been attributed to seismic activity.[7–9]

We have recently reported that transient seismic activity may significantly impact psychotic manifestations leading to increased admissions to a Psychiatry Unit.[10] Specifically, we found that admissions were significantly increased during periods with higher number of very small (magnitude <~3) earthquakes as compared to the period between February and July 2008, characterized by high seismicity in Southern Greece. Moreover, a daily resolution analysis revealed that an abrupt increase in the number of small earthquakes was followed by an increase in the number of admissions over the following 2 days. However, these analyses did not examine potential differences in the impact of seismic activity on schizophrenia and bipolar disorder. Despite some similarities in their clinical presentation, the mental disorders can be distinguished on several genetic and pathophysiological characteristics.[11] Of particular interest is that treatments involving electromagnetic fields, such as Electroconvulsive Therapy (ECT) and repetitive Transcranial Magnetic Stimulation (rTMS), are effective in patients with bipolar disorder, but they have only very limited utility in schizophrenia.[12,13] Based on the above, the goal of the present study was to assess whether there was a differential effect of seismic activity on hospital admissions of patients suffering from bipolar disorder versus schizophrenia in the sample of patients originally reported by Anagnostopoulos et al.[10] The geographical region surveyed in the present report (Crete, Greece) is characterized by high seismicity, given that it includes a major part of the Hellenic Arc and Trench system at the boundary, which marks the active subduction of the African lithospheric plate beneath the southern margin of the Eurasian plate. We hypothesized that large seismic activity would have a greater impact on bipolar disorder than schizophrenia patients.

Material and method

Study sample

The sample of this retrospective observational study included patients admitted to the Psychiatric Inpatient Unit of the University of Crete, between 2008–2010, based on the electronic database of the hospital with a primary diagnosis of bipolar Disorder or schizophrenia. The Psychiatric Unit consists of two separate wards: (1) the "acutely ill ward" (acute admissions), where agitated/aggressive patients are admitted, usually involuntarily, and (2) the "short-stay ward"(short-term admissions), where patients with less serious psychopathology are admitted. The Psychiatric Unit is the only public inpatient unit for adult patients in Eastern Crete, serving a population of 400,000 inhabitants. Diagnosis of bipolar disorder and schizophrenia was based on clinical evaluation by the attending psychiatrists of the Unit according to the DSM-IV TR criteria.[14]

The time period examined, i.e. 2008–2010, was selected because of the well-known storm of great earthquakes in Greece in 2008.[15] Earthquakes of magnitude ≥2.0 obtained by the European Mediterranean Seismological Centre (www.emsc-csem.org) were included in the analysis. Earthquakes were characterized based on their magnitude, as large (magnitude≥4.5), small (2.0≤magnitude<4.5), and very small (2.0≤magnitude<3.0). The time period examined was divided into two windows, based on the seismic activity: Period I (January-October 2008), characterized by an unusual storm of large earthquakes (i.e. 4.5≤magnitude≤6.9), and Period II (November 2008–December 2010), characterized by rarity of large earthquakes and a higher relative number of small earthquakes (magnitude<~3).

Statistical analysis

In the current analysis we included (1) monthly acute admissions associated with more severe psychopathology and loss for daily function, and (2) monthly total admissions, i.e. admissions in both

acute and short stay wards. The acute admissions were analysed during the two distinct time-periods with different seismological characteristics, i.e. Period I (large earthquakes) and Period II (small earthquakes). Associations between earthquakes and patient admissions data were analysed using linear regression.

In order to further investigate the effect of small earthquakes on schizophrenia versus bipolar disorder a correlation "peak to peak" analysis was conducted between the number of small earthquakes and the number of admissions. Furthermore, we explored the associations between the number of earthquakes with magnitude 2–4.5 for Periods I and II and admissions of patients with schizophrenia and bipolar disorder using Ordinary Least Square (OLS) regression. Finally, the time association between the number of earthquakes with magnitude 2–4.5 and admissions of patients with schizophrenia and bipolar disorder in Period II was assessed using lagged cross-correlation analyses, with time unit=1 month and lags ranging from k=0 tok=±8. Statistical levels of significance was set at $p<0.05$.

Results

During Period I (large earthquakes) the average number of acute admissions, were significantly reduced compared to the corresponding number in Period II, for both bipolar disorder and schizophrenia patients (figure 1). The reduction rate was significantly higher in bipolar disorder (91.2%) compared to schizophrenia patients (52.4%; $p<0.05$).

During Period II, when an increasing presence of small Earthquakes were recorded we found a strong and significant association between acute admission rates of schizophrenia ($r=0.659$; $p<0.001$) and bipolar disorder patients ($r= 0.661$; $p<0.001$) and the total number of earthquakes (figure 1). In the same period there was a positive trend of association between monthly acute admissions and total number of earthquakes in both schizophrenia ($\beta=0.170$, $p=0.138$) and bipolar disorder patients (trend $\beta=5.848$, $p<0.001$) (figure 1, grey lines).

To verify that the marked difference in admissions between Period I and Period II was not mainly due to the overall increase of admissions during Period II, but reflected a veritable reduction during Period I, we further compared Period I admissions to the admissions' during 2011 (01-01-2011 to 31-12-2011), which was a time-period without extreme seismic activity (large or small earthquakes). This comparison revealed similar results (data not shown).

We further investigated the effect of small earthquakes on admissions during Period II, using "peak to peak" correlation analysis (figure 2) and found that the rising trend of small earthquakes over time ($\beta=5.848$, $p<0.001$) was paralleled by a similar, rising trend of admissions of bipolar disorder patient ($\beta=0.298$, $p<0.001$). No such trend was noted for hospital admissions of schizophrenia patients.

Focussing on small earthquakes (magnitude 2–4.5) using OLS regression we found a positive association between the number of earthquakes and the number of admissions of both schizophrenia (figure 3c; $r=0.484$, $p=0.039$) and bipolar disorder patients (figure 3d; $r=0.703$, $p<0.001$). However, the effect on the bipolar disorder patients was much stronger compared to the effect on the schizophrenia patients ($p<0.001$ vs $p=0.039$). In contrast, during Period I characterized by large earthquakes this association did not approach significance neither for schizophrenia (figure 3a; $r=-0.214$, $p=0.498$) nor for bipolar disorder patients (figure 3b; $r=0.214$, $p=0.498$). The lack of association could be explained by the superseding effect of the large earthquakes (i.e. magnitude ≥ 4.5) over the effect of the small ones during this period.

Lagged cross-correlation analyses examining the temporal association between earthquakes of magnitude ≥ 2, and hospital admissions revealed that the highest correlation occurred at zero time lag in both patient groups (figure 4a,b). The zero-lag correlation coefficient was especially pronounced in patients with bipolar disorder ($r=0.703$, $p=0.001$; figure 4b). To further explore associations between admission rates and the type of earthquakes over time, we computed time-lagged cross-correlations between admission numbers and monthly ratio between "very small" ($2 \leq$ magnitude < 3) and larger earthquakes (magnitude ≥ 3). It should be noted that during this period, the ratio very small over magnitude ≥ 3 earthquakes was significantly reduced due to the increased number of "very small" Earthquakes

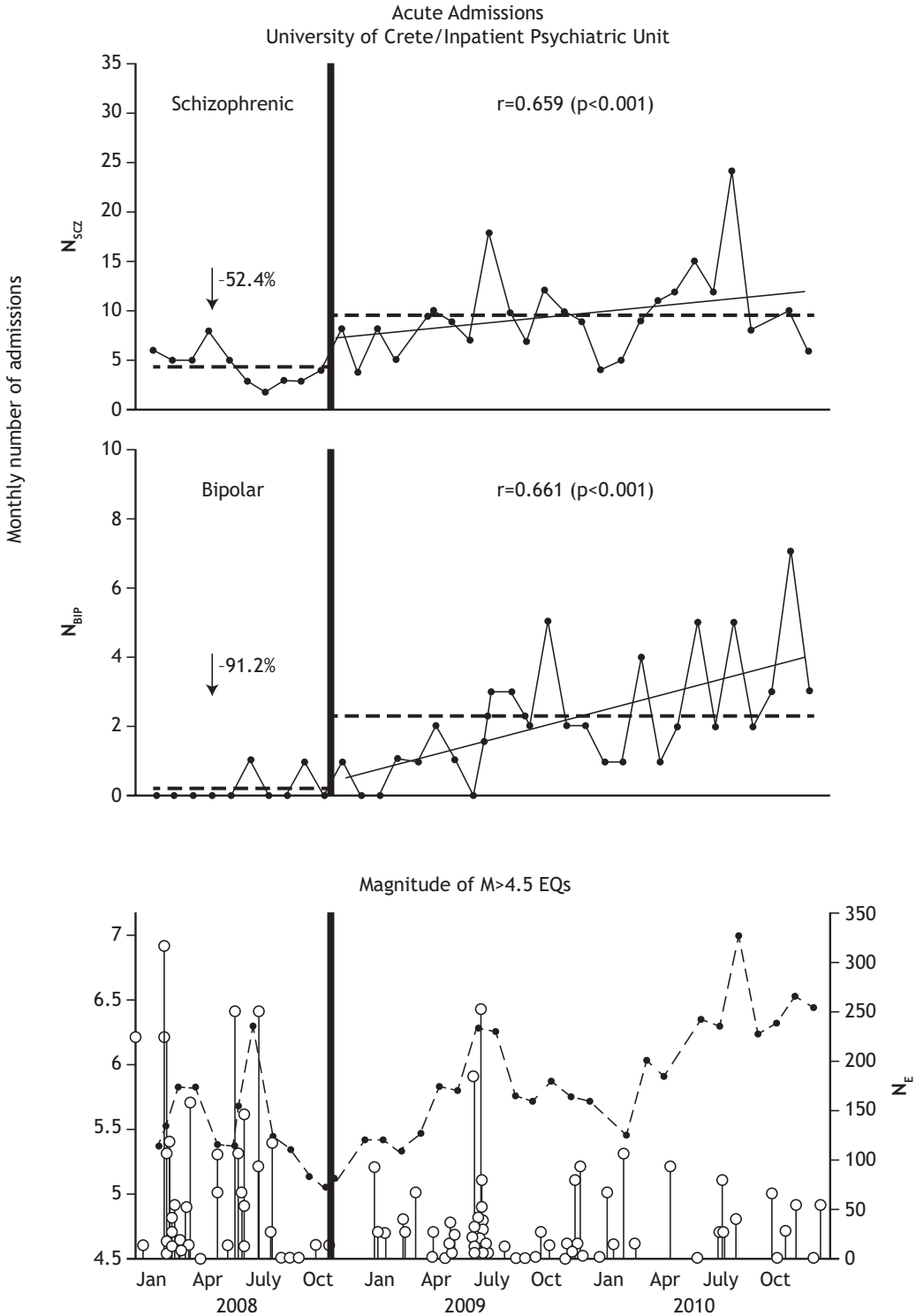

Figure 1. Monthly acute admissions to the Acute Psychiatric Unit of patients with Schizophrenia (N_{SCZ}, panel a) and the Bipolar Disorder (NBIP, panel b). The vertical line in each panel separate the period characterized by frequent, large-magnitude earthquakes (Period I) from the period of increased frequency of small earthquakes (Period II). Panel c displays the monthly variation in the number of M≥2 earthquakes (right-hand axis) M≥4.5 earthquakes (left-hand axis) in the region surrounding Crete during the years 2008–2010.

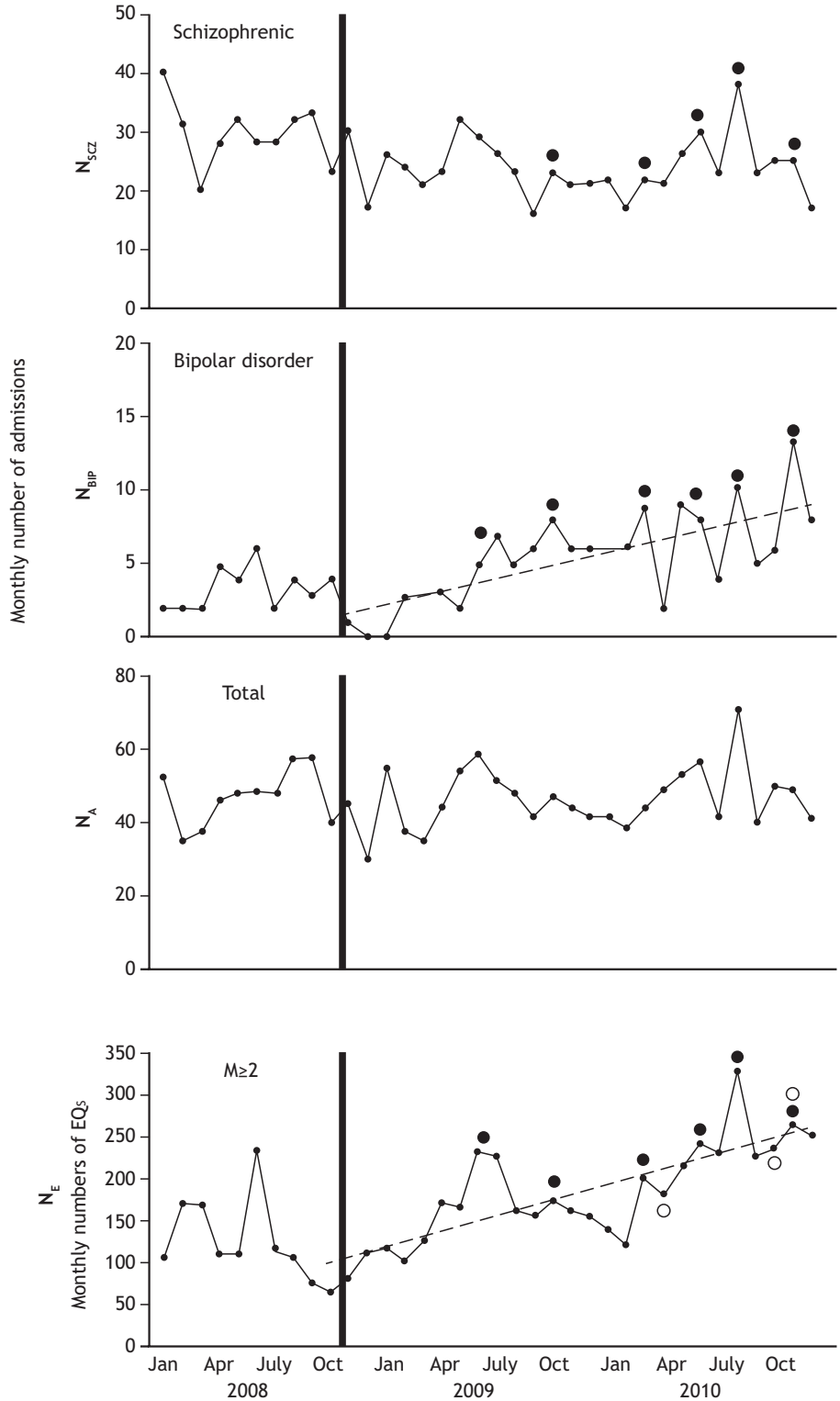

Figure 2. Peak to peak analysis of the monthly course of (a) Total admissions (acute and short-term units) of Schizophrenia patients [N_{SCZ}], (b) Bipolar Disorder patients [N_{BIP}], (c) the total numbers of admissions [N_A] in the acute psychiatric unit and, (d) number of earthquakes of magnitude ≥2 in the region surrounding Crete [N_E]. Solid circles indicate times of positive correlations between the four curves.

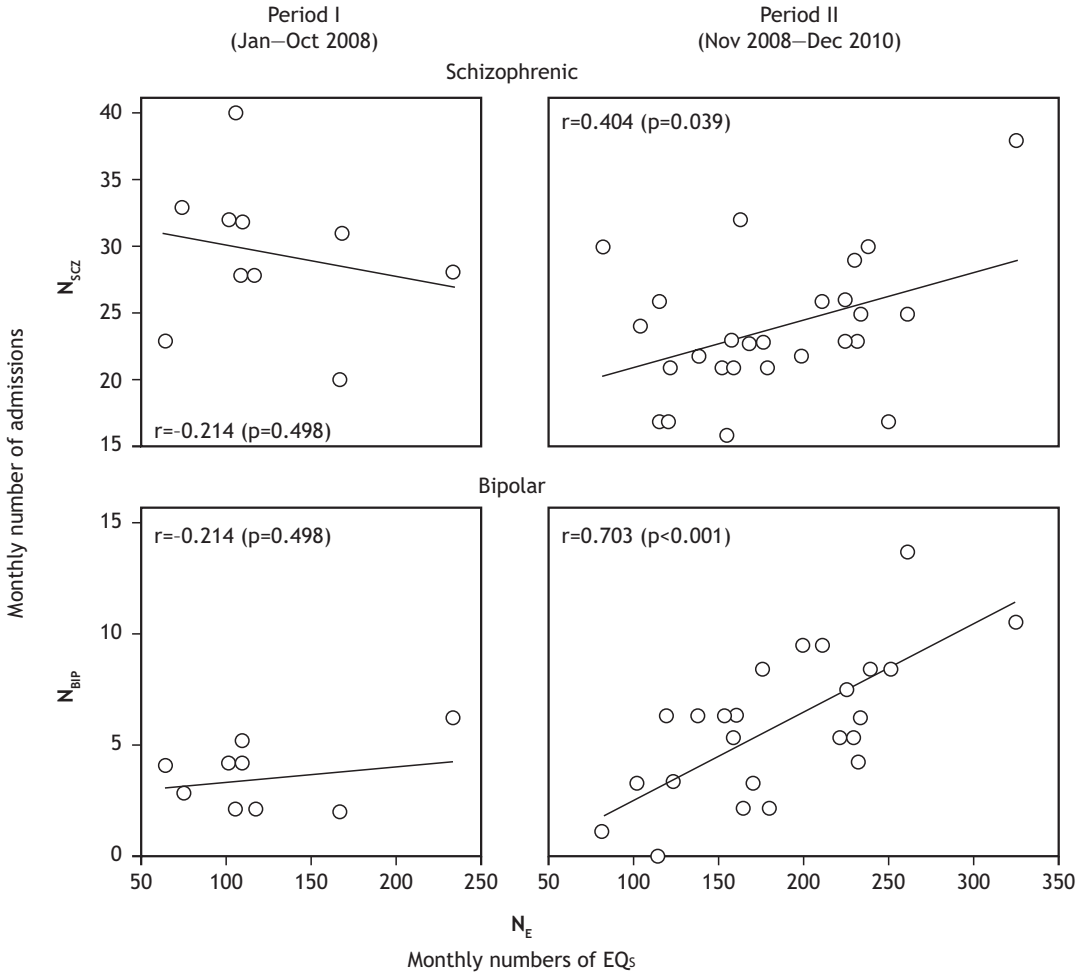

Figure 3. Ordinary Least Square (OLS) regression of the total number of admissions of Schizophrenia (N_{SCZ}) and Bipolar Disorder patients (N_{BIP}) against the total number of earthquakes (N_E) of magnitude ≥2 during Period I (featuring increased number of large earthquakes; panels a-b, respectively) and Period II featuring increased number of small earthquakes; panels c-d, respectively).

compared with the number of magnitude ≥3 earthquakes. Again, strong significant, negative correlations were found at lags around t=0 (–1 to 1) in bipolar disorder patients (figure 4d), whereas no significant correlation was found in schizophrenia patients at any time lag (figure 4c). This result suggests that the number of admissions in the former patient group is more closely associated with small than with magnitude ≥3 earthquakes.

Discussion

In summary, the present results revealed (a) a negative association between high magnitude seismic activity and hospital admissions with two major psychiatric diagnoses (Schizophrenia and, primarily, bipolar disorder) and, (b) a positive association between low magnitude seismic activity and hospital admissions, which was, again, greater among patients with bipolar disorder and followed a clear temporal pattern. These results extend our earlier report[10] by documenting that although seismic activity is a major factor influencing the stability of patients with bipolar disorders and schizophrenia, patients in the former group may be more sensitive to seismicity than patients in the latter group. These results may have a significant impact in developing new methods to prevent and treat major psychiatric disorders, such as bipolar disorder, and enhance our understanding of the underlying mechanisms.

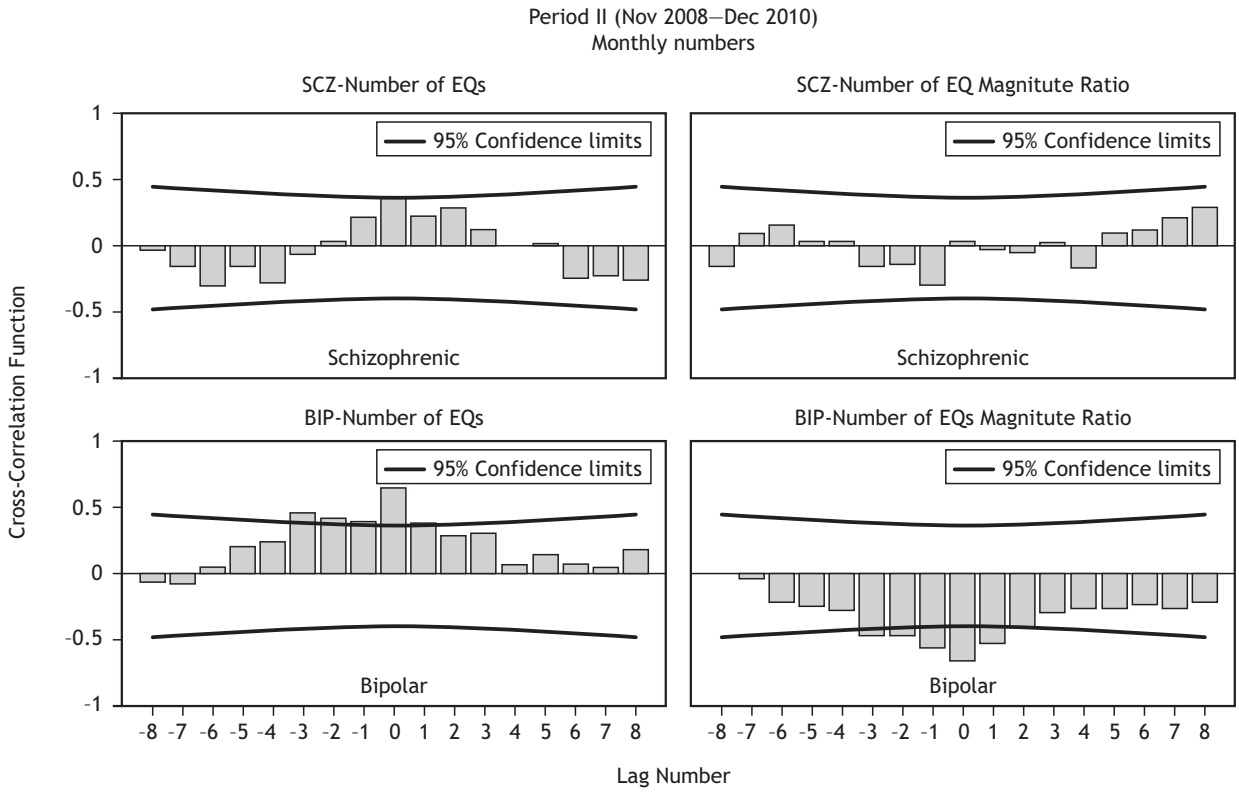

Figure 4. Cross-correlation coefficients and associated 95% confidence intervals for lags k=0, ±1, ±2,..., ±8 between monthly admission rates and the number earthquakes of magnitude M≥2 for schizophrenia (a) and bipolar disorder patients (b). Corresponding cross-correlations between monthly admission rates and the monthly ratios of the number of M≥3 earthquakes to the number of 2≤M<3 earthquakes (panels c, d) are displayed in panel (c) for patients with Schizophrenia and panel (d) for Bipolar Disorder patients during Period II (increased number of small earthquakes).

Protective effect

This is the first large study demonstrating the potential protective effect of a natural phenomenon, i.e. large-magnitude earthquakes, on both major types of severe mental disorders. Specifically, we showed that during the historic storm of large earthquakes in the area of Crete[15] with one earthquake with magnitude 6.9, three earthquakes with magnitude ≥6.4 and about 60 earthquakes with magnitude ≥4.5 during the 6-month period between January and October (2008), there was a marked reduction in the mean monthly acute admission rates of patients with bipolar disorder and schizophrenia in the order of 91.2% and 52.4% respectively, compared to the mean values of the admissions during the remaining portion of the 3-year period examined (2008–2010).

Electromagnetic treatments, such as ECT and rTMS, are well established methods for severe depressive illness, a prolonged or severe episode of mania, or catatonia.[12,13] It is also known that before large earthquakes the near-ground atmospheric electric field is increased from ~0.1 kV/m to values as high as 1–2 kV/m.[9,16] The present results raise the possibility that the low admission rate of patients with bipolar disorder and, to a lesser but still significant degree of patients with schizophrenia during periods of large earthquakes, is associated with increases of the near-Earth atmospheric electric field.[10]

Adverse effects

The second main finding of this study concerns the effect of small earthquakes on patients with psychotic disorders. Our analysis suggests a significant

positive correlation between the monthly number of small earthquakes and the number of acute admissions of patients with Bipolar Disorder, indicating that increased number of small earthquakes (magnitude 2–4) is associated with increased hospitalization rate of both bipolar and schizophrenia patients. Moreover, the positive correlation between hospital admissions and earthquakes became even stronger, mainly among patients with bipolar disorder, when only very small ($2 \leq M < 3$) earthquakes were considered.

The small earthquakes that either precede a large one for time periods as long as >1 month or those that often occur at the boundaries of tectonic plates, as is the case of the island of Crete, emit electromagnetic radiation at the Ultra Low Frequency (3–30 Hz) and the Extra Low Frequency (30–300 Hz) bands.[8,17–19] There is also evidence that Ultra Low Frequency and Extra Low Frequency radiation may interact with neurophysiological processes involved in emotion-related and cognitive functions.[10] Therefore, we suggest that the earthquake-induced Ultra Low Frequency/Extra Low Frequency electromagnetic radiation may exacerbate symptoms of schizophrenia and bipolar disorder, leading to increased hospital admissions among patients living in seismically active regions.

The present results are consistent with several other reports that physical and man-made Low Frequency/ Extra Low Frequency electromagnetic fields, such as geomagnetic disturbances and storms,[20] as well as Schumann resonances,[4,6] are partially responsible for inducing mental disorders and suicides.[21,22] Also, epidemiological studies have shown an association between symptoms of depression, anxiety, psychosis and suicides in people living near transmission lines, which radiate at 50–60 Hz[23,24] and workers in High Voltage Substations,[2] although this subject has been still controversial.

Neurophysiological mechanisms

The underlying mechanisms of the effects of electromagnetic Ultra Low Frequency/Extra Low Frequency emissions on mental disorders are still very poorly understood, but the existence of the electromagnetic effects themselves are supported by numerous reports. The effect of electromagnetic fields on neurotransmitter release and synaptic activity has been already known since the 80's.[25,26] Furthermore, the effects of electromagnetic Ultra Low Frequency/ Extra Low Frequency emissions on the function of specific brain structures are supported by an increasing number of studies in the last three decades. Although still under debate,[27] there have been reports that Extra Low Frequency fields reduce melatonin secretion produced by the pineal gland which in turn modify the monoamine activity in neuronal synapses.[28–31] Melatonin levels affects serotonin and dopamine release, which, by acting in the neuronal synapses in the temporal lobe and other cortical and limbic areas of the brain, may lead to hallucinations. The role of the hypothalamus in the regulation of cognition, as well as its important contribution to the maintenance of energy homeostasis and circadian rhythms has also been recognized.[32] Also, electromagnetic fields may modify the alignment of dendritic arbors and ion channel dendritic distribution in areas of the limbic system, such as hippocampus and mammillary bodies,[33–36] which are principally involved in emotion and behavior processes, the hippocampus's being one of the most electrically excitable parts of the brain, given that it is very sensitive to kindling.[37,38]

The mechanism by which large earthquakes may exert a protective effect on patients with bipolar disorder and schizophrenia is not understood, as is the case of rTMS. However, as we mentioned above, we suggest that an electric field most probably mediates the occurrence of large earthquakes and the protective mental effects.

Conclusions

In conclusion, our study provides evidence that large earthquakes are protective of relapses of major psychiatric disorders, primarily bipolar disorder. On the contrary, increased number of small earthquakes, not experienced by our senses, are associated with increased number of patients' admissions; these results support the hypothesis that these effects are mediated through earthquake-related electromagnetic phenomena and not through mechanical/ physical impact per se. The protective effect is consistent with the differential effectiveness of treatment methods, entailing application of electromagnetic fields, such as rTMS and ECT.

This new knowledge may serve to develop new tools for prevention and treatment of severe psychiatric disorders, since electromagnetic protection

from earthquake-induced Ultra Low Frequency/ Extra Low Frequency electromagnetic radiation is a rather simple application. For example, various types of protection from harmful electromagnetic radiation generated by electric/electronic and radiocommunication devices is available. Similarly, electromagnetic protection could be used to reduce relapses of psychotic disorders, such as bipolar disorder, by applying electromagnetic shielding to the human head and to buildings (homes and workplaces).

Διαφοροποιημένη επίδραση των σεισμών σε ασθενείς με διπολική διαταραχή έναντι σχιζοφρένειας: Ευρήματα από την Κρήτη, Ελλάδα 2008–2010

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Η ηλεκτρομαγνητική ακτινοβολία επηρεάζει με πολλούς τρόπους, τόσο τους ανθρώπους, όσο και τα ζώα. Οι σεισμοί είναι γνωστό ότι σχετίζονται με ηλεκτρομαγνητικά φαινόμενα. Σε μια πρόσφατη μελέτη δείξαμε, ότι οι μεγάλοι σεισμοί συσχετίστηκαν με μείωση των εισαγωγών, ενώ οι μικροί σεισμοί με αύξηση των εισαγωγών ασθενών με ψυχικές παθήσεις. Ο σκοπός της παρούσας μελέτης ήταν να διερευνηθεί η επίδραση της ηλεκτρομαγνητικής δραστηριότητας που σχετίζεται με σεισμούς, σε δύο χρόνιες και σοβαρές ψυχικές διαταραχές, όπως η διπολική διαταραχή και η σχιζοφρένεια. Αναλύθηκαν αναδρομικά στοιχεία που αφορούσαν τον μηνιαίο αριθμό εισαγωγών ασθενών με διάγνωση διπολικής διαταραχής και σχιζοφρένειας στην Ψυχιατρική Κλινική του Πανεπιστημιακού Γενικού Νοσοκομείου Ηρακλείου Κρήτης, μεταξύ 2008–2010, σε σχέση με τον αριθμό των μικρής και μεγάλης έντασης σεισμών στην περιοχή της Κρήτης την περίοδο αυτή. Η ανάλυση έδειξε ότι κατά τη διάρκεια περιόδου «καταιγίδας» μεγάλης έντασης σεισμών, υπήρξε σημαντική μείωση των εισαγωγών στο Τμήμα Οξέων Περιστατικών (κυρίως ακούσιες νοσηλείες), η οποία ήταν περισσότερο εκσεσημασμένη σε ασθενείς με διπολική διαταραχή (91,2%) σε σχέση με ασθενείς με σχιζοφρένεια (52,4%). Επίσης, κατά την περίοδο συχνών, μικρών σεισμών, βρέθηκε σημαντική αύξηση των εισαγωγών σε ασθενείς με διπολική διαταραχή. Από τα ευρήματα της μελέτης αυτής φαίνεται ότι τα ηλεκτροστατικά κύματα που συνοδεύουν τους μεγάλους σεισμούς πιθανόν να έχουν έναν προστατευτικό ρόλο σε ασθενείς με ψυχικές νόσους, κυρίως σε πάσχοντες από διπολική διαταραχή. Αυτά τα ευρήματα είναι σε συμφωνία και με την ευεργετική δράση των ηλεκτρομαγνητικών κυμάτων που χρησιμοποιούνται στην Ηλεκτροσπασμοθεραπεία (ECT) και τον Διακρανιακό Μαγνητικό Ερεθισμό (TMS) σε ασθενείς με διπολική διαταραχή. Μελλοντικές μελέτες που θα εστιάσουν στους υποκείμενους μηχανισμούς, πιθανόν να οδηγήσουν σε πιο εξειδικευμένες θεραπείες των ψυχικών παθήσεων.

Λέξεις ευρετηρίου: Ψύχωση, διαταραχές διάθεσης, υποτροπές, ηλεκτρομαγνητικά πεδία, σεισμοί, νοσοκομειακές εισαγωγές.

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Research article
Ερευνητική εργασία

Factor analysis and normative scores of Alcohol Use Disorders Identification Test (AUDIT) in a representative sample of the general population of Greece

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The most widely used screening instrument for alcohol use disorders (AUD) is the Alcohol Use Disorders Identification Test (AUDIT) which, although initially developed for use in primary care, is increasingly used in general population studies. Previous studies that have assessed the screening properties and the factorial structure of AUDIT were mostly based on clinical samples and did not take into consideration the possible differences in AUDIT factorial properties between subgroups according to age, sex and mental health status. Aim of the current study was to explore the distribution of AUDIT and AUDIT-Consumption (AUDIT-C) scores and the factorial structure of AUDIT in subgroups of participants according to sex, age and the presence of mental health disorder. Descriptive statistics and Exploratory/Confirmatory Factor Analysis of AUDIT were extracted in a general population representative sample of 4,894 Greek participants. Different cut-offs are suggested in order to screen 10% of the population with the highest severity of AUD into the aforementioned subgroups. Generally, a cut-off between 10–12 at AUDIT score is suggested for screening the 10% with the highest severity of alcohol use problems in subgroups of frequent alcohol consumers (e.g. younger males) and a cut-off between 4–5 would screen the 5% with the highest severity of alcohol use problems in subgroups of low alcohol-consumers (e.g. older women). A cut-off of 3 in AUDIT-C score is suggested for screening 25% of individuals with the heaviest alcohol consumption. The traditional three-factor model does not explain better the factorial structure of AUDIT compared to the 2-factors model. The AUDIT is a reliable instrument for assessing AUD and heavy alcohol consumption in the Greek general population. Age, sex and the presence of mental health disorders should be taken into consideration when selecting cut-offs for screening purposes in non-clinical samples.

Key words: Alcohol Use Disorders Identification Test (AUDIT), AUDIT-C, validation, community sample, factorial structure, Exploratory/Confirmatory Factor Analysis (EFA/CFA), Greece.

Introduction

Alcohol use disorders (AUD) are among the most prevalent mental disorders with an increasing health and social burden.[1] During the past decade, intensive research has led to the development of a range of effective treatments for AUD in primary care.[2,3] Screening with structured instruments for AUD is recognized as an essential step,[4] not only for identifying patients who are eligible for the available interventions but also for specifying the intensity or the type of these interventions.[5–8] However, despite the extensive research on screening instruments, AUD often remain unrecognized in clinical practice.[9]

The most widely used screening instrument for AUD is the Alcohol Use Disorders Identification Test (AUDIT) which consists of 10 questions, each scored using a five-point Likert scale (from 0 to 4). AUDIT two types of assessment: (1) a continuous (dimensional) measure of alcohol use problems and (2) a dichotomous assessment of the presence or absence of AUD ("abuse" and/or "dependence").[10] In the dimensional approach, cut-offs of AUDIT-score correspond to percentiles of the ascending (from less to more) total distribution of alcohol problems on the sampled participants, while in dichotomous approach cut-offs of AUDIT-score correspond to the presence (or absence) of an AUD diagnosis. Both types of measures are useful in screening alcohol use problems, for slightly different reasons.

The dimensional use of AUDIT-score is more useful from a public health perspective as it allows categorization of individuals in groups of increasing severity of AUD, taking into account the full spectrum of the distribution of alcohol related behaviors in a population ("levels of risk"). Additionally, it can serve as a valuable tool for counseling and prevention purposes.[5,8] On the other hand, the traditional use of dichotomizing the AUDIT-score, may be more useful in clinical settings where the need is to discriminate patients who meet the criteria for a specific diagnosis of AUD ("positive") from those who do not ("negative").

Several studies have tried to establish optimal AUDIT cut-offs for diagnosing AUD in various samples of patients and their differences imply that the use of universal AUDIT-cut offs for diagnosing AUD may be questionable.[11–14] The major differences in cut-off points for diagnosing AUD were observed between subgroups based on sex, age,[11,15,16] or the presence of another psychiatric diagnosis.[17,18] Moreover, an additional disadvantage of considering AUDIT score as a dichotomous measure has been raised by the inconsistency in the results from studies which examined the factorial structure of AUDIT. Most of these studies support that variations in the AUDIT items are explained by two latent factors, i.e. "consumption" (items 1–3) and "alcohol use problems" (items 4–10), arguing that there is no need to further differentiate "alcohol use problems" in "dependence" and "abuse".[19–28] Other studies argued for a three-factor model by considering two separate factors for items 4–10 ("abuse" and "dependence") rather than into one common factor.[29–31] The above findings cast doubts in the traditional approach where AUDIT corresponds to two distinct AUD diagnoses and indirectly support the dimensional approach of AUDIT score.

Examining the distribution of AUDIT score as well as the structural properties of AUDIT across populations with heterogeneity in alcohol consumption/norms could provide adequate information about the patterns of alcohol use and AUD in those populations.[11] Only one study from Greece examined the screening properties of AUDIT in a convenient clinical sample of patients and healthy controls.[32] This study concluded a relatively high[11] sensitivity and specificity using a cut-off of 8 for diagnosing AUD but did not examined possible differences between subgroups, according to sex or the presence of mental disorders as well as the factorial structure and score distribution of AUDIT.

Our aim is to validate AUDIT in the Greek general population by examining its factorial structure and the distribution of AUDIT score in a national representative sample of Greek participants as well as in subgroups based on sex, age and the presence of mental health problems. To our knowledge, there is no other study having used AUDIT with a large representative sample of the general population of Greece.

Material and method

General description of the dataset

The dataset was collected in the framework of the 2009–2010 "National Psychiatric Morbidity Survey", which was carried out in Greece, using a nationally representative sample of the adult population (18–70 years). The study was organized by the Ministry of Health and carried out by the Department of Psychiatry, University of Ioannina. Eligible for participation were all adults living in private households in Greece.

Sampling procedure

A three-stage sampling design was used with: (1) enumerator areas (one or more unified city blocks based on the 2001 census survey) selected at the first stage, (2) households within the selected areas at the second stage and (3) individuals within the households at the third stage.

The primary sampling units (enumerator areas) were first stratified according to the degree of urbanization (3 strata). The two major cities, Athens and Thessaloniki, were stratified different into 31 and 9 strata of equal size, respectively. The projected sample size for the whole survey was 9,800 individuals with a constant 0.085% sampling fraction for each stratum 0.085%.

Details of the sampling procedure can be found elsewhere.[33]

Data collection and response rate

Data was collected from lay- trained researchers/interviewers. All instruments used were computerized and responses to the questions were entered directly to a laptop computer. Overall response rate was 54% with a range between 51% and 60% among regions. Refusals were more common in the subgroups of women and middle-aged participants (40–55 years old). Differences between the sample and the 2001 census population data were small. A total number of 4,894 participants were included in our analysis.

Assessment of alcohol use Disorders

Alcohol use disorders were assessed with AUDIT 10 and alcohol consumption with AUDIT-C (Consumption subscale) comprised by the first three questions of AUDIT (consumption, frequency, binge drinking).[34] Total AUDIT score is ranging from 0 (totally abstain) to 40 and AUDIT-C score is correspondingly ranging from 0 to 12.

Assessment of sufferers from Depression/Anxiety

Psychiatric morbidity was assessed with the Greek version of the Revised Clinical Interview Schedule (CIS-R), a fully structured psychiatric interview designed to be used by trained lay-interviewers,[33] assessing the presence and severity of 14 different common psychiatric symptoms. Additional questions, including questions assessing the impairment of functioning and duration of symptoms, enable the diagnosis of six common mental disorders (depressive episode, generalized anxiety disorder, all phobias combined, panic disorder, obsessive compulsive disorder, mixed anxiety and depression disorder) according to the ICD-10. The participants who implement criteria for at least one of the previous diagnosis are labeled as sufferers from "Depressive/anxiety disorders" in our analysis.

Statistical analysis

The factorial structure of AUDIT was assessed using Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA).

The EFA was conducted using "principal factor analysis" method to examine the number of dimensions warranted to better explain the observed variability in responses. Initially, all the possible factors were extracted and eigenvalues were represented in relation to the number of extracted variables in scree-plots. In order to further compare the fitness of data between 2-factors and 3-factors models, we estimated the "factor loadings" of each question in the considered factors, after an orthogonal rotation of the loadings matrix. The "uniqueness" of each AUDIT-question was calculated separately into the 2-factor and 3-factor models, as a measure of "model fitness". Generally, questions with factor loading <0.4 in one factor, are considered as poorly correlated with this factor. Changes <10% in "uniqueness" of each question after the addition of one extra factor, indicate that the addition of this extra factor does not substantially improve the explanation of the structure of an instrument.

CFA was conducted to assess whether the 3-factors model ["consumption" (questions 1–3), "dependence" (questions 4–6) and "harmful use/abuse" (questions 7–10)] offer better fitness to the inter-relation of AUDIT questions (explain better the observed variability of the data) comparing to the 2-factors model ["consumption" (questions 1–3), "Alcohol use problems/disorders" (questions 4–10)].

The analyses were performed separately in subgroups based on sex, age and the presence of mental disorders. EFA was conducted using Statistical Package for Social Sciences (SPSS), Vol 10 (SPSS Inc., Chicago, IL, USA). CFA was performed with LISREL statistical package using «underlying variable approach» (UVA) method.

Results

Distribution of AUDIT score across subsamples of the general population

Males, sufferers from depression/anxiety disorders and younger participants (<35 years old) presented higher AUDIT-scores and consequently more alcohol related problems, comparing to women, participants without depression/anxiety and older individuals (>55 years old), respectively. Abstinence or occasional alcohol use were more common in women and older individuals (table 1). In general, the distribution of AUDIT score varies between subgroups according to sex, age group and the presence of psychiatric morbidity (figure 1).

Considering participants without depression/anxiety disorders, in the subgroup of higher alcohol consumption (i.e. younger males), a cut-off point of 11 in AUDIT-score would effectively screen around 10% of the participants with the highest severity of AUD. In the subgroup of lower alcohol consumption (i.e. older women) a cut-off point of 4 was needed to screen 5% of the participants with the highest severity of AUD. Considering mental health sufferers, the above-mentioned cut-off points would screen 25% and 10% of participants with the highest severity of AUD, respectively (table 2).

Regarding AUDIT-C, in the subgroup of participants without depression/anxiety diagnosis, a cut-

Table 1. Prevalence of AUD and AUDIT (or AUDIT-C) cut-offs for ascending percentiles of the total AUDIT (AUDIT-C) score according to age group, sex and the presence of Depressive/anxiety disorders.

	Presence of AUD		Cut-offs of AUDIT (or AUDIT-C) in Percentiles of severity of Alcohol Use Problems				
	Abuse (AUDIT≥8)[i]	Dependence (AUDIT≥15)[i]	25th	50th	75th	90th	95th
Age group							
18–35	12.8%	2.7%	1 (1)	2 (2)	4 (4)	9 (5)	12 (7)
36–55	11.0%	3.4%	1 (1)	2 (2)	4 (3)	8 (6)	13 (7)
56–70	6.9%	1.7%	0 (0)	1 (1)	3 (3)	6 (5)	9 (6)
Sex							
Male	19.0%	5.1%	2 (1)	3 (3)	6 (5)	11 (7)	15 (9)
Female	2.6%	0.5%	0 (0)	1 (1)	2 (2)	4 (3)	6 (4)
Psychiatric disorder[ii]							
Yes	13.8%	6.0%	0 (0)	2 (1)	4 (3)	10 (6)	15 (8)
No	10.2%	2.2%	1 (1)	2 (2)	4 (3)	8 (5)	11 (7)

Note: cut-off in parentheses refer to AUDIT-C scores

(i) cut-offs proposed by the developers of the AUDIT and a previous study in a Greek sample (Moussas et al 2009:32), (ii) Any Anxiety/Depressive ICD-10 Diagnoses according to CIS-R

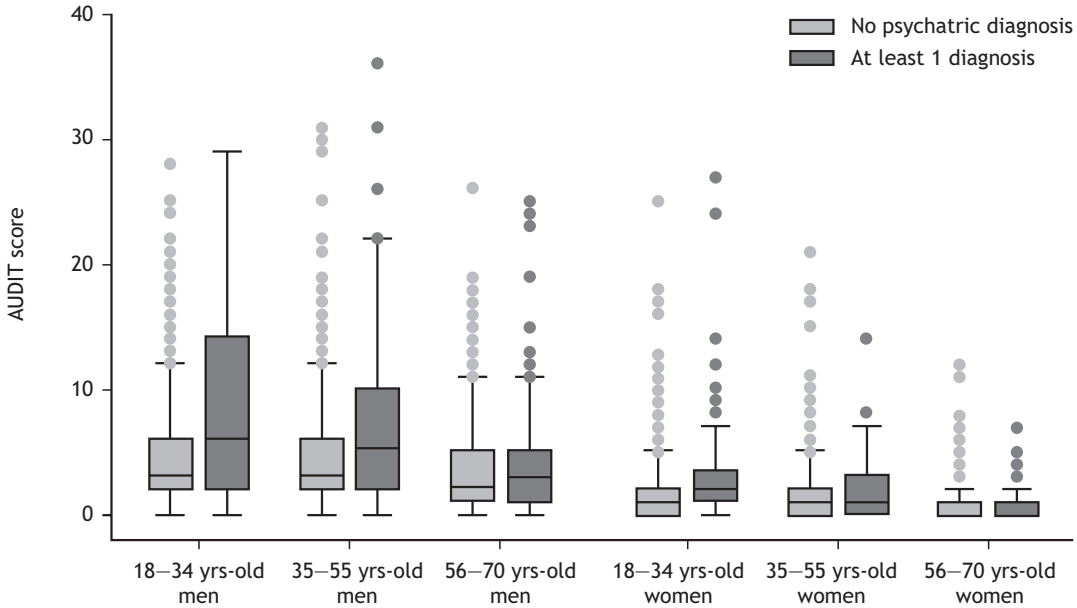

Figure 1. Boxplot of AUDIT score distribution.

Table 2. Cut-off values of AUDIT (or AUDIT-C) score of 75th 90th and 95th percentile of severity of Alcohol Use Problems in subgroups based on Age Sex and the presence of Depression/Anxiety Diagnosis in a nationally representative sample of Greek participants.

Percentiles of AUDIT (or AUDIT-C) score		**75th**	**90th**	**95th**	**75th**	**90th**	**95th**
Age			**Men**			**Women**	
	18–35	7 (5)	12 (7)	14 (8)	3 (2)	5 (4)	6 (5)
	36–55	6 (5)	12 (7)	16 (9)	2 (2)	4 (3)	5 (4)
	56–70	5 (4)	9 (6)	13 (8)	1 (1)	2 (2)	4 (3)
Sex			**No Psychiatric Diagnosis**			**Psychiatric Diagnosis**	
	Male	6 (5)	10 (6)	14 (8)	9 (5)	17 (8)	21 (10)
	Female	2 (2)	4 (3)	5 (4)	3 (2)	4 (3)	7 (4)
Sex	**Age**		**No Psychiatric Diagnosis**			**Psychiatric Diagnosis**	
Men	18–35	6 (5)	11 (6)	14 (8)	13 (7)	19 (8)	21 (9)
	36–55	6 (5)	11 (7)	14 (9)	10 (6)	19 (9)	21 (10)
	56–70	5 (4)	9 (6)	12 (8)	5 (4)	11 (5)	15 (9)
Women	18–35	2 (2)	4 (4)	6 (5)	3 (3)	7 (4)	9 (6)
	36–55	2 (2)	3 (3)	5 (4)	3 (2)	4 (4)	7 (4)
	56–70	1 (1)	2 (2)	4 (3)	1 (1)	2 (2)	4 (3)

Note: cut-off in parentheses refer to AUDIT-C score

off score of 6 would effectively screen 10% of the male individuals with the heaviest alcohol consumption while a cut-off of 4 would screen 5% of the females with the heaviest consumption. In the subgroup of participants with depression/anxiety disorders, the previously mentioned AUDIT-C cut-offs would screen 20% of the males and 5% of the females presenting the heaviest alcohol

consumption. The variability in the distribution of scores across subgroups of the total sample is less for AUDIT-C scale comparing to AUDIT (table 2). Generally, an AUDIT-C score of 3 or less could be considered as a cut-off point of moderate use (<75th percentile of alcohol consumption distribution) across the studied subgroups, with the exception of women, where an AUDIT-C score of 3 corresponds to 90th percentile (table 1).

Factorial Structure of AUDIT score across subsamples of the general population

Based on the scree-plots, it is not clear whether a 3-factor solution explains sufficiently better the observed variability of the answers compared to a 2-factor solution (figure 2).

Exploratory factor analysis

The consideration of 3 subsequent factors in the factorial structure of AUDIT does not yield better values for the "uniqueness" of each item, comparing to the 2-factors solution. The variability of the "uniqueness" of each item between the two models (bi-factorial & tri-factorial) is <10% for all items (table 3). The same results can also be concluded when the EFA was performed separately in subgroups based on sex, age and the presence of depression/anxiety disorders. Taken into account the above, the two factors solution is considered adequately to explain factorial structure of AUDIT.

In the 1st factor, items 1–3 present the higher loadings, corresponding to "consumption". In the 2nd factor, items 4–8 present the higher "loadings", corresponding to "alcohol use problems". Items 9 (alcohol related accidents) and 10 (advice to quit drinking) present relatively lower "loadings" in both previously mentioned factors. Item 9 is better correlated with the "alcohol problems" factor (2nd factor) and item 10 with "consumption" factor (1st factor). The 3 first AUDIT questions are correlated more strongly with the "consumption" factor (1st factor) comparing to the correlation of the items 4-8 with the "alcohol problems" factor (2nd factor).

Especially for the subgroup of participants with "depression/anxiety disorders", item 4 (unable to stop), item 7 (guilt) and – secondarily – item 5 (role failure) and item 10 (advice to quit drinking) are associated more strongly with the "consumption" factor comparing with the "alcohol problems" factor. Reversely, items 6 (morning drinking) and 8 (blackouts) are more strongly associated with the "alcohol problems" factor. Item 9 shows low relevance ("loading") with each of the 2 considered factors in women, older individuals and sufferers from depression/anxiety.

Confirmatory factor analysis

Factor loadings for each AUDIT-question for the bi-factorial (factor 1: items 1–3, factor 2: items 4–10) and tri-factorial model (factor 1: items 1–3, factor 2: items 4–6, factor 3: items 7–10) were estimated. All items present similar factor-loadings in both models after confirmatory analysis performed in the whole sample as well as in subgroups based on sex (table 4). This non-significant change in factor loadings after the inclusion of one additional factor at the bi-factor model, illustrates that the separation of items 4–10 into two further factors does not improve factorial structure of AUDIT.

Regarding the "consumption" factor, item-3 (binge drinking) presents the higher factor loading followed by item-2 (frequency) and item-1 (quantity in each session). Concerning "alcohol use problems" factor, items with higher loadings are in descending order: 4 (unable to stop), 5 (role failure), 7 (guilt), 8 (blackouts), while items 6 (morning drinking), 10 (advice to quit) and 9 (accidents) present the lowest loadings comparing to the other items.

The results of CFA confirm the previously mentioned results of EFA. An exception is Item-10 (advice to quit) which presents acceptable factor loading to the "alcohol use problems" in CFA, while in EFA the loading of item-10 was marginally unacceptable.

Discussion

AUDIT and AUDIT-C are valid instruments for assessing AUD and alcohol consumption, respectively, in the Greek general population. Distribution of AUDIT scores varies across subgroups with different levels of alcohol consumption: Generally, a cut-off

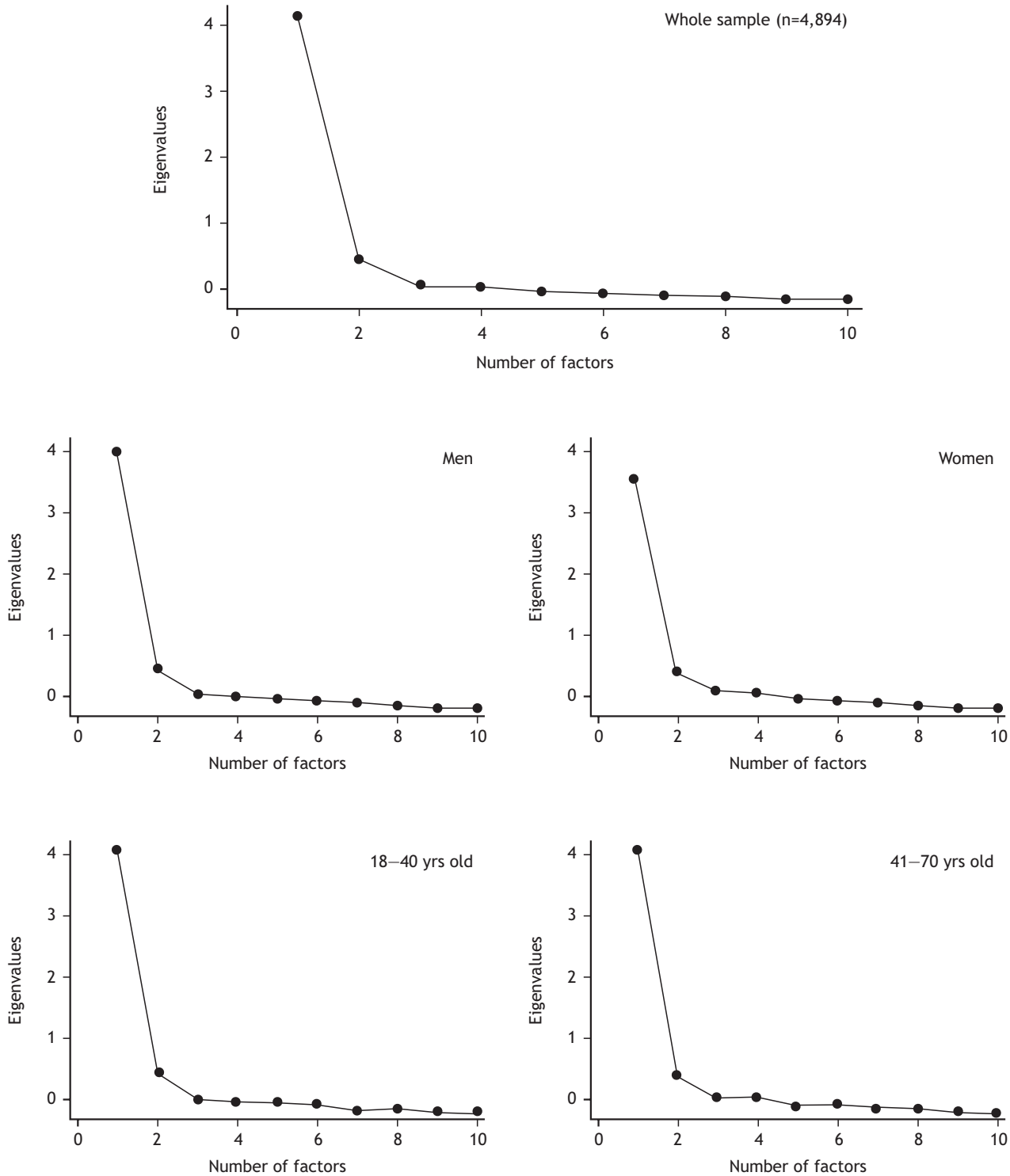

Figure 2. Scree plots of eigenvalues and number of extracted factors after Exploratory Factor Analysis.

point ranged between 10 and 12 at AUDIT score is adequate to screen 10% of participants with the higher severity of AUD in the subpopulation of highest alcohol consumers (e.g. younger males). Respectively, a quite different cut-off, ranging between 4 and 5, screens 5% of the population with

Table 3. Factor Loadings and Uniqueness of 10 AUDIT questions in 2- & 3-factors model in a Greek general population representative sample of 4894 participants performing Exploratory Factor analysis.

AUDIT Questions	bi-factorial model			tri-factorial model			
	factor 1	factor 2	Uniqueness	factor 1	factor 2	factor 3	Uniqueness
1	0.16	0.56	0.668	0.15	0.55	0.09	0.666
2	0.31	0.72	0.390	0.31	0.72	0.04	0.388
3	0.31	0.78	0.291	0.32	0.78	0.04	0.289
4	0.63	0.40	0.430	0.64	0.40	0.03	0.424
5	0.66	0.36	0.441	0.66	0.36	0.05	0.437
6	0.51	0.21	0.689	0.51	0.21	0.07	0.689
7	0.57	0.41	0.508	0.57	0.40	0.09	0.508
8	0.61	0.34	0.512	0.61	0.33	0.10	0.512
9	0.36	0.18	0.840	0.33	0.17	0.22	0.813
10	0.39	0.45	0.643	0.36	0.44	0.22	0.621

the higher severity of AUD in the subpopulation of relatively low alcohol consumers (e.g. older women). The above cut-off points would screen 25% of the population with the higher severity of AUD in the subpopulation of sufferers from depression/anxiety. Such an increase in the percentage of the positive screened individuals with the same cut-offs (from 10% to 25%), is justifiable and useful for screening purposes due to the increased vulnerability on alcohol use problems that depression/anxiety sufferers may present.[35]

Concerning the factorial structure of AUDIT, the two-factor solution explains the structure of alcohol-related symptoms equally well as the three-factor solution, implying that the further separation of "alcohol use problems" factor (Items 4–10) into 2 subsequent factors, namely "dependence" and "harmful use", is not necessary. Our finding that the 3 first AUDIT questions are strongly correlated with the "consumption" factor across all subgroups of participants, indirectly confirms the high validity of AUDIT-C[34] in assessing alcohol consumption.

Interestingly, items 9 (alcohol related accidents) and 10 (advise to quit drinking), are poorly correlated with the "alcohol use problems" factor, demonstrating the lower relevancy that these items may have with AUD. A possible explanation of this finding is that due to the fluctuation that AUD exhibit over the life-span[36,37] the presence of "alcohol-related accidents" and the "concern of others" in the past may be underreported or overlooked by the patients during their self-assessment of current alcohol use problems status. Thus, extra attention may be needed during the assessment of patients with possible AUD in order to elicit the association between current alcohol use and involvement in accidents or other hazardous situations in the past.

Moreover, in the subgroup of participants with depression/anxiety disorders, the items 4 (unable to stop), 5 (role functioning), 7 (guilty), and 10 (advice to quit drinking) are more strongly correlated with the "consumption" factor compared to the "alcohol use problems" factor. This finding may imply that alcohol use may have different determinants among psychiatric cases: Specifically, depressed individuals may use alcohol to alleviate their symptoms ("self-medication" hypothesis),[38] leading them to increase the amount of alcohol consumed, without necessarily facing other "alcohol use problems". Moreover, mental health sufferers may more easily feel guilty or report restrictions in role-functioning after a drinking session, even at the absence of other signs of alcohol use problems, due to the depressive ideation or because of the direct pharmacological properties of alcohol on psychiatric symptoms. Thus, the presence of guilty and role-function restriction after alcohol consumption in a

Table 4. CFA for tri-factorial and bi-factorial model of AUDIT structure in a nationally representative sample of Greek participants.

Factor Loading	3-factor model[i]			2-factor model*		3-factor model[ii]			2-factor model[i]		3-factor model[ii]			2-factor model[i]	
factors	factor 1	factor 2	factor 3	factor 1	factor 2	factor 1	factor 2	factor 3	factor 1	factor 2	factor 1	factor 2	factor 3	factor 1	factor 2
AUDIT Question	Total sample (n=4894)					Men (n=2425)					Women (n=2469)				
1	0.57			0.57		0.64			0.64		0.38			0.38	
2	0.80			0.80		0.79			0.79		0.71			0.71	
3	0.89			0.89		0.87			0.87		0.81			0.81	
4		0.79			0.77		0.77			0.73		0.79			0.76
5		0.78			0.75		0.79			0.75		0.71			0.70
6		0.55			0.54		0.56			0.53		0.48			0.49
7			0.73		0.72			0.74		0.74			0.82		0.77
8			0.71		0.70			0.67		0.69			0.82		0.78
9			0.39		0.39			0.37		0.39			0.28		0.26
10			0.60		0.58			0.52		0.54			0.57		0.54

(i) factor 1: "alcohol consumption» (items 1–3) & factor 2: "Alcohol Use Disorders" (items 4–10), (ii) factor 1: "alcohol consumption" (items 1–3), factor 2: "alcohol dependence" (items 4–6) & factor 3: "harmful alcohol use" (items 7–10)

patient with anxiety/depression may be primarily associated with the quantity of alcohol consumed –or the severity of depression– and secondarily with the presence of "alcohol use problems". Similarly, regarding item 10, sufferers of depression/anxiety are more possible to attract the concern of others based on the total amount of alcohol consumed, independently of the presence of other alcohol-related behavioral problems while in non-sufferers from mental disorders the advice to quit alcohol comes mainly after the development of AUD, especially in countries where alcohol consumption is socially acceptable like Greece.

Although AUDIT was originally designed for use in primary care settings, it has been increasingly used in general population samples,[15,39] which are quite different from clinical samples.[19] The use of AUDIT as a dichotomous measure in the general population may deprive useful information for symptoms distribution and sub-threshold cases[40] while the consideration of AUDIT score as a continuous/dimensional measure may be more consistent with evidence supporting that AUD lie in a continuum of severity rather than represent distinct situation with clear cut-offs.[41,42]

The observed differences in alcohol use and the factorial structure of AUDIT across subgroups based on age, sex and the presence of depression/anxiety, may imply corresponding differences in the presentation of AUD across subpopulations and cultures.[39,43] Those differences highlight the usefulness of subgroups- or culture- specific data for planning cost-effective treatment interventions, as the application of global cut-off points for screening AUD may have questionable diagnostic efficacy across subgroups.[44,45] Special attention needs to be paid in the subgroup of individuals with mental health problems, where alcohol use may have different rationale and meaning, comparing to the general population.

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Παραγοντική ανάλυση και κατανομή βαθμολογιών στο εργαλείο Ανίχνευσης Διαταραχών Χρήσης Αλκοόλ (Alcohol Use Disorders Identification Test, AUDIT) σε ένα αντιπροσωπευτικό δείγμα του ελληνικού πληθυσμού

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Το Alcohol Use Disorders Identification Test (AUDIT) αποτελεί το πλέον διαδεδομένο εργαλείο διαλογής για τις διαταραχές χρήσης αλκοόλ (ΔΧΑ) το οποίο, αν και αρχικά αναπτύχθηκε για να χρησιμοποιηθεί στην πρωτοβάθμια φροντίδα υγείας, παρουσιάζει ολοένα και αυξανόμενη χρήση σε μελέτες του γενικού πληθυσμού. Οι προηγούμενες μελέτες που ασχολήθηκαν με τη μελέτη των ιδιοτήτων του εργαλείου ως μέσου διαλογής, βασίστηκαν κυρίως σε κλινικά δείγματα και δεν έλαβαν υπόψη τις πιθανές διαφορές στην παραγοντική δομή του εργαλείου μεταξύ υποομάδων συμμετεχόντων με διαφορές ως προς την ηλικία, το φύλο και την κατάσταση ψυχικής υγείας τους. Στόχος της παρούσας μελέτης είναι η μελέτη της κατανομής της συνολικής βαθμολογίας του εργαλείου AUDIT και του εργαλείου μέτρησης κατανάλωσης αλκοόλ AUDIT-C καθώς και της παραγοντικής δομής του AUDIT σε υποομάδες συμμετεχόντων που ορίζονται με βάση το φύλο, την ηλικία και την παρουσία ή μη ψυχικής νόσου. Παρουσιάζεται η κατανομή της βαθμολογίας του AUDIT και η Διερευνητική/Επιβεβαιωτική Παραγοντική Ανάλυσή του σε ένα δείγμα 4.894 συμμετεχόντων, αντιπροσωπευτικό του ελληνικού γενικού πληθυσμού. Διαφορετικές βαθμολογίες στο AUDIT (διαγνωστικό κατώφλι/"cut-off") προτείνονται για τη διάγνωση του 10% του πληθυσμού με την υψηλότερης βαρύτητας ΔΧΑ στις προαναφερόμενες ομάδες συμμετεχόντων. Ειδικότερα, συνολική βαθμολογία στο AUDIT μεταξύ 10–12 αντιστοιχεί στο 10% του πληθυσμού με την υψηλότερη βαρύτητα προβλημάτων χρήσης αλκοόλ στις υποομάδες του γενικού πληθυσμού που παρουσιάζουν συχνότερη χρήση αλκοόλ (π.χ. νέοι άνδρες), ενώ AUDIT-score μεταξύ 4–5 οδηγεί, αντιστοιχεί στο 5% του πληθυσμού με την υψηλότερη βαρύτητα ΔΧΑ στην υποομάδα των συμμετεχόντων με λιγότερο συχνή κατανάλωση αλκοόλ (π.χ. γυναίκες μεγαλύτερης ηλικίας). Βαθμολογία 3 ή μεγαλύτερη στο AUDIT-C αντιστοιχεί στο 25% των συμμετεχόντων με τη βαρύτερη κατανάλωση αλκοόλ. Το κλασικό μοντέλο 3 παραγόντων δεν ερμηνεύει καλύτερα την παραγοντική δομή του AUDIT σε σύγκριση με το μοντέλο των 2 παραγόντων. Το AUDIT αποτελεί ένα αξιόπιστο εργαλείο για τον προσδιορισμό των ΔΧΑ και της βαριάς κατανάλωσης αλκοόλ στον ελληνικό γενικό πληθυσμό. Η ηλικία, το φύλο και η παρουσία ψυχικών διαταραχών πρέπει να λαμβάνονται υπόψη προκειμένου να προσδιοριστεί το διαγνωστικό κατώφλι του AUDIT που θα οδηγήσει στην αποτελεσματικότερη διαλογή των ατόμων με ΔΧΑ σε μη-κλινικά δείγματα.

Λέξεις ευρετηρίου: Alcohol Use Disorders Identification Test (AUDIT) - Εργαλείο Μέτρησης Διαταραχών Χρήσης Αλκοόλ, AUDIT-C, κοινοτικό δείγμα, κατώφλια διαλογής, Παραγοντική Δομή/Ανάλυση, Ελλάδα.

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Research article
Ερευνητική εργασία

Bullying victimization: Associated contextual factors in a Greek sample of children and adolescents

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School bullying is increasingly recognized as an important factor affecting both individual's well-being and social functioning. Several studies provide evidence for the potential role of contextual factors that relate to bullying victimization such as the socioeconomic status of the parents/family, the quality of family and home environment, the school climate, structure and ethos, and also various community characteristics. The objectives of this school-based, cross-sectional study were to report the prevalence of the perception of being bullied in a sample of Greek children and adolescents from 6 to 17 years of age and to investigate the relations among the subjective impression of bullying victimization and several sociodemographic and socioeconomic factors. We hypothesized that influences external to individual children and adolescents play a decisive role to their perception of being victimized. Bullying victimization was measured through a simple "yes/no" question, which confirmed or rejected respectively the fact that the child or adolescent has been at some time victimized in the school environment. Also, demographic and socioeconomic data about the families of children and adolescents were collected. A total of 1,588 children (51.8% females, mean age ± SD: 12.9±2.8 years) were assessed. The overall prevalence of victimization was 10.4%. Multiple logistic regression analysis on the probability of being victimized identified that living at a main urban center (Odds Ratio[OR]: 2.63, CI: 1.78–3.87, p<0.001), presence of a person with a chronic illness at home (OR: 1.90, CI: 1.12–3.20, p=0.016), poor family economic status (OR: 1.83, CI: 1.05–3.20, p=0.032),and increased number of adults at home (OR: 2.00, CI: 1.00–3.77, p=0,041) had a positive correlation with the prevalence of reported bullying victimization. Moreover, higher parental educational level related to lower probability of victimization (OR: 0.88, CI: 0.78–0.99, p=0.05). These findings demonstrate that several demographic and socioeconomic factors play a potential role in bullying victimization among schoolchildren. Our results also highlight the need to consider the influence of contextual factors in the design of targeting efforts countering and/or preventing bullying victimization.

Key words: School bullying, victimization, demographic factors, socioeconomic status, contextual factors.

Introduction

School bullying is increasingly recognized as an important factor affecting both individual's well-being and social functioning.[1] Bullying is defined as a specific type of aggressive behavior which encompasses three elements: (1) The behavior is intended to harm or disturb, (2) The behavior occurs repeatedly over time, and (3) There is an imbalance of power, with a person or group of persons regarded of higher status than or of greater strength than the victim.[2] The individuals involved in the social phenomenon of school bullying may be bullies (perpetrators of bullying behavior), victims (targets of bullying behavior), or bullies/victims.[3]

Studies show worldwide prevalence rates for the overall phenomenon of bullying that vary from 8% in Germany to 29.9% in the United States and 30% in Italy.[1,4,5] In a study on prevalence rates of 11– to 16– year-old children involved in bullying across 25 countries, on average, 10% of children admitted bullying others, 11% reported being the victims of bullying and 6% reported being both bullies and victims.[6] Although boys appear to be more often perpetrators than girls, the rates of victimization do not differ between the two sexes.[7,8]

Bullying victimization has been associated by epidemiologic evidence with physical and psychological health outcomes for children and adolescents.[9,10] This evidence casts light on bullying victimization as a problem of public health proportions and underlies the importance of investigation for predictive factors associated with the phenomenon. There are at least two levels of predictors for bullying victimization: individual characteristics and contextual characteristics of the setting.[11] Individual characteristics, including conduct problems, social problems, prior victimization and internalizing behaviors, have been identified as predictors of victimization.[12] Also, special health care needs, poor physical or mental health status, poor academic achievement and sexual orientation are risk factors for child and adolescent victimization.[1,13–16] In a large representative sample of children and adolescents from 11 European countries, the factors most strongly associated with the perception of being bullied were younger age, being overweight/obese, having psychological/mental problems, lacking social support and having a low level of parental education.[3]

In regard to contextual factors that relate to bullying victimization, several studies provide evidence for the potential role of the socioeconomic status (SES) of the parents/family.[17] Specifically, the risk of being a bullying victim has been higher among children and adolescents with parents from lower socioeconomic positions expressed as poor parental education, low parental occupation or low affluence.[18–20] Other contextual factors that have been associated with bullying victimization at school are family and home environment, school climate, structure and ethos, community factors, peer status and peer influence.[11] More precisely, at the family level, child abuse, overprotectiveness for the boys and threats of rejection for the girls have been associated with victimization.[21] Also, an authoritarian parental style and the experience or witnessing of violence at home through conflicts between parents are major risk factors for manifestation of bullying behaviors at school.[22] Finally, at the peer group-level the most robust predictors of bullying victimization are the high peer rejection and the low peer acceptance.[21]

This study focuses on the subjective perception of bullying victimization without differentiating the group of victims from the group of bully-victims. The objectives of this study were to report the prevalence of the perception of being bullied in a sample of Greek children and adolescents from 6 to 17 years of age and to investigate the relations among the subjective impression of bullying victimization and several sociodemographic and socioeconomic factors.

Material and method

Participants

The present school-based, cross-sectional study was conducted during a 6-month period (January 2014–June 2014), following approval by the Ministry of Education of Greece. The study was conducted in the context of a broader epidemiological research protocol investigating psychosocial factors related to functional gastrointestinal disorders in children.[23] All children participated in the study with their legal representatives' written informed consent. All procedures were in accordance with the Declaration of Helsinki and approved by both the Scientific and the Ethics

Committee of the Children's Hospital. The target population was children attending primary (6–11 years of age), intermediate ("gymnasium") (12–14 years of age) and high school ("lyceum") (15–17 years of age).

Study design

Schools were selected from different regions of Greece, but no specific sampling procedure was applied; therefore, this cannot be regarded as a nationwide representative study. Nevertheless, all efforts were made to include schools from different geographic regions and socioeconomic backgrounds to incorporate as much information, related to those factors, as possible. Specifically, nine primary schools (all in Athens), 12 gymnasiums (5 in Athens, and 1 each in Thessaloniki, Pylos, Kalamata, Volos, Heraklion, Zakynthos and Lefkada) and 12 lyceums (5 in Athens, and 1 each in Thessaloniki, Pylos, Kalamata, Volos, Heraklion, Zakynthos and Lefkada) were selected in terms of accessibility by the participating researchers. All were public schools except for two private gymnasiums and lyceums.

At the next step, questionnaires along with a letter (including a blank informed consent form) inviting the parents to participate in the study were distributed to the pupils of selected gymnasiums and lyceums or given directly to the parents of children attending primary schools. Consent was verified by telephone contact between the two school visits. For children aged 6–11 years, the questionnaires were filled-in by their parents. Older children filled-in the questionnaires on their own, during the second visit at school. During the second visit, a few days after the first, the signed informed consent forms and the questionnaires were collected either directly from the children (in gymnasiums and lyceums) or from their parents (primary schools). Anonymity was retained at all stages of the analysis.

Assessments

Bullying victimization

Being a bullying victim was assessed by using a simple "yes or no" question, asking if the child has ever reported that he/she was a bullying victim at school. For children between 6–11 years of age the answer was given by their parents or caregivers. For older children, from 11 to 17 years of age, the answer was given by children themselves.

Other measurements

Collected Demographic and Socioeconomic data included: (i) Geographic data: urban/rural, continental areas/islands, main urban centers/elsewhere, (ii) Gender, (iii) Age, (iv) Parental origin: Both parents Greeks, one parent Greek and both parents non-Greeks, (v) Paternal and maternal educational level: primary school, gymnasium, lyceum, higher degree, (vi) Family's economic status (subjective view): poor, average, good, (vii) Number of adults at home, (viii) Number of children at home, (ix) Family size (persons at home): 2–3 persons, 4–5 persons, 6–8 persons, (x) Parental presence at home: single-parent families or not, (xi) TV-exposure (hours per day): ≤1 hour per day, 1–3 hours per day, >3 hours per day, (xii) Presence of at least one person with a severe health problem at home: yes/no, (xiii) Level of physical exercise (days per week): none, 1–3 days per week, 4–7 days per week.

To reduce the number of assessed covariates, paternal and maternal educational level (primary school=0, gymnasium=1, lyceum=2, higher degree=3) were combined (by summing) to form a new parameter (0–6 scale), the combined parental educational level, which was treated as a continuous variable.

Statistical analyses

Continuous variables are described by mean ± standard deviation (SD) or median and interquartile range in case of skewing. Comparisons were assessed by the Student t-test or the Mann-Whitney U test, respectively. Categorical data were described as absolute (n) and relative (%) frequencies and compared by the Fisher's exact test. Initially, bivariate analyses were used to identify parameters related to the probability of bullying. Subsequently, a stepwise backward multiple regression analysis was performed to establish a multivariate model. In the bivariate analyses, the significance level was set to 0.05. In the stepwise backward multiple regression analysis, the probability for entering a factor in the model was set to 0.05, whereas the probability for removing it was set to 0.051. The results of the logistic regression are presented as odds ratios (OR) along with 95% confidence intervals (ci). All analyses were performed using the Stata 11.0 MP statistical software (Stata Corp, TX, USA).

Results

Descriptive statistics and bivariate analyses

A total of 1,588 children and adolescents (51.9% females, aged 12.9±2.8 years) were included in the analysis. Bullying was reported in 165 children corresponding to a prevalence of 10.4% in our population. Correlations between bullying and demographic and socioeconomic factors are illustrated in table 1.

Multivariate analyses

The final model that resulted after the stepwise regression analysis is presented in table 2. All the parameters that were significantly related to bullying in the bivariate analyses were retained in the final equation, with the exception of school group (primary school versus high school), where the observed effect in the bivariate analyses was absorbed

Table 1. Demographic and socioeconomic characteristics and their relation to the probability of victimization (1a. Categorical parameters, 1b. Continuous parameters).

1a. Categorical parameters

	Probability of victimization	p^i
Group, n (%)		0.001
Primary school (6–12 yrs), 416 (26.2%)	14.9%	
High school (Gymnasium & Lyceum, 12–18 yrs), 1172 (73.8%)	8.8%	
Gender, n (%)		0.8
Females, 825 (51.9%)	10.2%	
Males, 763 (48.1%)	10.6%	
Urban vs rural, n (%)		0.01
Urban, 1088 (68.5%)	11.7%	
Rural, 500 (31.5%)	7.4%	
Islands vs continental areas, n (%)		0.27
Islands, 268 (16.8%)	8.2%	
Continental areas, 1320 (83.2%)	10.8%	
Main urban centers, n (%)		<0.001
Athens & Thessaloniki, 876 (55.2%)	13.4%	
Elsewhere, 712 (44.8%)	6.6%	
Parental origin, n (%)		0.065
Both parents Greeks, 710 (44.7%)	11.7%	
One parent Greek, 98 (6.2%)	14.3%	
Both parents non-Greeks, 780 (49.1%)	8.7%	
Paternal educational level, n (%)		0.43
Primary school, 78 (4.9%)	15.4%	
Gymnasium, 232 (14.6%)	9.5%	
Lyceum, 630 (39.7%)	10.8%	
University, 647 (40.8%)	9.7%	
Maternal educational level, n (%)		0.038
Primary school, 78 (4.9%)	19.2%	
Gymnasium, 126 (7.9%)	8.7%	
Lyceum, 647 (40.8%)	8.8%	
University, 737 (46.4%)	11.1%	

Continues

Table 1. Demographic and socioeconomic characteristics and their relation to the probability of victimization (1a. Categorical parameters, 1b. Continuous parameters) *(Continued)*.

1a. Categorical parameters

	Probability of victimization	p[i]
Family's economic status, n (%)		0.002
Good, 601 (37.8%)	8.0%	
Average, 890 (56.1%)	11.1%	
Poor, 97 (6.1%)	19.6%	
Number of adults at home, n (%)		0.055
One, 111 (7.0%)	12.6%	
Two, 1282 (80.7%)	9.5%	
Three, 126 (7.9%)	12.7%	
Four, 65 (4.1%)	18.8%	
Family size (persons at home), n (%)		0.26
2–3 persons, 269 (17.0%)	13.0%	
4–5 persons, 1124 (70.8%)	9.7%	
6–8 persons, 194 (12.2%)	10.8%	
Parental presence at home, n (%)		0.3
Single parent, 139 (8.8%)	13.0%	
Both parents, 1449 (91.2%)	10.1%	
Days of physical exercise per week, n (%)		0.9
None, 270 (17.0%)	10.4%	
1–3 days, 885 (55.8%)	10.3%	
4–7 days, 432 (27.2%)	10.7%	
Television exposure (hours per day), n (%)		0.19
1 hour or less, 575, (36.2%)	11.3%	
1–3 hours, 923 (58.1%)	9.4%	
More than 3 hours, 90 (5.7%)	14.4%	
Person at home with a severe health problem, n (%)		0.004
No, 1470 (92.6%)	9.7%	
Yes, 118 (7.4%)	18.6%	

1b. Continuous Parameters

	Overall[ii]	Bullying[ii]	No bullying[ii]	p
Age (years)	12.9±2.8 13.3 (11.9–14.5)	12.3±3.1 13.0 (9.6–14.3)	12.9±2.7 13.3 (12.0–14.5)	0.011[iii]
Number of children at home	2.23±0.89 2 (2–3)	2.17±1.00 2 (2–3)	2.23±0.88 2 (2–3)	0.093[iv]
Parental combined educational level	4.4±1.5 5 (4–6)	4.4±1.6 5 (4–6)	4.5±1.5 5 (4–6)	0.73[iv]

Note: $p<0.05$ was considered as statistically significant; Parental combined educational level is a 0–6 scale resulting from summing the maternal and paternal educational level: primary school: 0, gymnasium: 1, lyceum: 2, higher degree: 3

(i) Fisher's exact test, (ii) mean ± standard deviation, median (interquartile range), (iii) Student's t-test, (iv) Mann-Whitey U-test

Table 2. Logistic regression analysis on the probability of victimization.

Parameter	Odds Ratio	95% CI	p
Main urban centers or not			
Athens/Thessaloniki vs Elsewhere	2.63	1.78–3.87	<0.001
Person with a chronic health problem at home			
Yes vs No	1.90	1.12–3.20	0.016
Family's economic status			
Poor vs Good	1.83	1.05–3.20	0.032
Parental combined educational level	0.88	0.78–0.99	0.05
Number of adults at home			
Four vs Two	2.00	1.00-3.77	0.041

Note: Stepwise backward multiple logistic regression was conducted; $p<0.05$ was considered as statistically significant; Combined parental educational level is a 0-6 scale resulting from summing the maternal and paternal educational level: primary school: 0, gymnasium: 1, lyceum: 2, higher degree: 3. It was treated as continuous variable; CI=Confidence interval

by the other covariates in the final model. In detail, living at a main urban center (2.6 times higher probability of bullying), the presence of a person with a chronic illness at home (1.9-fold increased probability), reporting poor financial status compared to good (1.8 times increased risk) and increased number of adults at home (4 vs. 2.2-fold higher probability) had a positive correlation with the prevalence of reported bullying victimization. The parental educational level had an inverse mode of association, with an estimated decrease of 12% in the risk of bullying per one unit higher educational level in our 0-6 scale (table 2).

Discussion

We investigated the prevalence of the perception of being bullied in a large school-based sample of Greek children and adolescents from 6 to 17 years of age and explored the relations among the subjective impression of bullying victimization and several sociodemographic, socioeconomic, physical, and psychosocial factors.

Overall, 10.4% of our school-based sample reported being bullied. In a representative sample of Greek late adolescents, the prevalence of pupils involved in bullying-related behaviors at least once monthly either as victims, perpetrators or both was 26.4%, while the prevalence of victims only and victims-perpetrators was 12.8%.[24] Bullying at school takes place in almost all countries although its prevalence is highly variable.[1,9] The cross-cultural variations of the prevalence of bullying may reflect the different culture-specific risk factors among countries or may be the result of differences in study design, the nature of the sample, the definition of bullying used and the target population (perpetrators, victims or both).[3,24]

The multivariate analysis pointed out that living at a main urban center, the presence of a person with a chronic illness at home, poor financial status, increased number of adults at home and low parental educational level are associated with a perception of being bullied.

Age and gender

In our sample, percentages of children being bullied were higher in the younger age group as indicated by the school grade. In addition, the group of children reporting victimization was significantly younger than children and adolescents who did not report victimization. Also, there was no significant difference in the prevalence of reported victimization between the two sexes. These findings are in line with previous studies assuming that a factor strongly associated with victimization is younger age, while sex has not been observed to have an impact on the frequency of being bullied reports.[1,9,25] However, age per se did not modify any of the associations and was not a significant predictor of victimization in the multivariate model.

Geographic data

Bullying is by definition a phenomenon that occurs within a social context. The factor most strongly associated with the perception of being a bullying victim was the residency in main urban centers. This finding needs to be considered in the context of previous research on the association of school and/or neighborhood factors with the prevalence of bullying victimization. More precisely, it has been previously reported that school overcrowding and larger school size are key factors in the likelihood of becoming a bullying victim.[26,27] Also, hostile interactions in the neighborhood level, which are more common in main urban centers, may lead to reproduction of such bullying behaviors in the school context.[28] Moreover, this finding may reflect to a certain extent the low degree of social cohesion that characterizes the large urban centers in comparison to rural areas and small cities, where children's friendships and close peer networks function as protective factors for bullying victimization.[29] Finally, a possible alternative explanation of the higher probability of victimization in urban centers may reside in factors including heightened awareness and less fear or shame from the part of the children or/and their parents respecting the declaration of the bullying victimization incident.

Socioeconomic status (SES)

Our approach to measuring SES comprised as indicators the paternal education, the maternal education, the combined parental educational level and the economic status of the family. The multivariate analysis showed that both lower educational level of parents and lower economic status of the family are independently associated with a higher risk of children being bullying victims. The findings concerning the parental educational level are in line with previous studies indicating that poor parental education is associated with a significant increased risk of victimization.[3,18,30] A possible explanation of this pattern is that high level of parental education is accompanied by greater access to intellectual resources and positive family environment, which are both related to children's development of adequate social skills, positive self-related cognitions and problem-solving skills.[11,18] Furthermore, our study has pointed out a positive relation between the lower economic status of the family and the reported victimization. In accordance with our findings, there is a broad agreement to date suggesting that victimization is positively related to low SES.[17,31] An explanation of this finding may reside in the fact that being different from the peer group is a main motivator for victimization.[32] In addition, low parental SES has appeared to be associated with more adverse home environments.[17] The positive association between low self-reported parental affluence and bullying victimization in our sample may reflect the degree of socioeconomic disparities within the Greek society. In addition, it could be argued that except from the SES as an absolute value, the focus of interest should be on the degree of socioeconomic inequality among children in the school as a factor of higher risk of victimization.

Family context

The presence of a person with a chronic illness at home and increased number of adults at home correlated positively with the prevalence of those perceiving themselves to be victims of bullying. Although it would be premature to make a hypothesis about these associations until future studies are conducted, explanation for these relations should be considered. Most studies on the impact of disease on family members have shown that a wide variety of aspects of family quality of life can be affected in multiple ways across all medical specialties.[33] Several impact areas have been identified, including familial psychological and emotional functioning, financial resources, family interpersonal relationships, education and work, leisure time, and social activities.[34,35] As a consequence, parents' emotional distress may disrupt both parenting and the interactions between parent and child leading to poor outcomes of children's physical and emotional health and their cognitive and social functioning.[36] Negative family environment, emotional instability, internalizing problems, low self-esteem and lack of adequate social problem-solving skills are significant predictors and have been consistently associated with bullying victimization.[3,11] We have no clear explanation for the positive influence of the number of adults at home to the perception of being victimized. In previous studies it was suggested

that having a calm and well-structured home environment characterized by warm relationships within the family is important for positive development in all children.[37] This may reduce overall stress levels in victimized children and increase the potential of achieving positive social adaptation.[37] We suppose that the presence of more than two adults in the household potentially increases the amount of adult time available to a child but may lead to role confusion and complicate the difficulties inherent in parenting.[36]

Strengths and limitations of the study

The major strengths of the study are the large epidemiological sample of 1,588 children from a wide range of ages, as well as the geographical distribution of the sample, including urban and rural areas all over the country. However, our findings should be interpreted cautiously in the light of several limitations. First and foremost, the cross-sectional design of the study does not allow determining the directionality of the associations. In addition, parents and adolescents were called to answer in a simple "yes or no" question assessing the subjective perception of being victimized. Thus, a potential confounding factor is the personal differences in understanding of the term of bullying victimization.[38] Another limitation may stem from the fact that all variables were self-reported and not based on objective data. Also, although the list of variables was extensive, it was not exhaustive given that individual factors, which have been shown to be predictors of victimization, were not included. Finally, for the precise interpretation of our results it should be taken into account that the group of victims and the group of bully-victims are treated as a single group and also, the different types of bullying (i.e. direct/indirect, verbal/physical etc.) were not assessed.

Conclusions

Our findings demonstrate the extent to which influences external to individual children and adolescents play a decisive role to their perception of being victimized. Thus, our results highlight the need to also consider the influence of contextual factors in the design of targeting efforts countering and/or preventing bullying victimization. Finally, while this study may add to our knowledge of the prevalence and potential risk factors of bullying victimization among Greek children and adolescents, further research with prospective studies is needed.

Σχολικός εκφοβισμός: Σχετιζόμενοι παράγοντες πλαισίου σε ελληνικό δείγμα παιδιών και εφήβων

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Το φαινόμενο του σχολικού εκφοβισμού αποτελεί σημαντικό παράγοντα αρνητικής επίδρασης στη σωματική και ψυχική υγεία του ατόμου καθώς και στην ευρύτερη κοινωνική λειτουργία. Μελέτες παρέχουν δεδομένα για τη σχέση παραγόντων πλαισίου με τη θυματοποίηση στο πλαίσιο σχολικού εκφοβισμού. Στους παράγοντες πλαισίου περιλαμβάνονται ανάμεσα σε άλλους το κοινωνικοοικονομικό επίπεδο των γονέων/της οικογένειας, η ποιότητα του οικογενειακού περιβάλλοντος, γενικά και ειδικά χαρακτηριστικά του σχολικού πλαισίου, όπως το μέγεθος του σχολείου

και η δομή του καθώς επίσης και ποικίλα χαρακτηριστικά της κοινότητας. Η παρούσα αναδρομική μελέτη εστιάζει στη σχέση ορισμένων δημογραφικών και κοινωνικοοικονομικών παραγόντων με την υποκειμενική αντίληψη θυματοποίησης στο πλαίσιο σχολικού εκφοβισμού σε δείγμα από τον ελληνικό πληθυσμό παιδιών και εφήβων 6–17 ετών. Υποθέσαμε ότι επιδράσεις εξωτερικές των μεμονωμένων ατόμων διαδραματίζουν αποφασιστικό ρόλο στην υποκειμενική αντίληψη θυματοποίησής τους στο σχολικό περιβάλλον. Η αξιολόγηση της θυματοποίησης έγινε μέσω ερώτησης τύπου «ναι/όχι», η οποία επιβεβαίωνε ή απέρριπτε αντίστοιχα το γεγονός ότι το παιδί ή ο έφηβος έχει υπάρξει κάποια στιγμή θύμα εκφοβισμού στο σχολικό περιβάλλον. Συγχρόνως, συλλέχθηκαν από τους γονείς πληροφορίες σχετικά με δημογραφικά και κοινωνικοοικονομικά στοιχεία των οικογενειών των παιδιών και των εφήβων. Συνολικά συμπεριλήφθηκαν στη μελέτη 1.588 παιδιά και έφηβοι (51,8% κορίτσια, μέση ηλικία: 12,9±2,8 έτη). Ο επιπολασμός της υποκειμενικής εντύπωσης θυματοποίησης στο σύνολο του δείγματος ήταν 10,4%. Ανάλυση πολλαπλής λογιστικής παλινδρόμησης έδειξε θετική συσχέτιση της πιθανότητας θυματοποίησης με την κατοικία σε κύρια αστική περιοχή (Odds Ratio [OR]: 2,63, CI: 1,78–3,87, p<0,001), την παρουσία στο σπίτι ενός ατόμου με χρόνια νόσο (OR: 1,90, CI: 1,12–3,20, p=0,016), το χαμηλό οικογενειακό οικονομικό επίπεδο (OR: 1,83, CI: 1,05–3,20, p=0,032) και τον αυξημένο αριθμό ενηλίκων στο σπίτι (OR: 2,00, CI: 1,00–3,77, p=0,041). Επίσης, το υψηλότερο μορφωτικό επίπεδο των γονέων συσχετίστηκε με χαμηλότερη πιθανότητα σχολικού εκφοβισμού (OR: 0,88, CI: 0,78–0,99, p=0,05). Τα ευρήματα της παρούσας μελέτης καταδεικνύουν ότι δημογραφικοί και κοινωνικοοικονομικοί παράγοντες διαδραματίζουν σημαντικό ρόλο στην υποκειμενική αντίληψη θυματοποίησης από σχολικό εκφοβισμό μεταξύ παιδιών και εφήβων. Επομένως, υπογραμμίζεται η ανάγκη να συμπεριλαμβάνονται στον σχεδιασμό παρεμβάσεων πρόληψης ή/και αντιμετώπισης του σχολικού εκφοβισμού παράγοντες που αφορούν στο ευρύτερο δημογραφικό και κοινωνικοοικονομικό πλαίσιο.

Λέξεις ευρετηρίου: Σχολικός εκφοβισμός, θυματοποίηση, δημογραφικοί παράγοντες, κοινωνικοοικονομική κατάσταση, παράγοντες πλαισίου.

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Research article
Ερευνητική εργασία

Film clips smoking behavior and nicotine craving: The interrelationship between stress, smoking cues and craving

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An abundance of research has demonstrated that substance addicted individuals, when they are exposed to a substance related stimulus, show a positive correlation between physiological measurements, such as an increase in heart rate and sweating, and behavioral reactions, that include craving and substance use or consumption. Films depicting smoking behavior are regarded as cues to induce smoking behavior. The current study aimed to investigate the effects of smoking behavior portrayed in movies on actual craving experienced by smokers who watch on screen actors consume tobacco products. In addition, the effects of receiving orally administered nicotine (chewing gum), a regular chewing gum or no additional intervention were examined. In particular, the study aimed to investigate how these factors impact nicotine craving as well as the heart rate and sweating. The majority of the participants were University of Bedfordshire students and staff. Thirty smokers (12 males and 18 females) having received a nicotine gum, a regular chewing gum or no gum, were exposed to a digital video clip showing actors smoking. The participants chose the type of chewing gum they wanted. Heart rate (HR) and galvanic skin response (GSR) were measured during the course of the experiment. Prior to and after watching the movie clip participants completed the Brief Questionnaire of Smoking Urges (QSU-Brief) and the Perceived Stress Scale (PSS). According to the results, the craving was increased when compared to the baseline score ($t=-3.76$, $p<0.001$). Additionally, a correlation was found between the baseline level of craving and perceived stress before and after the movie ($r=0.39$). Nicotine chewing gum was found to have a significant impact on participants' heart rate ($p<0.05$) but not on GSR. A significant difference was found in participants in the normal chewing gum condition reporting higher levels of craving than the other two groups ($p<0.05$). Age was found to positively related to post-measures of nicotine craving which was found to be higher for young respondents ($r=-0.47$, $p<0.01$). The data further show that the depiction of smoking behavior in the media is likely to have a significant im-

pact on smoking craving, smoking behavior and nicotine consumption. The current study confirms and replicates some of the previous findings within the field of smoking behavior and nicotine craving such as high susceptibility of younger adults to media influence.

Key words: Film clips, galvanic skin response, heart rate, smoking craving, stress.

Introduction

Tobacco consumption is frequently depicted by the media in one form or another, in both grown-ups and adolescents of both gender and varied ethnicity, occupational and socio-economic status.[1] There is little evidence of whether and how movies may be experienced as cue exposure stimuli for smokers and whether they could be a factor in smoking relapse, resulting from individuals observing the actors smoke.[2] Specific behaviours, attitudes, cue exposure, and social norms influence the behavioural status of the individual, which may be related to smoking initiation. Smoking cues and smoking-influential stimuli, which are movie-related, are underlying different cognitive mechanisms, which can greatly influence an individual's smoking behaviour.[3] This can imply that an individual is attracted subconsciously to the smoking character, which in turn can lead the smoker to experience episodic craving levels, which accordingly will lead the individual to light a cigarette.[3]

A study adopting an experimental design examined a total of 65 young participants who smoked daily and were shown a 41-minute clip movie (with or without smoking cue stimuli); the results suggested that there is no effect of smoking cues in movies on craving.[4] Another experimental study suggested that males had a significantly higher increase in the levels of craving than females when exposed to smoking cues by watching six different popular movie clips.[5] Both studies took craving measurements after the exposure but did not assess baseline scores. A school-based longitudinal study focusing on examining the relationship between the time spent exposed to movies and smoking onset, reported that 1,697 of the 9,987 adolescents started to smoke due to the exposure.[6] It is worth noting that the authors took into consideration factors such as age, gender, family influence, school performance, TV screen time and peer pressure. Furthermore, in a similar study it was found that individuals were experiencing a minimum of three cue encounters each week.[7] Taking the previous study into consideration it can be a valuable tool in order to understand that the environment of today's society is filled with cues that even if an individual wished to abstain or succeeded in smoking cessation it can make it difficult to maintain continued abstinence.

An abundance of research has demonstrated that individuals who are addicted to substance show an increase in heart rate and sweating as well as behavioural reactions, which include craving and substance use or consumption.[8–10] When an experiment is conducted, craving is measured by means of self-report and physiological measurements, which are commonly taken in the form of heart rate (HR), galvanic skin response (GSR) and, in some cases, by taking an electroencephalogram.[11] Studies support that an individual who smokes and is exposed to smoking-relating-cue, report an increase in cardiovascular reactivity and in episodic craving levels rather than the one exposed to neutral-related-cues.[12,13] Physiologically, tobacco consumption increases stress hormones and cortisol levels. Long-term use of smoking has an effect on hypothalamic pituitary adrenal axis, stress hormones resulting in secretions of cortisol which is higher than normal in individuals who smoke than those who don't.[14]

Intervations using virtual reality suggest that smoking cues lead to a significant increase in tobacco consumption. However, this does not provide us with enough evidence in order to suggest that those cues will have the same effect in real life scenarios.[15,16]

The aim of this study was to examine the effect of smoking behaviour portrayed in movies on actual craving experienced by smokers who watch actors

to consume tobacco products. In addition, the effect of receiving orally administered nicotine (chewing gum), a regular chewing gum or no additional intervention was examined. In particular, the study aimed to investigate how these factors may impact physiological measurements such as HR and GSR. It was expected that significant correlations would be found between physiological measurements and self-reported measures of stress, between stress and smoking craving measures, between pre- and post-measures of the smoking craving, while younger participants would be more susceptible to smoking cues shown in movies.

Material and method

Design

The current research project used an experimental design, employing a number of quantitative measures. There were three independent variables: (1) viewing of a movie clip depicting scenes involving smoking, which are shown to all participants, (2) the level of current smoking behaviour, as assessed by self-report (participants were asked to categorise themselves as low, medium or heavy smokers based on their personal perception of their level of nicotine consumption), and (3) the influence of nicotine gum, a normal chewing gum or no gum on cigarette craving when watching others smoking on TV. Four dependent measures are recorded: (1) heart rate, (2) galvanic skin response while smoking craving, (3) stress levels, and (4) smoking craving.

Participants

The participants were a convenience sampling of totally 30 smokers (12 males and 18 females), students from the University of Bedfordshire (United Kingdom) or staff. Participants had to be at least 18 years.

The procedure:

1. Allocation to conditions

At the beginning of the experiment, participants were given a choice between receiving nicotine chewing gum (Nicorette icy white, 2 mg gum nicotine), regular chewing gum or no chewing gum.

Five respondents classified themselves with self-assessment as low smokers, thirteen as medium smokers and twelve reported being heavy smokers. This classification was based on their own subjective perception of their level of cigarette consumption.

2. Baseline measurement of nicotine craving and stress

Subsequently, participants were asked to complete the Brief Questionnaire of Smoking Urges (QSU-Brief) in order to take a baseline for smoking craving. The QSU-Brief[17] is composed of 10 items measuring smoking craving levels experienced in a particular moment by individuals. The answers are given on a 7-point Likert scale (1=strongly disagree to 7=strongly agree). The scale consists of two subscales; (i) Cigarette Craving (positive reinforcement of smoking, Factor 1, Items 1, 3, 6, 7, 10) and (ii) Coping Difficulties (negative reinforcement properties of smoking, Factor 2, Items 2, 4, 5, 8, 9).[17] Internal consistency of the QSU-brief has previously been reported to be very high with a Cronbach's alpha=0.97.[18]

Participants, also, completed the Perceived Stress Scale in order to control the initial stress level. The Perceived Stress Scale[19] (PSS) is widely used for the measurement of the perception of stress. It measures the extent of stress felt in situations that are regarded as stressful by individuals. The PSS is composed of 10 items evaluating the responses from the last month. The scoring is ranged from 0 (Never) to 4 (Fairly Often). Internal consistency has been found to be high.[20]

3. Galvanic skin response and heart rate

The materials used included an IBM compatible computer with a Power Lab 26T data acquisition system, running chart 5.5.1 software used with a finger pulse transducer to measure the participant's HR and finger electrodes to measure GSR. Subjects were linked with Powerlab whilst they were watching a short video clip, which lasted 1:18 minutes showing a number of actors consuming tobacco products. HR and GSR were measured during the course of the experiment.

Following the movie clips, participants once again completed the QSU-Brief as a post measure.

All questionnaires, as well as the consent form, were completed online via Qualtrix software.

Statistical analysis

A number of correlations were run to investigate relationships between the dependent measures. Pre and post comparisons were used to determine the effect of watching the movie clips of actors consuming tobacco products. More specifically, t-test was used in order to compare the mean scores on the variables for the different groups of participants. Correlational analyses were used in order to explore the relationships between the pre and post measurement of smoking craving. A repeated measures t-test was used in order to determine whether there is statistical significance between pre and post measurements of the QSU-Brief. Two-way ANOVA was used in order to investigate the effect on the type of gum on the physiological and psychological measures (GSR, HR, craving). All data was parametric (GSR, HR and QSU-Brief), and as a result, parametric test was used.

Ethics

The study followed the British Psychological Society ethical guidelines and was approved by the Ethics Committee of the Department of Psychology, University of Bedfordshire. Conditions were allocated on a voluntary basis of participant choice. Individuals were given the option to choose if they wished to receive the nicotine chewing gum, the no-nicotine gum (normal gum) or no chewing gum at all. Participants were informed both verbally and on the consent form that: (i) they can withdraw anytime they wish without any penalty, (ii) they may experience high level of smoking craving and (iii) about the effects of watching smoking clips on nicotine craving as well as the effect of nicotine gum. For ethical reasons, participants were asked to create their unique identification code, which was composed by their age (e.g.: 25) followed by their date of birth (e.g.: 24/07/1988), followed by their initials (e.g.: PK.), overall a normal code would look like 25-24/07/1988/PK.

Results

Descriptive characteristics

Participants were aged between 20 and 54 (Mean= 26.2, SD=7.1). Means and standard deviations for the dependent variables were calculated for the dependent variables. The smoking craving levels were higher after the intervention than prior to the experiment. Perceived Stress scores produced an average of 18.6 out of 40 suggesting intermediate stress levels. HR was overall normal. An independent measures t-test showed that an overall increase of smoking craving (QSU-Brief) was found between pre and post measures. This increase could be observed for both the Cigarette Craving factor and the Coping Difficulties factor (table 1).

Table 2 displays means and standard deviations for the dependent measures across the three experimental conditions. HR was high in the nicotine

Table 1. Means and standard deviations for dependent measures and pre versus post comparisons.

		Mean	SD	t	p
QSU-Brief Total	Pre	30.0	10.4	–3.76	<0.001
	Post	46.5	17.0		
Cigarette Craving (Factor 1)	Pre	27.1	9.2	–3.58	<0.001
	Post	30.5	12.8		
Coping Difficulties (Factor 2)	Pre	7.9	3.1	–3.57	<0.001
	Post	11.6	5.3		
Perceived Stress Scale		18.6	4.4		
HR		80.4	15.3		
GSR		4.1	8.3		

Notes: SD=Standard Deviation; QSU-Brief=Brief Questionnaire of Smoking Urges; HR=Heart Rate; GSR= Galvanic Skin Response

Table 2. Comparisons between the three study conditions.

		Nicotine gum			Normal gum			No gum		
		Mean	SD	p	Mean	SD	p	Mean	SD	p
HR		89.3	17.6	<0.05	80.1	11.8		71.8	11.8	
GSR		2.03	4.89		6.71	13.3		3.72	3.29	
Perceived Stress Scale		18.2	3.43		20.2	5.57		17.4	3.71	
QSU-Brief Total	Pre	31.5	10.7		42.2	4.92	<0.05	31.4	11.1	
	Post	49.3	13.9		52.8	13.1		37.5	20.7	
Cigarette Craving (Factor 1)	Pre	14.0	2.9		20.4	3.1		13.2	2.5	
	Post	23.5	3.8	<0.05	22.8	3.6		16.0	2.3	
Coping Difficulties (Factor 2)	Pre	17.5	2.9		21.8	1.9		18.2	2.1	<0.05
	Post	25.8	2.1	<0.05	30.0	1.9	<0.05	21.5	1.9	

Notes: SD= Standard Deviation; HR=Heart Rate; GSR= Galvanic Skin Response; QSU-Brief=Brief Questionnaire of Smoking Urges; ANOVA Test was applied

gum condition and low in the regular gum condition. Conversely, GSR was found to be high in the normal gum group and low in the nicotine gum condition. Perceived stress level was high for the normal gum group and low for those who had not taken any gum. Nicotine craving was found to be increased after the intervention for all groups; however, the largest increase was observed for the nicotine gum group. Moreover, craving scores were found to be more wide spread after the intervention.

Correlations

Age was found to positively related to post-measures of nicotine craving which was found to be higher for young respondents as revealed by a bivariate correlation ($r=-0.47$, $p<0.01$). Upon closer examination of the previously identified factors, it became clear that this relationship arose from the smoking craving factor, ($r=-0.485$, $p<0.01$), while no correlation was found with the Coping Difficulties.

Self-reported classification as low, medium or heavy smokers was, also, investigated in relation to the dependent measures but was not found to have an impact on any of the variables in a series of independent measures ANOVAs. The three groups were consequently collapsed for further analyses.

A weak correlation was observed between pre and post measures of the QSU-Brief ($r=0.33$) which just failed to reach significance ($p=0.74$). This relationship was substantially stronger the smoking craving factor exhibiting a weak to a medium correlation between pre and post measurements ($r=0.44$, $p<0.01$). No relationship was found with the Coping Difficulties factor and no correlation was found with any of the post measures. A correlation was, also, found between perceived stress and pre scores of the QSU-Brief ($r=0.39$, $p<0.01$). Once more, the relationship occurred only for the pre-measure of the smoking craving factor ($r=0.42$, $p<0.05$) while no relationship was found with the post measures or either measure of the Coping Difficulties dimension. Also, while scores of the Cigarette Craving factor were found to be unrelated to Coping Difficulties prior to watching the video depicting smoking, a strong correlation was found for the post measurement following the intervention ($r=0.717$, $p<0.001$).

Two independent measures ANOVAs showed that the condition into which participants were entered (nicotine chewing gum, normal chewing gum or no chewing gum) did not have an effect on GSR but

was found to have an impact on HR with those having chosen the nicotine gum showing significantly more beats per minute than participants who did not chew any gum at all as revealed by the post-hoc analysis ($p<0.05$).

When analysing the baseline scores of the QSU-Brief in the pre condition, it was found that participants in the normal chewing gum group displayed significantly higher craving than those in the other two groups ($p<0.05$ for both) as revealed by an independent measures ANOVA. To accurately assess the post scores obtained, pre measures were controlled for in the subsequent ANOVA run on the post measures. Coping difficulties were greater for both chewing gum groups (nicotine and normal) than for the no chewing gum group ($p<0.05$ for both).

A mixed measures ANOVA was also run in order to investigate differences between participants who received nicotine gum, normal gum or no gum in both pre- and post- craving scores (QSU-Brief). No interaction was observed between pre and post measures and the three experimental conditions. However, breaking down scores for the three groups post-hoc analysis revealed that no increase in craving occurred for participants without chewing gum while an increase was observed for respondents who had received the normal chewing gum which fell just short of significance ($p=0.053$). Furthermore, a significant increase in smoking craving was found for individuals who had chosen the nicotine gum ($p<0.01$).

These effects were also investigated for the separate factors and it was found that at post measurement Cigarette Craving in participants who had received the nicotine chewing gum was higher than prior to the intervention, while no differences could be found in either of the other two groups.

Discussion

Craving was found to increase at a similar rate for both the total score of the QSU-Brief as well as the two factor dimensions, suggesting that watching the movie clips had a substantial impact on levels of smoking craving. It is interesting to note that while Cigarette Craving and Coping Difficulties measurements were not related at the start of the experiment, a strong, significant correlation emerged following the intervention. Since both dimensions also displayed a significant increase, this suggests that after watching the smoking scenes, participants were both, more likely to crave a cigarette and less able to cope with their desire.

There was expected to be a significant correlation between physiological measurements (HR and GSR) and self-reported (Perceived Stress Scale) measures of stress. Results indicate that it could not be confirmed in the experiment presented here as no correlation was found between physiological measures of stress and self-reported measures of stress although previous research has found clear links between physiological arousal and subjective perceptions of stress. Others[21] examined the hypothesis that psychological stress can induce changes in the heart rate.

A weak correlation observed between pre- and post-measures of the QSU-Brief just failed to significance, suggesting that the intervention was partly successful in altering the amount of craving experienced by the participants. Detailed examination showed that a stronger relationship existed between pre and post measures of the Cigarette Craving dimension, while no correlation could be found for the Coping Difficulties subscale. This suggests that while the overall amount of craving experienced may have been altered, the main effect was seen on how well participants could cope with their desire following exposure to the movie clips.

A correlation was also observed between baselines levels of craving and perceived stress. This is in line with previous findings showing that stress is a main mechanism in initiating smoking behaviour.[22,23] This relationship, once more emerged only between the pre measurement of Cigarette Craving, while post measures and measure of Coping Difficulties did not correlate with either physiological or self-reported measures of stress. In particular, it should be noted that the absence of a correlation between post measures of Cigarette Craving and perceived stress, suggests that craving experienced after the experiment is more likely to be due to the interven-

tion than to stress experienced before watching the movie clips.

While no overall difference in levels of craving was observed between those having received nicotine gum, normal gum or no gum, it appeared that both chewing gum groups experienced more difficulties in coping with their craving than the no gum group. This suggests that the action of chewing may have a negative impact on managing craving, possibly due to the oral involvement associated with both activities.[24]

A clearer picture could, however, be noticed when nicotine craving scores in the three conditions were compared between pre and post measures. While no difference was found between pre and post measurements for the no chewing gum group, an increase could be observed in respondents who had chosen the normal chewing gum. The difference was just above the significance level but it would be likely to become more pronounced in a larger sample.

A significant increase in craving was, also, found for the nicotine chewing gum group. In particular, it could be seen that scores increased on the Cigarette Craving dimension only for participants in the nicotine gum condition, while Coping Difficulties increased for both the nicotine gum and chewing gum group. These findings suggest that, contrary to the intended purpose of nicotine gum, nicotine gum increased cigarette craving rather than helped smokers control it.

In the current experiment chewing nicotine gum was found to have an impact on HR but not on GSR. This is likely due to the stimulating effects of nicotine, which increases blood flow and consequently leads to an increase in HR.[25] While a small increase was, also, observed for those with normal chewing gum, the difference was not significant and this may be due to the additional movement required for chewing. Others suggested that smokers reported fewer cigarette puffs and the time until they first lit their first cigarette increased significantly.[26] The chewing gum was, also, a factor that helped smokers to deal with withdrawal symptoms in relation to the control group.[27]

The current study did not find a relationship between gender and nicotine craving. Research evidence suggests that female individuals are more prone to nicotine intake than men. Furthermore, the smoking behaviour of females is influenced by a variety of different variables and not primarily related to the role of nicotine itself as it happens with males. Again, the association between gender and smoking behaviour is clouded by a variety of mixed results.[28] In general, it is suggested that, even though gender differences apply, the individual perception towards the smoking behaviour plays a vital role.

This study is subject to some limitations that need further examination. A larger group of participants would have revealed an overall statistical significance which could lead to a better explanation of the variables involved. Also, the classification of participants in the three categories (low, medium or heavy smokers) was not based on the number of cigarettes consumed per day but by the self-report method. The selection of participants to be included in the nicotine chewing gum group or in the other two groups is another limitation of this study since there is no comparison of the effect of nicotine with placebo. At the same time, it needs to be considered that each individual is adopting smoking behaviour for a variety of different factors determined by their personal life circumstances.

Conclusions

The current study built on existing research in the area but used a different approach that incorporates the effect of smoking in movies on current smokers and the effectiveness of nicotine chewing gum in regulating nicotine craving. Overall, the current study confirms and replicates some of the previous findings within the field of smoking behaviour and nicotine carving such as higher susceptibility of younger adults to media influence. Surprisingly enough, in this study, the findings that nicotine chewing gum increased the craving levels felt from the participants should be alarming to the medical community. Non-the-less, future studies and studies that can replicate those findings should be developed in order to retest the validity of the findings in a larger sample.

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Συμπεριφορά καπνίσματος στις κινηματογραφικές ταινίες και επιθυμία για νικοτίνη: Η σχέση μεταξύ στρες, ερεθισμάτων καπνίσματος και επιθυμίας

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Μια πληθώρα ερευνών έχει δείξει ότι τα εξαρτημένα από ουσίες άτομα, όταν εκτίθενται σε ένα ερέθισμα σχετικό με την ουσία, εμφανίζουν μια θετική συσχέτιση μεταξύ των φυσιολογικών μετρήσεων, όπως η αύξηση του καρδιακού ρυθμού και της εφίδρωσης, και των αντιδράσεων συμπεριφοράς όπως είναι η επιθυμία και η χρήση ουσιών. Οι ταινίες που απεικονίζουν συμπεριφορά καπνίσματος θεωρούνται ερεθίσματα για την πρόκληση συμπεριφοράς καπνίσματος. Η τρέχουσα μελέτη είχε στόχο τη διερεύνηση των επιπτώσεων της συμπεριφοράς καπνίσματος, που απεικονίζεται στις ταινίες, στην πραγματική επιθυμία των καπνιστών που παρακολουθούν στην οθόνη τους ηθοποιούς να καταναλώνουν προϊόντα καπνού. Επιπροσθέτως, διερευνήθηκαν τα αποτελέσματα τής από του στόματος χορηγούμενης νικοτίνης (τσίχλα νικοτίνης), της χορήγησης συνήθους τσίχλας και της μη χορήγησης νικοτίνης. Ειδικότερα, η μελέτη στόχευε να διερευνήσει πώς αυτοί οι παράγοντες επηρεάζουν την επιθυμία για νικοτίνη καθώς και την καρδιακή συχνότητα και την εφίδρωση. Η πλειοψηφία των συμμετεχόντων ήταν οι φοιτητές και προσωπικό του Πανεπιστημίου του Bedfordshire. Τριάντα καπνιστές (12 άνδρες, 18 γυναίκες) παρακολούθησαν κινηματογραφική ταινία που απεικόνιζε ηθοποιούς να καπνίζουν ενώ παράλληλα ελάμβαναν τσίχλα νικοτίνης ή συνήθη τσίχλα ή καμία τσίχλα. Οι συμμετέχοντες επέλεξαν οι ίδιοι τον τύπο της τσίχλας που επιθυμούσαν. Κατά τη διάρκεια της διαδικασίας μετρήθηκε ο καρδιακός ρυθμός και η γαλβανική απόκριση του δέρματος. Πριν και μετά την παρακολούθηση της ταινίας, οι συμμετέχοντες συμπλήρωσαν τις κλίμακες Βραχύ Ερωτηματολόγιο Παρωθήσεων για Κάπνισμα (Brief Questionnaire of Smoking Urges, QSU-Brief) και Κλίμακα Προσλαμβανόμενου Στρες (Perceived Stress Scale, PSS). Σύμφωνα με τα ευρήματα, το επίπεδο επιθυμίας για νικοτίνη αυξάνεται σε σύγκριση με το επίπεδο επιθυμίας πριν την παρακολούθηση ($t=-3,76$, $p<0,001$). Επιπλέον, διαπιστώθηκε συσχέτιση μεταξύ των επιπέδων της επιθυμίας για νικοτίνη και του προσλαμβανόμενου στρες πριν και μετά την παρακολούθηση ($r=0,39$). Η τσίχλα νικοτίνης βρέθηκε να επηρεάζει σημαντικά τον καρδιακό ρυθμό των συμμετεχόντων ($p<0.05$) αλλά όχι τη γαλβανική απόκριση του δέρματος. Σημαντική διαφορά παρατηρήθηκε επίσης στους συμμετέχοντες που χρησιμοποίησαν τη συνήθη τσίχλα, καθώς διαπιστώθηκαν σε αυτούς υψηλότερα επίπεδα επιθυμίας από τις άλλες δύο ομάδες ($p<0,05$). Η ηλικία βρέθηκε να σχετίζεται θετικά με την επιθυμία για νικοτίνη η οποία βρέθηκε να είναι υψηλότερη στους νεότερους ($r=-0,47$, $p<0,01$). Τα δεδομένα δείχνουν περαιτέρω ότι η απεικόνιση της συμπεριφοράς καπνίσματος στα μέσα ενημέρωσης είναι πιθανό να έχει σημαντικό αντίκτυπο στην επιθυμία του καπνίσματος, στη συμπεριφορά του καπνίσματος και στην κατανάλωση νικοτίνης. Η τρέχουσα μελέτη επιβεβαιώνει μερικά από προηγούμενα ευρήματα στον τομέα της συμπεριφοράς καπνίσματος και της επιθυμίας για νικοτίνη όπως η υψηλή ευαισθησία των νεαρών ενηλίκων στην επιρροή των μέσων ενημέρωσης.

Λέξεις ευρετηρίου: Ταινίες, γαλβανική απόκριση δέρματος, καρδιακός ρυθμός, επιθυμία για κάπνισμα, στρες.

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Research article
Ερευνητική εργασία

Validation of the Youth Efficacy/Empowerment Scale – Mental Health Finnish version

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Adolescents face mental health problems and still their mental health needs are often neglected. Empowerment provides adolescents with the skills to impact their own lives and communities in general. The aim of the study is to examine the validity and reliability of the Finnish version of the Youth Efficacy/Empowerment Scale – Mental Health (YES-MH). Data was collected through an online questionnaire from pupils aged 12–17 years in Western Finland, comprised of the following instruments; the YES-MH, the Goodman's the Strengths and Difficulties Questionnaire (SDQ), and the Warwick-Edinburgh Mental Wellbeing Scale. Exploratory factor analysis was carried out to evaluate construct validity and disclose underlying structures which yielded the following subscales: Self, Services, System. The internal consistency of subscales was analyzed with Cronbach's α. Construct validity was further investigated by computing the Pearson's correlations coefficients between the subscales. Furthermore, correlations with SDQ and mental well-being dimensions were explored as measures of convergent validity. In the final model all items the Youth Efficacy/Empowerment Scale – Mental Health were entered into the factor analysis. All factor loadings were more than 0.40, ranging from 0.63 to 0.89. All the scales exceeded the minimum reliability standard of 0.70 and all corrected item-total correlations were high. All the YES-MH subscales were significantly and positively correlated each other with correlations coefficients ranging from medium to high. Correlations of Mental Well-being score with Self and Services subscales were significant. Moreover, Self subscale was significantly correlated with all SDQ dimensions. Services subscale was significantly correlated with Emotional symptoms and total SDQ score, while System subscale was significantly correlated with Conduct problems. The exploratory factor analysis showed a clear factor structure and the results suggest that the YES-MH is a reliable scale for assessing empowerment among young people. The YES-MH can be useful for health professionals not only as an assessment tool but also

when they need to evaluate mental health interventions and examine empowerment as an outcome. However, further research can provide insights for the use of the scale in specific adolescent target groups and among different ethnic groups as well.

Key words: Youth, adolescents, efficacy, empowerment, Finland.

Introduction

Globally, 10% to 20% of children and adolescents are affected by mental health problems.[1] As young people experience adolescence, some confront particularly difficult struggles. While many young people will make at least minimally successful transitions to adulthood, a large number face problems that could jeopardize their future and have negative repercussions for broader society.[2] For this age group, mental health problems is a leading cause of health-related disability, although the mental health needs of children and adolescents are often neglected.[1]

Empowerment is a core concept of WHO's vision of health promotion.[3] Mental health promotion conceptualizes mental health in positive rather than in negative terms and delivers effective programmes designed to reduce health inequalities in an empowering, collaborative and participatory manner.[4] Mental health promotion is important as it significantly improves population's health and well-being.[5]

Empowerment is defined as a process through which people, organisations, and communities gain mastery over their lives.[6] Similarly, empowerment is defined as a process of gaining control over one's life and having the ability to influence organizational and societal structure in which one lives.[7]

WHO defines adolescents as those people between 10 and 19 years of age. In addition, the WHO uses the term young people for those between 10 and 24 years of age to combine adolescents and youth, while United Nations define the term youth for people between 15 and 24 years of age.[8]

Adolescents need guidance and support to use power effectively and adults have an important role in assisting this process, and conceptualizing adolescents as research partners with valuable voices promises to create future possibilities for important health promoting change.[9] Youth empowerment is the outcome by which youth, as change agents, gain the skills to impact their own lives and lives of other individuals, organizations and communities.[10] Empowerment embraces the idea that individuals have the right to make their own choices about their health care. Walker and colleagues[11] argue that young people should be encouraged to take an active role in shaping their own mental health care as well as the policies and decisions that affect mental health services and systems. Furthermore, it is found that data for some key aspects of development and well-being, such as adolescent empowerment, including decision-making, agency or self-efficacy, participation and civic engagement are limited.[12]

In a mental health context, empowerment refers to the level of choice, influence and control that users of mental health services can exercise over events in their lives.[3] One of the six key messages for action of the European Strategy for the prevention and control of non-communicable diseases is that people should be empowered to promote their own health, interact effectively with health services and be active partners in managing disease.[13] Using validated tools to measure empowerment will assist the design, implementation and evaluation of empowerment strategies in health promotion programmes.[14] Thus, the aim of the study was to examine the validity and reliability of the Finnish version of the Youth Efficacy/Empowerment Scale – Mental Health. Since there is no similar scale in Finnish, the Youth Efficacy/Empowerment Scale – Mental Health was selected because it is a scale that examines empowerment from the perspective of young people themselves. Hence, the ultimate goal is to provide a reliable scale for assessing empowerment among adolescents.

Material and method

Participants and procedure

Data collection was conducted in one randomly selected secondary school in Western Finland. Data was collected during a school day by an on-line

questionnaire from pupils aged 12–17 years. Data collection and participants' recruitment were facilitated by the headmaster and the school's teachers. Participants were included in the study if they were secondary school pupils understanding Finnish and their parents/guardians did not deny their participation in the study.

Ethical considerations

The study obtained ethical approval from the Ethical Committee of Turku University. In addition, all potential participants and their parents/guardians were informed about the study during recruitment emphasising the anonymity and voluntariness of participation. Parents/guardians could deny their child's participation and even when parents/guardians had agreed, it was pupils' choice to take part or not. Pupil's response to online questionnaire was considered their informed consent.[15]

Measures

The online questionnaire was comprised of the following instruments: the Youth Efficacy/Empowerment Scale – Mental Health (YES-MH),[16] the Goodman's Strengths and Difficulties Questionnaire (SDQ),[17] and the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS),[18] and a demographic characteristics questionnaire.

The YES-MH, developed by Walker & Powers,[16] is an adaptation from the Family Empowerment Scale.[19] It was designed to assess youth perceptions of confidence and efficacy with respect to managing their own mental health condition, managing their own services and supports, and using their experience and knowledge to help peers and improve service systems.[16]

The YES-MH consists of 20 items on subscales which reflect efficacy/empowerment at three levels: (1) self (confidence and optimism about coping with/managing one's condition), (2) services (confidence and capacity to work with service providers to select and optimize services and supports), and (3) system (confidence and capacity to help providers improve services and to help other youth understand the service system). The items are rated on a 5-point scale from "never or almost never" to "always or almost always". The total score for overall youth empowerment ranges from 20 to 100, with higher scores indicating higher levels of empowerment.

The method of forward- and back-translations was used as it is suggested by WHO[20] for the translation and adaptation of instruments. The YES-MH was translated into Finnish by two bilingual individuals (one of them is health care professional). An expert panel discussed and worked on reconciliation of the forward translated questionnaire. Then, the Finnish version was back-translated to English by a native English speaker, who was not familiar with the original version of the questionnaire. A cognitive debriefing process was also followed for the cultural adaptation of the questionnaire. In this step, the YES-MH was administered to a few adolescents in order to assess the clarity, appropriateness of wording and acceptability of the translated questionnaire. Then, the last adaptations to the questionnaire were made.

The SDQ is a brief psychiatric assessment and screening tool of 25 items. Each item is scored in 3-point scale from 0=not true, 1=somewhat true to 2=certainly true. Twenty of the items can be scored summative and shown as a score of total difficulties. The instrument can also be divided into five subscales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviour.[21] The Finnish version of SDQ was validated by Koskelainen, Sourander and Kaljonen.[22]

Finally, the WEMWBS[18] is consisted of 14 items on mental well-being. Items are Likert scaled from 1 (never) to 5 (all the time). The Finnish version was translated in 2015 by Finnish National Institute for Health and Welfare.[23]

Data analysis

Exploratory factor analysis was carried out to evaluate construct validity, disclose underlying structures and possibly reduce the number of variables of the study questionnaire. Principal component analysis was chosen as extraction method using Varimax rotation. The cut-off point for factor loadings was 0.40 and for eigenvalues it was 1.00. The internal consistency of subscales was analyzed

with Cronbach's alpha. Subscales with reliabilities equal to or greater than 0.70 were considered acceptable.

Construct validity was further investigated by computing the Pearson's correlation coefficients between the subscales. Furthermore, correlations with SDQ and mental well-being dimensions were explored as measures of convergent validity. Correlation coefficients between 0.1 and 0.3 were considered low, between 0.31 and 0.5 moderate and those over 0.5 were considered high. The questionnaire subscales were compared according to sex, age group and emotional or mental health difficulties using Student's t-tests. P values reported are two-tailed. The level of statistical significance was set at 0.05 and analysis was conducted using SPSS 22.0 Statistical Software.

Results

The sample consisted of 114 participants (43% boys and 55.3% girls) (table 1). There was a 6.1% of the participants who had received medication for emotional or mental health difficulties, while 8.8% had been given diagnosis for their emotional or mental health difficulties.

An exploratory factor analysis with principal component method and with Varimax rotation was conducted on the sample. Using the latent root criterion of retaining factors with Eigenvalues greater than 1.0, a three-factor structure was identified, with the extracted factors explaining 70.9% of the total variance. In the final model all items were entered into the factor analysis. All factor loadings were more than 0.40, ranging from 0.63 to 0.89. The three factors that were emerged in the current study were: Self, Services and System which were in accordance with the original version (table 2). In addition, the items did not differ in their loadings of that of the original version.

Cronbach's alpha estimated along with the mean scale scores for the extracted components (table 3). All the scales, exceeded the minimum reliability standard of 0.70 and all corrected item-total correlations were high. Cronbach's alpha was 0.93 for Self subscale, 0.94 for Services subscale and 0.93 for system subscale.

Table 1. Sample characteristics (n=114).

Characteristics	N (%)
Gender	
Boys	49 (43)
Girls	63 (55.3)
Other	2 (1.7)
Age, mean (SD)	14.2 (1.04)
Participants who have received medication for emotional or mental health difficulties	7 (6.1)
Participants who have been given a name or diagnosis for their emotional or mental health difficulties	10 (8.8)
Employed father	90 (78.9)
Employed mother	94 (82.5)
Educational level of the mother	
Basic education	5 (4.4)
Vocational education	15 (13.2)
Tertiary education	53 (46.5)
Don't know/don't want to answer	41 (36.0)
Educational level of the father	
Basic education	7 (6.1)
Vocational education	20 (17.5)
Tertiary education	40 (35.1)
Don't know/don't want to answer	47 (41.2)
Living situation now	
Independent/on its own	1 (0.9)
With both parents	72 (63.2)
With one parent	34 (29.8)
With other relatives	1 (0.9)
In a psychiatric hospital	1 (0.9)
In a correctional facility	1 (0.9)
Other	4 (3.5)

All subscales were significantly and positively correlated each other with correlations coefficients ranging from medium to high. Correlations of mental well-being (WEMWBS score) with Self and Services subscales were significant. Moreover, Self subscale was significantly correlated with all SDQ dimensions. Services subscale was significantly correlated with Emotional symptoms and total SDQ score, while System subscale was significantly correlated with Conduct problems (table 4).

Table 2. Factor loadings from the results of exploratory factor analysis.

Item	Self	Services	System
1. I focus on the good things in life, not just the problems	0.87		
2. I make changes in my life so I can live successfully with my emotional or mental health challenges	0.75		
3. I feel I can take steps toward the future I want	0.86		
5. I know how to take care of my mental or emotional health	0.75		
6. When problems arise with my mental health or emotions, I handle them pretty well	0.89		
7. I feel my life is under control	0.85		
8. When a service or support is not working for me, I take steps to get it changed		0.75	
9. I tell service providers what I think about services I get from them		0.71	
10. I believe that services and supports can help me reach my goals		0.80	
12. My opinion is just as important as service providers' opinions in deciding what services and supports I need		0.79	
13. I know the steps to take when I think that I am receiving poor services or supports		0.75	
14. I understand how my services and supports are supposed to help me		0.72	
15. I work with providers to adjust my services or supports so they fit my needs		0.75	
16. I feel I can help improve services or supports for young people with emotional or mental health difficulties			0.78
17. I have ideas about how to improve services for young people with emotional or mental health difficulties			0.79
18. I know about the legal rights that young people with mental health difficulties have			0.63
20. I take opportunities to speak out and educate people about what it's like to experience emotional or mental health difficulties			0.81
21. I feel that I can use my knowledge and experience to help other young people with emotional or mental health difficulties			0.86
22. I tell people in agencies and schools how services for young people can be improved			0.85
23. I help other young people learn about services or supports that might help them			0.86

No significant differences were found on sex, age and emotional or mental health difficulties, with the exception of the score on System subscale that was significantly greater in adolescents aged 15 or more years as compared to those that aged less than 15 years (table 5).

Discussion

The aim of this study was to validate a questionnaire assessing empowerment among youth aged 12–17 in Finland. Adolescents are developing and consolidating their sense of self, they want greater independence and responsibility and they want to do something about the social issues that they encounter in their lives.[12] Furthermore, empowerment is important for the young people at risk.[24,25] Thus, there is a need for available instruments that contribute to a better understanding and assess empowerment among adolescents.

The exploratory factor analysis showed a clear factor structure and our results suggest that the YES-MH is a reliable scale for assessing empower-

Table 3. Corrected item-total correlations, internal consistency reliability and mean values for the YES-MH questionnaire.

	Corrected Item – Total Correlation	Cronbach's a if Item Deleted	Cronbach's a	Mean (SD)
Self			0.93	12.0 (5.5)
item 1	0.85	0.91		1.9 (1)
item 2	0.71	0.93		2.2 (1.1)
item 3	0.80	0.92		1.9 (1)
item 5	0.70	0.93		2.0 (1.2)
item 6	0.88	0.90		2.0 (1.1)
item 7	0.84	0.91		1.9 (1.1)
Services			0.94	19.3 (8.3)
item 8	0.78	0.94		2.7 (1.4)
item 9	0.75	0.94		3 (1.4)
item 10	0.88	0.93		2.7 (1.4)
item 12	0.79	0.94		2.9 (1.4)
item 13	0.81	0.93		2.6 (1.3)
item 14	0.80	0.93		2.6 (1.3)
item 15	0.85	0.93		2.9 (1.4)
System			0.93	23.3 (8.8)
item 16	0.83	0.93		3.1 (1.5)
item 17	0.87	0.93		3.4 (1.4)
item 18	0.75	0.93		3.2 (1.4)
item 20	0.79	0.93		3.3 (1.4)
item 21	0.88	0.93		3.3 (1.4)
item 22	0.90	0.93		3.6 (1.4)
item 23	0.92	0.94		3.5 (1.4)

Table 4. Pearson's correlation coefficients between the subscales of YES-MH, SDQ and mental well-being.

	Self	Services	System
Self		0.57[iii]	0.32[ii]
Services			0.67[iii]
Emotional symptoms	0.42[iii]	0.33[iii]	0.06
Conduct problems	0.30[ii]	0.03	–0.20[i]
Hyperactivity/ inattention	0.37[iii]	0.17	–0.10
Peer relationship problems	0.38[iii]	0.08	–0.15
Prosocial behaviour	–0.19[i]	0.06	0.13
Total SDQ score	0.47[iii]	0.21[i]	–0.09
Mental well-being	–0.38[iii]	–0.20[i]	–0.08

(i) $p<0.05$, (ii) $p<0.01$, (iii) $p<0.001$

Table 5. Association of YES-MH subscales with sex, age & emotional/mental health difficulties.

	Self	p*	Services	p*	System	p*
	Mean (SD)		Mean (SD)		Mean (SD)	
Gender						
Boys	11.9 (5.8)	0.855	17.8 (7.8)	0.145	22.0 (8.7)	0.186
Girls	11.7 (5.2)		20.1 (8.6)		24.3 (9.0)	
Age						
<15	12.2 (5.5)	0.770	18.1 (8.0)	0.192	20.4 (9.4)	0.002
≥15	11.9 (5.6)		20.2 (8.5)		25.4 (7.8)	
Received medication for emotional or mental health difficulties						
Yes	13.9 (9.1)	0.363	18.9 (8.6)	0.874	19.6 (9.9)	0.247
No	11.9 (5.3)		19.4 (8.3)		23.6 (8.8)	
Given a name or diagnosis for their emotional or mental health difficulties						
Yes	11.8 (4.9)	0.901	18.1 (6.2)	0.624	19.5 (6.9)	0.152
No	12.0 (5.6)		19.5 (8.5)		23.7 (8.9)	

*Student's t-test

ment among young people. According to Costello and Osborne,[26] factors with loadings greater than 0.50, made up of 4 or more items, are solid and of practical relevance. In the current exploratory factor analysis, factor loadings ranged from 0.63 to 0.89.

Finally, the mean scores of each subscale did not differ significantly from those of previous studies using the original version. Specifically, in the current study which included general population, the mean scores for the subscales Self, Services and System were 12 (SD=5.5), 19.3 (SD=8.3) and 23.3 (8.8), respectively. Walker, Thorne & Powers[10] found mean score 22.88 on Self subscale (SD=4.51), on Service 26.77 (SD=5.78) and on System 23.08 (SD=7.06). Later, Huscroft-D'Angelo et al,[27] in their study among youth departing therapeutic residential care, found a mean score on Self 23.63 (SD=4.82), on Services 26.17 (SD=5.69) and on System 22.79 (SD=6.96).

It was also found in the current study that the System subscale was significantly greater in adolescents aged 15 or more years as compared to those that aged less than 15 years. However, a study among adolescents and young adults with cancer showed that low levels of empowerment were associated with low levels of autonomy and social support, female sex, and coping difficulties.[28]

Moreover, correlations of mental well-being (WEMWBS score) with Self and Services subscales were found significant. This can be explained since the subscale Self included items in regards to the individual's mental health and wellbeing and in the subscale of Services there are items about the provided services that may provide the needed support to each individual. In addition, the Self subscale was significantly correlated with all SDQ dimensions which was expected since the SDQ includes items that reflect one's self. Services subscale was significantly correlated with Emotional symptoms since these items refer to several personal complains and total SDQ score which refers to the one's difficulties. System subscale was significantly correlated with Conduct problems which includes items about conduct difficulties and thus can be correlated with the System which includes

items that reflect the ability to help others and the services to be improved.

Although the YES-MH presents sufficient evidence of validity and reliability, there were some limitations in the current study: the participants were recruited from the general population, in a school setting and the study did not target only participants who are challenged with emotional or mental health problems. Further research is needed in order to validate the YES-MH among different young populations. Moreover, the results did not show any differences between boys and girls which may be affected by the number of participants. A larger study should explore for possible gender differences.

Based on the above, it can be concluded that the Finnish version of the YES-MH is a solid and robust instrument to assess empowerment, which can help health professionals to better understand its conceptual and empirical foundations. Its application is simple and not time consuming. WHO[12] claims that the unique nature and importance of adolescence mandates explicit and specific attention in programmes.

Hence, the YES-MH can be useful for health professionals not only as an assessment tool but also when they need to evaluate mental health interventions and examine empowerment as an outcome. However, further research can provide insights for specific adolescent target groups and among different ethnic groups as well.

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Στάθμιση της φινλανδικής εκδοχής της κλίμακας Αποτελεσματικότητας/Ενδυνάμωσης των Νέων – Ψυχικής Υγείας

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Οι έφηβοι αντιμετωπίζουν προβλήματα ψυχικής υγείας, αλλά ακόμα συχνά παραμελούνται οι ανάγκες ψυχική υγείας τους. Η ενδυνάμωση παρέχει στους εφήβους τις δεξιότητες για να επηρεάσουν τη ζωή τους αλλά και την κοινότητα εν γένει. Σκοπός της μελέτης είναι να εξετάσει την εγκυρότητα και την αξιοπιστία της φινλανδικής εκδοχής της Κλίμακας Αποτελεσματικότητας/Ενδυνάμωσης των Νέων - Ψυχικής Υγείας (Youth Efficacy/Empowerment Scale – Mental Health, YES-MH). Η συλλογή των δεδομένων πραγματοποιήθηκε μέσω ερωτηματολογίου στο διαδίκτυο από μαθητές ηλικίας 12–17 ετών στη Δυτική Φινλανδία. Το ερωτηματολόγιο περιλάμβανε τα ακόλουθα εργαλεία: την κλίμακα YES-MH, το Ερωτηματολόγιο Δυνατοτήτων και Δυσκολιών (Goodman's, the Strengths and Difficulties Questionnaire, SDQ) και η Κλίμακα Ψυχικής Ευεξίας Warwick-Edinburgh (Warwick-Edinburgh Mental Wellbeing Scale, WEMWBS). Διεξήχθη διερευνητική ανάλυση παραγόντων για τον έλεγχο της δομικής/εννοιολογικής εγκυρότητας καθώς και να παρατεθούν οι υποκείμενες δομές καταλήγοντας στις εξής υποκλίμακες: Εαυτός (Self), Υπηρεσίες (Services), Σύστημα (System). Η εσωτερική συνάφεια των υποκλιμάκων υπολογίστηκε με τον συ-

ντελεστή Cronbach α. Η δομική/εννοιολογική εγκυρότητα εξετάστηκε περαιτέρω με υπολογισμό των συντελεστών συσχέτισης Pearson μεταξύ των υποκλιμάκων. Επιπλέον, διερευνήθηκε η συγκλίνουσα εγκυρότητα μέσω συσχετισμών με το ερωτηματολόγιο SDQ και την κλίμακα WEMWBS. Στο τελικό μοντέλο εισήχθησαν στην ανάλυση παραγόντων όλα τα λήμματα της κλίμακας YES-MH. Όλες οι φορτίσεις των παραγόντων ήταν περισσότερο από 0,40 (κυμαινόμενες από 0,63 έως 0,89). Όλες οι κλίμακες υπερέβησαν το ελάχιστο 0,70 αξιοπιστίας. Όλες οι υποκλίμακες εμφάνισαν σημαντικά θετική συσχέτιση μεταξύ τους (συντελεστές συσχετισμού: μέσο έως υψηλό). Οι συσχετίσεις της Κλίμακας Ψυχικής Ευεξίας με τις υποκλίμακες Εαυτός και Υπηρεσίες ήταν σημαντικές. Επιπλέον, η υποκλίμακα Εαυτός ήταν σημαντικά συσχετισμένη με όλες τις διαστάσεις του SDQ. Η υποκλίμακα Υπηρεσίες συσχετίστηκε σημαντικά με τα συναισθηματικά συμπτώματα και το συνολικό σκορ του SDQ, ενώ η υποκλίμακα Σύστημα συσχετίστηκε σημαντικά με τα προβλήματα συμπεριφοράς. Η διερευνητική ανάλυση παραγόντων έδειξε μια σαφή δομή των παραγόντων και τα αποτελέσματα έδειξαν ότι η κλίμακα YES-MH είναι μια αξιόπιστη κλίμακα για την εκτίμηση της ενδυνάμωσης των νέων. Η κλίμακα YES-MH μπορεί να είναι χρήσιμη για τους επαγγελματίες υγείας ως εργαλείο εκτίμησης, αλλά και για την αξιολόγηση παρεμβάσεων ψυχικής υγείας και την εξέταση της ενδυνάμωσης ως αποτέλεσμα. Ωστόσο, περαιτέρω μελέτη μπορεί να προσφέρει ικανές πληροφορίες για τη χρήση της σε συγκεκριμένες πληθυσμιακές ομάδες εφήβων καθώς και σε έφηβους διαφορετικών εθνοτήτων.

Λέξεις ευρετηρίου: Νέοι, έφηβοι, αποτελεσματικότητα, ενδυνάμωση, Φινλανδία.

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General article
Γενικό άρθρο

Is psychosis a dysmyelination-related information-processing disorder?

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Numerous lines of evidence implicate myelin and oligodendrocyte function as critical processes affecting neuronal connectivity, which is a central abnormality in schizophrenia. Neurodevelopmental models related to dysmyelination have suggested its relation with different schizophrenia-like symptoms. Post-mortem studies in patients with schizophrenia have reported 14–22% reduction in the density and the quantity of oligodendrocytes. Several myelin-related candidate genes have been linked oligodendrocyte and myelin dysfunction with neurocircuitry abnormalities in schizophrenia. A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours, and genomic, especially GWAS, studies identified new schizophrenia loci related to oligodendrocyte genetic polymorphisms. It is known that myelin acts as electrical insulation for the ensheathed axon, which helps to preserve the amplitude and to increase the conduction velocity of the propagating axon potential. A growing body of evidence points towards the involvement of dysmyelination of the prefrontal cortex in the development of the cognitive symptoms of psychosis. Neuroimaging investigations have linked processing speed to brain anatomical connectivity, and have pointed the role of processing speed among the predictors of clinical changes in schizophrenia. The dysmyelination-induced delays in patients with psychosis may cause a discrepancy in sensory feedback mechanisms, which results in prediction error. The myelin abnormalities and the resulting conduction delays vary during the course of the multiple sclerosis and this type of cycles are possibly associated with fluctuations in conduction velocity in psychosis. It is worthy of note that the major histocompatibility complex (MHC) is responsible for the genetic overlap in both multiple sclerosis and schizophrenia. Multiple sclerosis manifests sensory and motor symptoms, and schizophrenia disordered cognition and emotion. Having in mind the interdependent relationship of oligodendrocytes and the axons they myelinate, we could suggest that both multiple sclerosis and schizophrenia may use in central nervous system a common pathway of disordered information-processing. Recent research suggests that adaptive myelination could normalize neuronal electrical excitability, which in turn can modify myelin plasticity, resulting to neural activity and behavior modulation. We may suggest that interventions that preserve white matter integrity or ameliorate white matter disruption may enhance information-processing and functional outcome in psychosis.

Key words: Schizophrenia, dysmyelination, information-processing, conduction velocity, processing speed.

Psychosis and cortical dysmyelination

Schizophrenia is a severe and chronic mental disorder that afflicts approximately 1% of the world's population. Typically, the age of onset is late adolescence to early adulthood, with a tendency for earlier occurrence in males. Clinical manifestations of the disorder display great heterogeneity ranging from positive, such as delusions or hallucinations, to negative symptoms, such as affective blunting, poverty of speech or lack of motivation. Other aspect of schizophrenia that has an impact on patients' life is the progressive emergence of neurocognitive dysfunction.[1]

The prefrontal cortex has a central role in cognition, by being the region that integrates highly processed information. A characteristic feature is its relatively slow maturation process, which is not complete until early adulthood, the age that marks the refinement of cognitive functions, such as reasoning and executive functioning. This timing also coincides with the onset of schizophrenia, suggesting that developmental abnormalities of the prefrontal cortex could contribute to the psychosis etiology. Many studies have demonstrated a correlation between the distortion of these maturational processes and the emergence of schizophrenia, leading to the hypothesis that schizophrenia is a disorder of the cortex.[2]

A recent review suggested that the neurological soft signs scores stay in between the low values characteristic for healthy controls and elevated values typical for patients with chronic schizophrenia, i.e., the subjects with an increased genetic vulnerability toward the disorder.[3] Neurological soft signs refer to changes in the whole motor system in particular a cerebello-thalamo-prefrontal network rather than to deficits in discrete cerebral sites.[4] Neuroimaging studies identified the sensorimotor cortices, the supplementary motor area, the basal ganglia, the thalamus and the cerebellum as important sites for neurological soft signs.[5] Moreover, neurological soft signs are associated with cognitive deficits ranging from attention/psychomotor speed and executive dysfunctions to complex neuropsychological abilities, such as logical memory, autobiographic episodic memory, and theory of mind.[6]

On the other hand, many neurodevelopmental models related to dysmyelination suggested its relation with different schizophrenia-like symptoms. Zhang et al,[7] suggested the myelination deficit in a phencyclidine-induced neurodevelopmental model of schizophrenia. Evidence suggests a critical role for dysmyelination in patients with schizophrenia. Intracortical myelination have been found reduced in patients with schizophrenia, while certain antipsychotic agents can restore this defect.[8] Post-mortem studies in patients with schizophrenia have reported 14–22% reduction in the density and the quantity of oligodendrocytes.[9]

Maternal immune activation induces changes in myelin and metabolic proteins, some of which can be prevented with risperidone in adolescence,[10] while abnormal expression of myelination genes is related with prenatal viral influenza infection in mice.[11] A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours.[12,13] Genomic, especially GWAS, studies identified new schizophrenia loci related to oligodendrocyte genetic polymorphisms.[14] The candidate marker for schizophrenia Neuregulin-1 is possibly related to oligodendrocyte dysfunction and defective myelination,[15] while several other myelin-related candidate genes have been linked oligodendrocyte and myelin dysfunction with neurocircuitry abnormalities in schizophrenia.[16]

Dizocilpine (also known as MK-801), a N-methyl-d-aspartate receptor [NMDAr] antagonist and pharmacological model of schizophrenia seem to affects the metabolic processes of oligodendrocytes rather than neurons *in vitro*.[17] Moreover, clozapine counters the metabolic effects of MK-801 and promotes glycolysis and myelin lipid synthesis in cultured oligodendrocytes.[18,19]

Information monitoring

The supervisory attentional system incorporates the prefrontal cortex as a core structure. Indeed, the prefrontal cortex seems to play a role in this system in various ways.[20] Both the visual perceptual process and visual mental imagery seem to stimulate similar neural networks, such as the primary visual cortex, the posterior parietal cortex, temporal areas and the dorsolateral prefrontal cortex. An important distinction arises in the fact that neural networks involved in imagery result to the triggering of top-down processes, whereas neural networks in perception are

associated with bottom-up processes.[21] Movement behavior begins with projections from the prefrontal cortex to the striatum, followed by the globus palidus and from there to the anteroventral and ventrolateral thalamic nuclei, which in turn project to the premotor area and the supplementary motor area and to the anterior cingulate.[22,23] Malfunction in any of these areas may lead to disorders such as Parkinson's disease, while the positive symptoms of schizophrenia have also been associated with a failure in monitoring movements, accounted for by deficits between premotor areas and the striatum. This is supported by the symptom of a sense of movement, as if controlled by external forces, in patients with metachromatic leukodystrophy, where the white matter connectivity of several cortical areas, and in particular the frontal cortex is upset.[24]

Cortical lesions and damage in the medial part of the mid-dorsolateral prefrontal cortex (BA 46 & 9/46) lead to deficits in tasks of the monitoring of information in working memory, where the capacity for an epoptic processing of information is evaluated, while the architectonic areas 46 & 9/46 of the prefrontal cortex appear to be linked with specific segments of the inferior parietal lobe through the superior longitudinal fasciculus. The inferior part of the posterior parietal cortex seems to be a crucial area for the updating of information in the working memory and the BA 46 & 9/46 encode it into an "abstract/symbolic form", in order to achieve the controlled monitoring in the active mnemonic process. This system has the capacity to hold symbolically coded information in an active state, in order to supervise the between them relation and their relation with the intended programmed behavior.[25]

Computer generated models on information-processing attempted to describe mechanisms through which the development of some symptoms takes place. The isolation of some computer parts led to several consequences, such as leading to conclusions irrelevant to the incoming data or the independent uncontrolled functioning of some parts. Applying these observations to cognitive contexts, Hoffman & McGlashan[26] hypothesized that if, for instance, some brain areas responsible for speech were isolated from the network of movement initiation, such as the supplementary motor area during the period of cortical pruning, the development of some form of subvocal speech would be possible perceived by the patient as independent of other intellectual processes and thus interpreted as a hallucination or as some thought deficit. A similar proposal was made by David in 1994,[27] who supported that the excessive neural activity between two brain areas, known as dysmodularity, provides a more accurate explanation for the pattern of cognitive deficits and neuroanatomical findings in patients with schizophrenia. This also presupposes the burdening of the cognitive system and reduced brain hemispheric asymmetry, as suggested by Crow in 1990.[28]

Saliency detection and error prediction

Patients with schizophrenia suffer from predictive coding impairments.[29] In the context of predictive coding, information-processing is updated every 50 ms and this time window is longer in patients, which suggests that updating is slower in patients with schizophrenia.[30,31] This displays a connectivity disorder, which account for disturbances in recurrent loops subtending the constant updating of information-processing and the detection of prediction errors.[32,33] Patients with schizophrenia display a disturbed ability to detect new and unexpected stimulus, and the amplitude of the EEG response to these stimulus is reduced.[34] This results in difficulties distinguishing between relevant and irrelevant information, causes patients to assign the wrong salience to events,[35] and possibly results in delusional beliefs.[36] All these difficulties may be explained in the context of predictive coding.[37]

Theories of self-monitoring and error-checking agree with the theory concerning the use of a salience network. According to Corlett et al,[38] there are two types of error prediction associated with schizophrenia and the development of delusional beliefs, playing opposite roles: one that overweights the prediction versus and one that underweights the prediction. The over-weighting of the prediction may be prioritized due to its pathogenetic nature, occurring first, and is followed by the under-weighting of the prediction, which bears as a result a state of fatigue and withdrawal. Neurobiologically, the hyperactivation of the salience network is likely followed by the hyper-activation of the default mode network and subsequently by the suppression of the salience and attention network. This initial hyper-

activation seems to be normalized by antipsychotics, since they dampen the salience of these abnormal experiences and by doing so permit the resolution of symptoms.[35]

Several studies have suggested that some prediction aspects are impaired in patients with schizophrenia.[29,39,40] They manifest a confusion at the initiation of the actions, and hence passivity experiences in the case of willed motor actions, and auditory hallucinations in the case of willed cognitions. Some studies have been shown that the dysmyelination-induced delays may cause a discrepancy in sensory feedback mechanisms, which may represent a prediction error and a phenomenological and neurophysiological salient event.[41] Extending this aspect, Whitford et al[42] suggested that passivity symptoms and auditory hallucinations could arise initially because of dysmyelination-induced conduction delays in the efference copies. The resultant increases in the phasic activity of midbrain dopaminergic neurons could amplify these symptoms and concurrently trigger additional psychotic symptoms. The authors concluded that on a phenomenological level, these prediction errors cause confusion, giving rise to passivity experiences and auditory hallucinations. On a neurophysiological level, these prediction errors give rise to a second cause of psychotic symptoms, by increasing the phasic activity of midbrain dopaminergic neurons.[42]

Myelination and conduction velocity

Myelin ensheath the axons of nearby neurons. Myelinated axons with similar destinations tend to bundle together into white matter fasciculi. The myelin acts as electrical insulation for the ensheathed axon, which both helps to preserve the amplitude and increase the conduction velocity of the propagating axon potential.[43] Myelinated axons typically have higher conduction velocities than unmyelinated axons of the same caliber and damage to the myelin can result in conduction delays in neural discharges. Such conduction delays might be expected to result in a temporal discoordination between the activities of spatially discrete populations of neurons.[42,44] The myelin abnormalities and the resulting implication in conduction delays vary in magnitude over the course of the multiple sclerosis and this possibility would be akin to the cycles of demyelination and remyelination often experienced by patients with multiple sclerosis.[45] These cycles have been shown to be associated with fluctuations in conduction velocity[46] and symptomatology, including psychotic symptomatology.[47,48] A similar idea has previously been proposed by Garver and colleagues (p. 49)[49] who suggested that the patients in their study may have experienced "compromised myelin integrity during psychosis with repair during remission".

Pharmacology studies suggest that dysfunction of neurotransmitters is one of the primary etiologies of schizophrenia, while antagonists or selective-agonists of dopamine, serotonin and/or glutamate receptors were developed and used as major antipsychotic drugs in clinical practice during recent years. Concerning the action of antipsychotic drugs on white matter, a recent neuroimaging study using diffusion tensor imaging (DTI) assessed the myelin integrity among normal control and acutely psychotic, drug-free patients with schizophrenia, before and after antipsychotic drugs treatment. It was found that a decrease of myelin integrity was partially restored in drug-responding schizophrenia patients, whereas the poorly responsive patients did not appear to be related to a disordered myelin.[49] Moreover, it seems that haloperidol and olanzapine stimulate proliferation but inhibit differentiation of oligodendrocytes via different molecular mechanisms. Quetiapine, however, is diametrically opposed to the above processes, although it targets the similar receptors as does olanzapine. Therefore, the improvement of myelin/oligodendrocyte dysfunction by antipsychotic drugs may not rely on canonical neurotransmitters but rather that cross-communication may exist through different molecular mechanisms.[50]

Dysmyelination and psychopathology

Waller et al in 2017[51] reviewed findings from 22 studies that examined the relationship between white-matter microstructure and antisocial behavior across development. They found that adult antisocial behavior was associated with greater diffusivity across a range of white-matter tracts, including the uncinate fasciculus, inferior fronto-occipital fasciculus, cingulum, corticospinal tract, thalamic radiations, and corpus callosum. The pattern of findings among

youth studies was inconclusive: both higher and lower diffusivity found across association, commissural, projection and thalamic tracts.

There is preliminary evidence for a role of lipid biology in the onset of psychosis, along with well-established evidence of its role in myelination of white matter tracts. Several lines of evidence suggest that polyunsaturated fatty acids (PUFAs) play a role in myelination, and there is substantial evidence documenting decreased PUFA concentrations in schizophrenia. Reviewing the relative studies, Vijayakumar et al[52] pointed that there is growing evidence of reduced polyunsaturated fatty acids (PUFA) concentration in ultra-high risk for psychosis (UHR) samples, highlighting the need for research to examine the relationship between PUFA and white matter integrity in high-risk samples and age-matched healthy controls. Peters et al[53] assessed in 30 male patients with a recent-onset psychotic disorder, erythrocyte membrane PUFA concentrations and diffusion tensor imaging was performed with voxelwise analysis. Membrane PUFA concentrations appeared to be robustly related to brain white matter integrity in early phase psychosis. The authors suggested the possible effects of PUFA supplementation on white matter integrity and associated symptomatology in early psychosis.

Patients with a deletion at chromosome 22q11.2 (22q11DS) have 30% lifetime risk of developing a psychosis, while people fulfilling clinical criteria for ultra-high risk (UHR) for psychosis have 30% risk of developing psychosis within 2 years.[54] Both high-risk groups show white-matter abnormalities in microstructure and volume compared to healthy controls, which have been related to psychotic symptoms. Bakker et al (2016)[54] found that UHR and 22q11DS patients share a susceptibility for developing psychosis yet were characterized by distinct patterns of white-matter alterations. While UHR patients were typified by signs suggestive of aberrant myelination, 22q11DS subjects showed signs suggestive of lower axonal integrity.

Fujino et al[55] found impaired empathic abilities and reduced white matter integrity in patients with schizophrenia. The patients showed a significant white matter fractional anisotropy (FA), a measure of white matter integrity, reduction in bilateral deep white matter in the frontal, temporal, parietal and occipital lobes, a large portion of the corpus callosum, and the corona radiata. The authors suggested that disrupted white matter integrity in these regions constitutes a pathology underpinning specific components of empathic disabilities in schizophrenia, highlighting that different aspects of empathic impairments in the disorder would have, at least partially, distinct neuropathological bases.

Summarizing, evidence implicate myelin and oligodendrocyte function as critical processes that could affect neuronal connectivity, which has been implicated as a central abnormality in schizophrenia. Phenocopies of schizophrenia with a known pathological basis involving demyelination or dysmyelination may offer insights into the biology of schizophrenia itself. While classical clinical-neuropathological correlations have established that disruption in myelination can produce a high fidelity phenocopy of psychosis similar to schizophrenia, the role of dysmyelination in schizophrenia remains controversial.[56]

Dysmyelination and cerebral communication in psychosis

Evidences suggest that the normal integration of cerebral communication may be compromised in schizophrenia and white matter abnormalities are integral to these functional deficits. Diffusion tensor imaging (DTI) is a neuroimaging technique which has increasingly been used to study white matter through quantitative indices of its structural and orientational characteristics. Identifying the white matter differences early in the course of schizophrenia may assist in prevention, early diagnosis and identification of treatment targets. Davis et al[57] found white matter changes and evidence for myelin-related dysfunction in schizophrenia. In schizophrenia patients it is possible an aberrant myelination of the frontal white matter fasciculi during periadolescent neurodevelopment causes. Several studies also have observed white matter abnormalities in patients with schizophrenia, either postmortem, with electron microscopy, or in vivo with structural MRI or DTI.[41,58–60] Especially, schizophrenia patients exhibit a range of myelin-specific abnormalities, including reduced numbers of oligodendrocytes or irregular myelin microstructure,[58,59] subnormal expression of myelin-related genes,[61] and irregularities in the nor-

mative processes of periadolescent myelination.[62] Abnormalities in the white matter fasciculi have been implicated in schizophrenia, particularly by disconnectivity theories that emphasize the role of abnormal interactions between brain regions in the etiology of psychosis.[63–65]

Samartzis et al[66] reviewed white matter integrity in the early stages of schizophrenia as inferred by DTI, in relation age, duration of illness and treatment. Although the pattern of white matter differences is not totally consistent frontal, fronto-temporal and fronto-limbic connections, with tracts including the superior longitudinal fasciculus, cingulum bundle, uncinate fasciculus and corpus callosum seem to be affected. The authors suggested that these differences may depend on the developmental stage of the subjects, the duration of illness and exposure to antipsychotic medication. Patients with bipolar disorder also showed lower fractional anisotropy than healthy controls in several white matter tracts. However, compared with schizophrenia patients, bipolar disorder patients showed lower fractional anisotropy in the cingulum, internal capsule, posterior corpus callosum, tapetum, and occipital white matter including posterior thalamic radiation and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus. The findings suggested that different pathophysiological mechanisms may underlie white matter microstructural abnormalities in bipolar disorder and schizophrenia.[67]

Dysmyelination and information-processing in psychosis

Neuroimaging investigations have also linked processing speed to brain anatomical connectivity. Sánchez et al[68] first pointed the role of processing speed among the predictors of longitudinal changes in schizophrenia. Individuals in the early stages of psychosis appear to have less consistent white matter as well as grey matter changes than chronic patients. There is also a 5-year period following the first psychotic episode, called the "critical period" by Birchwood and colleagues,[69] during which the most severe brain changes appear to occur. Karbasforoushan et al[70] found that white matter integrity of the corpus callosum, cingulum, superior and inferior frontal gyri, and precuneus was reduced in schizophrenia. The authors concluded that cognitive impairment in schizophrenia is mediated by reduced white matter integrity and that diffusion-weighted imaging (dMRI) are important in explaining deficits in the processing speed.

Mediation analyses and structural equation modeling were used by Kochunov et al[71] to analyze the associations among processing speed, working memory, and white matter microstructures. Their findings suggested that information-processing speed contributes to the association between white matter microstructure and working memory in schizophrenia. Moreover, the white matter impairment in schizophrenia was found to be regional tract-specific, particularly in tracts normally supporting processing speed performance. It should be noted that processing speed is a cognitive ability that could be defined as the time it takes a person to do a mental task. It is related to the speed in which a person can understand and react to the information they receive. Processing speed implies a greater ability to easily do simple or previously-learned tasks. This refers to the ability to automatically process information, which means processing information quickly and without doing it consciously.

White-matter alterations that occur in the early stages of psychosis may parallel the course of the illness and differentiate the clinical subtypes.[72] In their recent study, Griffa et al[73] suggested that inter-subject white matter variability in connections vulnerable to psychosis could mediate inter-subject variations in the processing speed. The study revealed an association between white matter-connectivity alterations and clinical stages in schizophrenia. These alterations were spatially diffused in the brain but they converged on a vulnerable subnetwork that spans frontal, inter-hemispheric, cortico-thalamic and striatal circuits. This vulnerable subnetwork includes the main brain-network hubs, namely, the superior frontal and superior parietal cortices, precuneus, insula and thalamus, which are implicated in schizophrenia pathophysiology. Moreover, within the subnetwork, the most significant effects have been found in the left hemisphere, in the superior parietal and frontal cortices, which are associated for developing psychosis,[74] and in the pars opercularis of the inferior frontal gyrus, a language area that, to-

gether with the Heschle's gyrus, has been related to auditory hallucinations[75] (figure 1).

Furthermore, we could suggest that both multiple sclerosis and schizophrenia may use in central nervous system a common pathway of disordered information-processing. Multiple sclerosis results in sensory and motor symptoms and schizophrenia in disordered cognition, perception, and emotion. The major histocompatibility complex (MHC) is responsible for the genetic overlap in both multiple sclerosis and schizophrenia, since a GWAS noted the involvement of similar HLA alleles in multiple sclerosis and schizophrenia.[76] In addition to the well-known demyelinating and dysmyelinating diseases such as multiple sclerosis, neuromyelitis optica, and the leukodystrophies, myelin deficits resulting from altered glial structure/function and or glial/neuronal interactions are seen in human psychiatric disorders[77] and developmental disorders including autism spectral disorder, sensory processing delay disorder, and attention deficit hyperactivity disorder.[78] Numerous studies have demonstrated an interdependent relationship of oligodendrocytes and the axons they myelinate. Moreover, adaptive myelination implies that

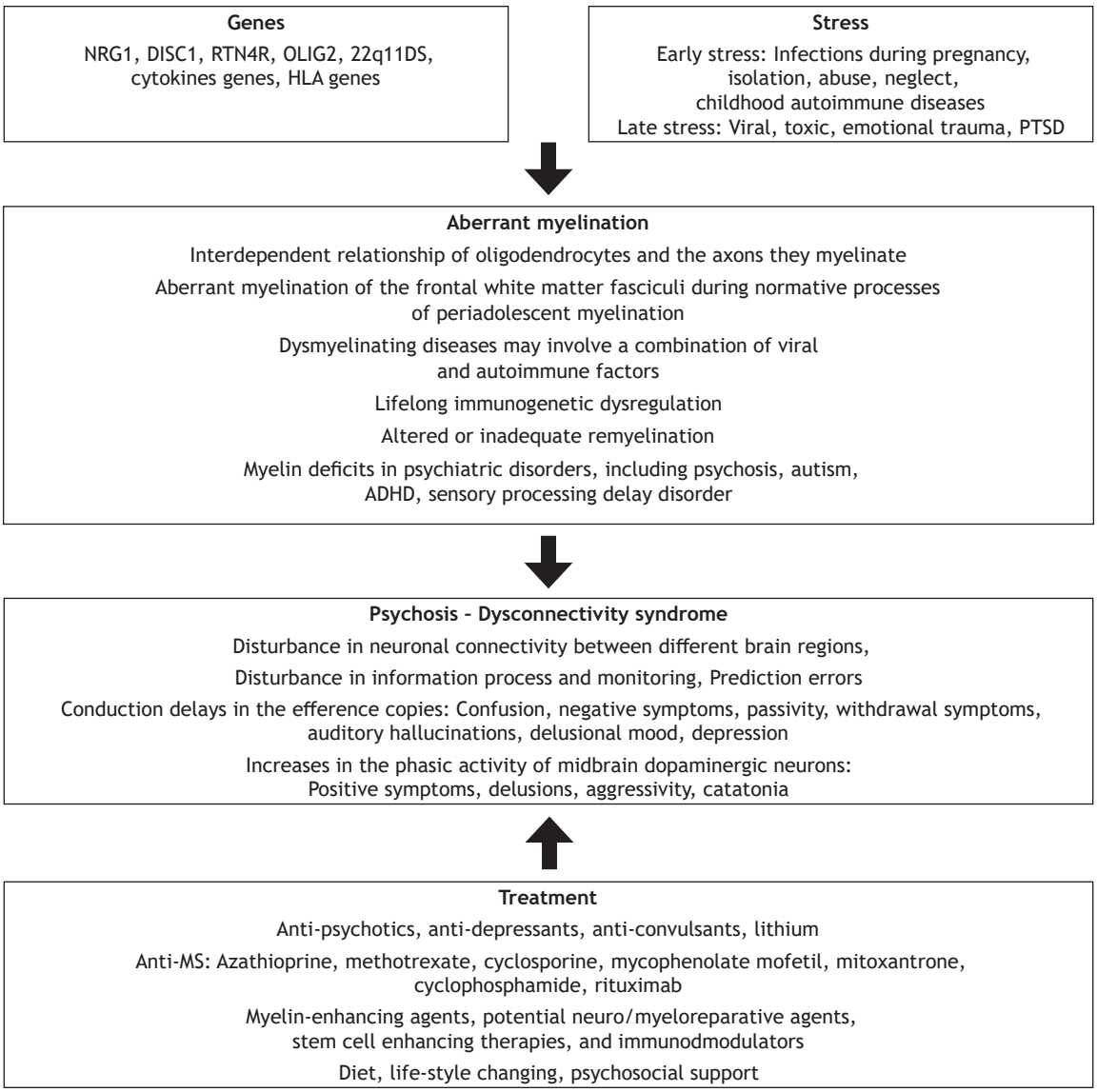

Figure 1. Dysmyelination, brain dysconnectivity, and the resulting information-processing disorder in psychosis.

neuronal electrical excitability modifies myelin plasticity and that myelin plasticity in turn feeds back to modulate neural activity and behavior.[79]

Conclusion

Summarizing, multiple lines of evidence now converge to implicate oligodendroglia and myelin in pathophysiology of schizophrenia. Neuroimaging investigations have linked processing speed to brain anatomical connectivity, and have pointed the role of processing speed among the predictors of longitudinal changes in schizophrenia. The dysmyelination-induced delays in patients with psychosis may cause a discrepancy in sensory feedback mechanisms, which may represent a prediction error and a salient event. A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours, while genomic, especially GWAS, studies identified new schizophrenia loci related to oligodendrocyte genetic polymorphisms. Palaniyappan et al[80] pointed the need to revise our current "deficit-oriented" models of neurobiology of psychosis to the concept of a dynamic process of cortical reorganization, suggesting that early deficits are temporally restricted to the first few years but ameliorate with time, probably owing to a reorganization process. Future studies that employ additional dMRI-techniques for white matter microstructural assessment could better characterize the neurobiological processes that underlie macro-scale connectivity alterations across psychosis stages. Establishing the neural basis of processing speed impairment may inform the treatment and etiology of schizophrenia and interventions that preserve white matter integrity or ameliorate white matter disruption may enhance information-processing and functional outcome in schizophrenia.[72,73,81,82]

Είναι η ψύχωση μια διαταραχή επεξεργασίας της πληροφορίας που σχετίζεται με δυσμυελίνωση;

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Πολλές έρευνες υποστηρίζουν την εμπλοκή της λειτουργίας της μυελίνης και των ολιγοδενδροκυττάρων στη νευρωνική συνδεσιμότητα, η οποία φαίνεται να αποτελεί κεντρικό παθολογικό στοιχείο της σχιζοφρένειας. Νευροαναπτυξιακά μοντέλα που περιλαμβάνουν τη δυσμυελίνωση, υποστηρίζουν τη σχέση της με διάφορα συμπτώματα της σχιζοφρένειας. Μεταθανάτιες έρευνες σε ασθενείς με σχιζοφρένεια αναφέρουν μείωση 14–22% της πυκνότητας και της ποιότητας των ολιγοδενδροκυττάρων. Αρκετά υποψήφια γονίδια που σχετίζονται με τη μυελίνη έχουν συνδεθεί με δυσλειτουργία της μυελίνης και των ολιγοδενδροκυττάρων στην εκδήλωση των νευρωνικών ανωμαλιών της ψύχωσης. Ένας αριθμός μοντέλων γονιδιακής σίγασης της μυελίνης σε ποντίκια υποδεικνύει σχιζοφρενικόμορφες συμπεριφορές, ενώ οι γενομικές έρευνες, ιδιαίτερα οι μελέτες GWAS, έχουν ταυτοποιήσει νέες γονιδιακές θέσεις για τη σχιζοφρένεια, οι οποίες σχετίζονται με γενετικούς πολυμορφισμούς που αφορούν στα ολιγοδενδροκύτταρα. Είναι γνωστό ότι η μυελίνη δρα ως ηλεκτρική μόνωση του επενδεδυμένου νευρώνα, γεγονός που βοηθά στη διατήρηση του εύρους δυναμικού αλλά και στην αύξηση της ταχύτητας αγωγής (conduction velocity) του διατρέχοντος δυναμικού στον νευράξονα. Υπάρχουν συνεχώς αυξανόμενες ενδείξεις σχετικά με την εμπλοκή της δυσμυελίνωσης στον προμετωπιαίο φλοιό την ανάπτυξη νοητικών συμπτωμάτων σε ασθενείς με ψύχωση. Οι νευροαπεικονιστικές έρευνες έχουν συνδέσει την ταχύτητα επεξεργασίας (processing speed) με την ανατομική συνδεσιμότητα (anatomical connectivity) του εγκεφάλου και έχουν αποδείξει τον ρόλο της ως προγνωστικό παράγοντα των κλινικών αλλαγών

στη σχιζοφρένεια. Αυτή η καθυστέρηση ταχύτητας επεξεργασίας στους ασθενείς με ψύχωση μπορεί να προκαλεί ανωμαλία στον μηχανισμό ανατροφοδότησης των αισθήσεων, γεγονός που καταλήγει σε σφάλμα πρόβλεψης (prediction error). Έχει φανεί ότι οι ανωμαλίες της μυελίνης και οι απορρέουσες καθυστερήσεις ταχύτητας επεξεργασίας ποικίλλουν στην πορεία της νόσου της πολλαπλής σκλήρυνσης (multiple sclerosis), και η μορφή αυτών των διακυμάνσεων συνδέεται πιθανόν με τη διακύμανση της συμπτωματολογίας στους ασθενείς με ψύχωση. Να σημειωθεί επίσης ότι το μείζον σύμπλεγμα ιστοσυμβατότητας (MHC) φάνηκε να παρουσιάζει γενετική αλληλεπικάλυψη στην πολλαπλή σκλήρυνση και τη σχιζοφρένεια. Η πολλαπλή σκλήρυνση εκδηλώνεται με αισθητικά και κινητικά συμπτώματα, ενώ η σχιζοφρένεια με νοητικές και συναισθηματικές διαταραχές. Έχοντας όμως υπόψη την αλληλοεξαρτώμενη σχέση μεταξύ ολιγοδενδροκυττάρων και νευρωνικών αξόνων, μπορούμε να υποθέσουμε ότι τόσο η πολλαπλή σκλήρυνση όσο και η σχιζοφρένεια έχουν στο κεντρικό νευρικό σύστημα ως κοινό τύπο διαταραχής την επεξεργασία της πληροφορίας (information processing disorders). Η πρόσφατη έρευνα υποστηρίζει ότι η προσαρμοστική μυελίνωση (adaptive myelination) μπορεί να ομαλοποιήσει τη νευρωνική ηλεκτρική διεγερσιμότητα, η οποία με τη σειρά της τροποποιεί τη μυελινική πλαστικότητα, γεγονός που καταλήγει σε τροποποίηση της νευρωνικής δραστηριότητας και συνεπώς της συμπεριφοράς. Μπορούμε λοιπόν να υποθέσουμε ότι παρεμβάσεις οι οποίες διατηρούν την ακεραιότητα της λευκής ουσίας ή επουλώνουν τις κατά τόπους ή κατά περιόδους διασπάσεις αυτής, θα είναι σε θέση να βελτιώσουν τη δυνατότητα επεξεργασίας της πληροφορίας και επομένως τη λειτουργικότητα στην ψύχωση.

Λέξεις ευρετηρίου: Σχιζοφρένεια, δυσμυελίνωση, επεξεργασία πληροφορίας, ταχύτητα αγωγής, ταχύτητα επεξεργασίας.

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Review
Ανασκόπηση

Aggravating factors and assessment tools for Posttraumatic Stress Disorder in children after hospitalization

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Posttraumatic stress disorder (PTSD) is a mental disorder caused by several distressing events that are related with psychotrauma. It is very frequent in childhood and untreated traumatic stress symptoms in children and adolescents often result in debilitating consequences on development with increased risks for a variety of physical and mental disorders. It has been found that PTSD symptoms are reduced as soon as therapeutic interventions have been applied. The aim of the present review was to summarize the available literature regarding aggravating factors associated with the development of PTSD in children after hospitalization and assessment tools for a quick and reliable screening of children who are at risk for developing PTSD. A review of published papers was conducted until April 10, 2019 to identify articles that discuss the aggravating factors and the assessment tools for PTSD in children after hospitalization published in English, German or Greek language. Search was performed on PubMed with the following combination of key-words: "PTSD" and "children" and "hospitalization", using the filters ''human'' and "Publication date from 30/11/2007 to 09/04/2019" and choosing "all fields'' in PubMed Advanced Search Builder. Of the 115 articles reviewed, 16 relevant articles were included, 10 of them referred to the aggravating factors and the remaining 6 were related to the assessment tools. Significant aggravating factors associated with the development of PTSD were: traumatic injuries and illness/medical-related hospital admission, previous health problems, Pediatric Intensive Care Unit (PICU) hospitalization, attendance at a hospital for child and adolescent psychiatry, female gender and psychotherapy and initial high Posttraumatic Stress Symptoms (PTSS) in parents. As for assessment tools, it was observed that the Child Trauma Screening Questionnaire (CTSQ)-Heart Rate (HR), the alternative PTSD algorithm (PTSD-AA), the Child Stress Disorders Checklist-Short Form (CSDC-SF), the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) model for PTSD symptom categories, the Posttraumatic Stress Disorder Semi-Structured Interview (PTSDSSI), the

Preschool Children's Assessment of Stress Scale (PCASS) and the diagnostic interview for children and adolescents (DICA-P) led to the identification of children who were likely to develope or had already developed PTSD symptoms, in the study population wherein each was implemented. The greatest limitation – but also a significant finding – of this review is the scarceness of published studies on this topic. Overall, there is a variety of aggravating factors associated with the development of PTSD in children after hospitalization. Assessment tools should be able to identify immediately the children who are likely to or have already developed PTSD symptoms.

Key words: PTSD, children, aggravating factors, assessment tools, hospitalization.

Introduction

Hospitalization has been associated with a variety of adverse psychological events in pediatric patients, including posttraumatic stress symptoms at both diagnostic (PTSD) and subsyndromal levels (posttraumatic stress symptoms: PTSS).[1,2] PTSD is associated with traumatic injuries or illness/medical-related hospital admission, with prevalence rates of clinically elevated levels of posttraumatic distress ranging from 6% to 45% following trauma such as falls and burns and 5 to 32% following medical-related hospital admission, such as cardiac surgery.[1,3] Moreover, factors related to the general experience of hospitalization, such as invasive medical procedures, lack of sleep and separation from parents may also be distressing and could lead to the development of PTSD.

It has been shown that untreated traumatic stress symptom in children may persist for years, even into adulthood, often having destructively consequences on their development.[4] For instance, PTSD has been associated with decreased total and cerebral brain volume and attenuated frontal lobe asymmetry.[5,6] Moreover, PTSD increases the risk for a variety of physical and mental disorders, including circulatory, endocrine, musculoskeletal and digestive diseases, substance abuse, eating disorders and depression.[7] Although there are many interventions that have been shown to significantly reduce PTSD symptoms in traumatized children, their effectiveness may be decreased as time from trauma exposure elapses.[8–10] This finding indicates a reasonable need for assessment tools that can accurately assess traumatic stress symptoms in at-risk children, immediately after the trauma exposure.

What is more, these assessment tools should be accessible to health professionals working in settings where injured or medically ill children are treated such as emergency rooms and medical inpatient units. Particularly, measures should (a) be short enough to be easily integrated into numerous acute clinical settings, (b) based on sources readily available and (c) require minimal training to administer and interpret.[11]

The purpose of the current review was to summarize the available literature regarding aggravating factors associated with the development of PTSD in children after hospitalization and assessment tools for a quick and reliable screening of children who are at risk for developing PTSD.

Material and method

A review of published papers was conducted until April 10, 2019 to identify articles that discuss the aggravating factors associated with the development of PTSD in children after hospitalization and assessment tools for screening the children who are at risk for developing PTSD. Search was performed on PubMed with the following combination of key-words: "Posttraumatic stress disorder" and "children" and "hospitalization'', using the filters "human'' and "Publication date from 30/11/2007 to 09/04/2019" and choosing "all fields'' in PubMed Advanced Search Builder. Studies were excluded if they:

- were case studies, editorials and letters to the editors;
- were not published in English, German and Greek language;
- did not refer to the aggravating factors and the assessment tools; or

- focused solely on parents and/or did not include findings on children.

All the articles were read and evaluated by two independent reviewers (CT, VM) in order to determine applicability for inclusion. Out of the 115 articles reviewed, 16 relevant articles were finally included in this review.

Results

Of the 16 studies reviewed, 10 referred to the aggravating factors[12–21] (table 1) and the remaining 6 were related to the assessment tools (table 2).

Aggravating factors

A comparison study[12] investigated and compared psychological responses in children 1 month after traumatic injuries or illness/medical-related hospital admission. This study concluded that clinically elevated PTSD symptom levels were more frequent in children admitted for traumatic injuries (18%) than illness/medical-related causes (4%) and there was a significant relationship (positive) between length of stay and the development of PTSD. Another study[13] examined the prevalence of PTSD in pediatric burn survivors who had been treated for acute stress disorder (ASD) symptoms during their initial hospitalization and compared them with patients who had been asymptomatic for ASD symptoms and found that the prevalence of PTSD was similar in children with ASD symptoms and those without ASD symptoms.

Moreover, according to Bruce et al,[14] greater endorsement of both monitoring and blunting attentional coping styles were significantly correlated with elevated PTSS in childhood brain tumor survivors (ß=0.24, p=0.01 and ß=0.18, p=0.02, respectively). Furthermore, a study[15] that explored the risk of PTSD development and PTSS in patients at a hospital for child and adolescent psychiatry and psychotherapy, came to the conclusion that almost one of four patients of child mental health service could be identified with clinically significant PTSS. A systematic review[16] examined the research literature on children's psychological responses to PICU hospitalization, showed that increased parental distress, length of PICU stay, delusional memories and emergency admission were possible aggravating factor for PTSD.

What is more, according to Landolt et al,[17] children with injuries had higher rates of PTSS than children with diabetes and cancer and initially high levels of PTSS in mothers and fathers were longitudinally related to poorer remission of PTSS in the child. A cohort study[18] concluded that the past health problems and sepsis were significant independent predictors of PTSS in children aged 5–16 years old admitted to intensive care with meningoencephalitis, sepsis and other critical illnesses ($p<0.04$).

Another study[19] showed that younger age, admission for traumatic injury and cognitive/affective factors including confusion, peritrauma panic, and sensory memory quality were associated with acute PTSS following PICU admission. Furthermore, Stowman et al[20] examined the potential mediators of later PTSS following PICU hospitalization and showed that youth acute stress disorder symptoms (ASDS), parent ASDS, youth anxiety, negative affect and hospital fear mediated later youth PTSS. Last but not least, a meta-analysis[21] concluded that the female children and adolescents who exposed to interpersonal traumatic injury are in particular risk of developing PTSD after traumatic injury.

Assessment tools

In 2010, a study[22] was published which (1) examined PTSD symptom structure in two samples of children (8 to 17 years of age) assessed an average of 6 months after unintentional injury: a combined dataset of 479 children assessed with a PTSD symptom checklist and a sample of 204 children assessed via a standardized clinical interview, (2) evaluated the fit of six alternative models for the factor structure of PTSS and the association of PTSS clusters with indicators of functional impairment and (3) evaluated three models for the structure of PTSD and depression symptoms jointly to examine specificity of PTSD versus general distress or mood symptoms.

The PTSD symptom checklist used in the first sample was the Child PTSD Symptom Scale (CPSS),[23] which is a 24-item self-report instrument that yields both a PTSD symptom severity score and a determi-

Table 1. Aggravating factors associated with the development of PTSD in children after hospitalization/

Authors	Objective	Sample	Results
Murray et al[12]	Investigation of psychological responses in children one month after traumatic injuries and illness/medical -related hospital admission	205 children (aged 7–16 years)	Clinically elevated PTSD symptom levels were more prevalent in children admitted for traumatic injuries (18%) than illness/medical reasons (4%)
Rosenberg et al[13]	Examination of the prevalence of PTSD in pediatric burn survivors	183 participants	The prevalence of PTSD was similar in children with and without ASD symptoms
Bruce et al[14]	the exploration of the relationship between objective illness parameters, parent–child interactions, coping styles and PTSS	62 brain tumour survivors (8 to16 years old)	Greater endorsement of both monitoring and blunting attentional coping styles were significantly correlated with elevated PTSS
Münzer et al[15]	Exploration of PTSS of patients attending a hospital for child and adolescent psychiatry and psychotherapy	413 children and adolescents at their first attendance at the clinic	Clinically relevant PTSS were reported in 22.9% of the children and adolescents
Rennick and Rashotte[16]	Children's psychological outcomes following PICU hospitalization	28 papers	Increased parental distress, length of PICU stay, delusional memories and emergency admission were possible aggravating factors for PTSD
Landolt et al[17]	Examination of the presence of PTSS and PTSD in children and the mutual influence of child and parental PTSS	287 children (aged 6.5–16 years), their mothers (n=239) and fathers (n=221)	Children with injuries had higher rates of PTSS than children with diabetes and cancer and initially high levels of PTSS in mothers and fathers were related to poorer recovery of PTSS in the child
Als et al[18]	Investigation of basal cortisol regulation in 5–16 years old children, 3–6 months following PICU admission	47 cases and 56 healthy controls	Past health problems and sepsis were significant independent predictors
Dow et al[19]	Association between premorbid, trauma, and cognitive/affective variables acute PTSS following PICU admission.	95 children aged 6–16 years	Younger age, admission for traumatic injury and cognitive/affective factors were associated with acute PTSS
Stowman et al[20]	Examination of potential mediators of later PTSS FOLLOWING PICU admission	50 youth aged 9–17 years	Youth ASDS, parent ASDS, youth anxiety, negative affect and hospital fear mediated later youth PTSS
Alisic et al[21]	Investigation of the incidence of PTSD in traumatic injury-exposed children and adolescents	72 peer-reviewed articles on 43 independent samples (n=3,563)	Female gender and interpersonal traumatic injury are significant aggravating factors

PTSD: Posttraumatic stress disorder, ASD: Acute stress disorder, PTSS: Posttraumatic stress symptoms, PICU: Pediatric intensive care unit, ASDS: Acute stress disorder symptoms

Table 2. Assessment tools for a quick and reliable screening of children who are at risk for developing PTSD.

Authors	Objective	Sample	Results
Kassam-Adams et al[22]	Examination of the factor structure of PTSS in children and adolescents who had experienced an acute single-incident trauma	Two samples of children (479 and 204 respectively. 8 to 17 years of age) assessed an average of 6 months after unintentional injury	The DSM-IV model for PTSS categories was a reasonable fit for these child data, but several alternative models fit equally well or better
Olsson et al[27]	Investigation of the utility of the CTSQ plus HR to identify children likely to develop PTSS at 1 and 6 months post-injury	79 children (aged 7–16 years	CTSQ-HR was better than the CTSQ or HR alone at identifying children likely to develop PTSS
Enlow et al[30]	The development of a user-friendly scale that measures traumatic stress responses in injured children.	147 children and adolescents (ages 6–18) hospitalized with burns or acute injuries	The CSDC-SF demonstrated test–retest reliability and predictive validity comparable to that of the full scale
Dow et al[32]	Exploration of PTSD in children and adolescents following PICU admission	59 children aged 6–16, admitted to PICU for at least 8 hours	The PTSD-AA was found to provide the most valid measure of PTSD at 6 months
Ari et al[35]	Assessment of the frequency and characteristics of symptoms of persistent psychological distress in children following surgery utilizing the PTSDSSI and the PCASS	Parents of 79 children (aged 1–6)	A significant portion of children suffer from psychological distress 3–5 months after hospitalization
Stoddard et al[38]	Evaluation of PTSD diagnosis and symptoms utilizing DICA-P module and the PTSDSSI	42 families	A high percentage of young children with burns manifested some PTSS one month after discharge.

PTSS: Posttraumatic stress symptoms, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, CTSQ: Child Trauma Screening Questionnaire, HR: Heart rate, CSDC-SF: Child Stress Disorders Checklist-Short Form, PTSD: Posttraumatic stress disorder PICU: Pediatric intensive care unit, PTSD-AA: Alternative PTSD algorithm, PTSDSSI: The PTSD Semi-Structured interview, PCASS: The Preschool Children's Assessment of Stress Scale, DICA-P: The diagnostic interview for children and adolescents

nation of PTSD diagnostic status. The first 17 CPSS items correspond to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) symptom criteria, rated on a four-point Likert scale ("not at all" to "five or more times a week"). The remaining seven items assess functional impairment from those symptoms, rated as absent or present. The CPSS has shown excellent internal consistency, test-retest reliability, and convergent validity with structured clinical interview measures of PTSD.[24] On the other hand, the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA)[25] was used in the second sample, which is a semi-structured interview that assesses DSM-IV diagnostic criteria for PTSD. Interviewers evaluate the frequency and intensity of each PTSD symptom as well as the impact of these symptoms on developmental, social, and scholastic functioning. Psychometric data indicate good internal consistency for each CAPS-CA subscale, and concurrent validity with other measures of PTSD. Regarding the DSM-IV Diagnostic criteria for PTSD,[26] they include a history of exposure to a traumatic event and symptoms from each of three symptom clusters: intrusive recollections, avoidant/numbing symptoms, and hyper-arousal symptoms, a fifth criterion concerned duration of symptoms and a sixth criterion stipulated that PTSD symptoms must cause significant distress or functional impairment.

This study concluded that the (DSM-IV) 3-factor model, that contains the factors: DSM-IV re-expe-

riencing symptoms, DSM-IV avoidance symptoms and DSM-IV arousal symptoms, fit reasonably well for these child data, but several alternative models [two four-factor models: the Numbing model that contains the factors: DSM-IV re-experiencing symptoms, effortful avoidance symptoms, emotional numbing symptoms and DSM-IV arousal symptoms, and separates effortful avoidance from emotional numbing, and the Dysphoria model which contains the factors: DSM-IV re-experiencing symptoms, effortful avoidance symptoms, dysphoria symptoms and arousal symptoms (startle/hypervigilance only), and separates PTSD-specific symptoms from general emotional distress] fit equally well or better suggesting improvements to the current diagnostic criteria for PTSD in children.

Another study[27] investigated the utility of combining the Child Trauma Screening Questionnaire (CTSQ)[28] and children's heart rate (HR) (HR was measured in emergency department and 24-h post-admission) to identify children likely to develop PTSS at 1 and 6 months post-injury. The CTSQ is a 10-item measure of child traumatic stress assessing five symptoms of re-experiencing and five symptoms of hyper-arousal. The CTSQ has been shown to have good convergent validity with the Children's Impact of Event Scale and to be predictive of PTSD at 1 and 6 months posttrauma.[25] The internal consistency was satisfactory.[28] Children are required to respond yes (scored 1) if they have experienced the symptom since the event or no (scored 0) if they have not. Scores ≥5 indicate a positive screen for trauma symptoms. Regarding HR, there might be an association between elevated HR and the development of PTSD due to the fact that during trauma, stress hormones are released which increase blood pressure and heart rate (HR) to prepare the individual's 'fight or flight' response in reaction to aversive stimuli.[29] In this study, it was found that a combination of the CTSQ plus HR (CTSQ-HR) was better than the CTSQ alone or HR alone at identifying children likely to develop PTSS.

Moreover, Enlow et al[30] carried out a study to develop a user-friendly scale that measures traumatic stress responses in injured children based on the Child Stress Disorders Checklist (CSDC),[31] a 36-item observer-report measure of traumatic stress symptoms. In this scale, the measure consists of one traumatic event item, five immediate response items and 30 symptom items. Each of the symptom items is rated on a three-point scale (0="not true," 1="somewhat true," 2="very true"). A prior examination of the CSDC, which included the burn participants, demonstrated reliability and validity of the symptomatology total score.[31] The researchers managed to create a four-item scale (CSDC-Short Form, CSDC-SF). The CSDC-SF contains the following items: ''child reports more physical complaints when reminded of the trauma (headache, stomachache, nausea, difficulty breathing, etc.)'', ''child avoids doing things that remind him or her of the trauma, child startles easily (for example, he or she jumps when hears sudden or loud noises)'' and ''child gets very upset if reminded of the trauma''. Moreover, it is very short and does not require specialized training for administration or interpretation and demonstrated test–retest reliability and predictive validity comparable to that of the full scale.

Furthermore, a cohort study[32] explored (1) the diagnosis of PTSD in children and adolescents following PICU admission (6 months post-discharge) and (2) the validity of the DSM-IV PTSD algorithm and alternative PTSD algorithm (PTSD-AA)[33] in school-aged children and adolescents. With regard to PTSD-AA,[33] it was developed by modifying DSM-IV PTSD symptom wordings, to make them more objective, behaviorally anchored, and developmentally sensitive to young children. This approach used DSM-IV criteria as a starting point, but modified the criteria and studied the effects of those modifications in a series of studies on young children. The major changes are a modification to lower the requirement for the C criterion (numbing and avoidance items) from three out of seven items to just one out of seven items and the omission of A2 (The person's response involved intense fear, helplessness, or horror). It was more reliable and more valid for diagnosing PTSD in infancy than DSM-IV criteria.[34]

The results of this study showed that the alternative PTSD algorithm (PTSD-AA) excluding Criterion C3 (inability to recall aspects of a trauma) provided the most valid measure of PTSD at 6 months. As for

the ability of each algorithm to identify children with functional impairment it was revealed that PTSD-AA was more sensitive than DSM-IV PTSD in identifying children with functional impairment and it was more diagnostically valid in school-aged children and adolescents, since the frequency of PTSD-AA diagnosis (n=17; 29%) was slightly higher than the frequency of DSM-IV PTSD diagnosis (n=15; 25%).

What is more, Ari et al[35] carried out a study to assess the frequency and characteristics of symptoms of persistent psychological distress in children following surgery, using two parent-report questionnaires that assess PTSS among children aged 1 to 6. The first one was The Posttraumatic Stress Disorder Semi-Structured Interview (PTSDSSI)[36] which is concerned with the child's response during and after the traumatic event and includes 29 items with an amount of agreement of 1 to 3 on a Likert scale. The internal consistency of PTSDSSI was good, and a strong correlation was found between PTSDSSI scores and the severity and number of symptoms found in a clinical interview several months later.[36] The second one was the Preschool Children's Assessment of Stress Scale (PCASS).[37] This measure is concerned with symptoms of anxiety, fear, sleep difficulties, mood changes, and developmental regression, and includes 29 items with an amount of agreement of 1 to 5 on a Likert scale. The internal consistency of PCASS was good.[37]

The responses to the PTSDSSI indicated that 10.39% of the children exhibit PTSS and that 28.6% of parents reported that the child's distress causes dysfunction and adjustment difficulties. The results on the PCASS emphasized the parents' concerns regarding the child's behavior, function and health following hospitalization, with a significant rise between the parents' reports of their conception of the child's state before and after surgery.

Last but not least, another study[38] investigated the prevalence of PTSD in young children hospitalized for burns 1 month after discharge, using both the diagnostic interview for children and adolescents (DICA-P)[39] module and the PTSDSSI.[36] The DICA-P addresses six symptoms clusters: meeting criteria for experiencing a traumatic event (A cluster), re-experiencing (B cluster), avoidance (C cluster), numbing/arousal (D cluster) and persistence of symptoms for over a month with clinically significant impairment (E and F, respectively). It has also been used extensively, including with samples of traumatized children and burn survivors and has demonstrated good reliability and validity.[40]

This study found that 4 of the 42 and 1 of 39 participants who completed the DICA-P and PTSDSSI respectively, met full criteria for a diagnosis of PTSD (10% and 3%, respectively). One more finding was that 27% of the subjects met partial criteria on the DICA-P versus the 16% on the PTSDSSI, without impairment. Finally, 67% of subjects met DICA-P criteria for the re-experiencing cluster and 54% met the PTSDSSI re-experiencing criteria.

Discussion

The aim of the present review was to identify and report the existing literature with respect to the aggravating factors and the assessment tools for PTSD in children after hospitalization. After extensive literature search using PubMed, 10 articles were found related to risk factors and 6 related to assessment tools. Regarding the aggravating factors, it was found that they do not only have to do with the cause of hospital admission (traumatic injuries or illness/medical-related), but also with factors related to the general experience of hospitalization. As for the assessment tools, there are tools that provide a quick and reliable screening of children who are in danger of or have already developed PTSD or PTSS. However, future research is required to improve the reliability and validity of the existing tools and make them more user-friendly.

Aggravating Factors

The results of the[10] studies showed that there is a variety of aggravating factors associated with the development of PTSD. Specifically, two studies[12,17] found that hospital admission because of traumatic injuries (e.g. falls, burns) lead to higher risk of developing PTSD than illness/medical-related hospital admission. This may be due to the fact that accidents are more immediate events going along with pain and emergency response that are experienced as frightening and distressing more directly by the child, independent of cognitive development, in

contrast to severe disease like cancer and diabetes where children do not completely understand the implication of their disease.

Furthermore, three studies[16,17,20] concluded that parental distress is a very important risk factor. A reason for this might be that the parents' own symptoms prevent them from adequately addressing the children's needs after the traumatic event. However, the children do not receive the protection of an optimal caretaking relationship. Another serious aggravating factor that all healthcare workers should take into account is the length of stay into the hospital and especially in PICU.[12,16] As length of stay increases, children's event related distress also increases for children admitted for traumatic injuries and illness/medical-related reasons. An additional aggravating factor worth to be analyzed is previous health problems.[18] Children who suffer from chronic diseases and mainly psychiatric illnesses or have been hospitalized in the past, are extremely susceptible to develop PTSD and the necessary measures should be taken to limit this risk.

Assessment tools

As for assessment tools, the six studies had some very interesting findings. In particular, in the study of Kassam-Adams et al,[22] although the DSM-IV factor structure received some support, the stronger support for the four-factor numbing model suggested the distinction between active and passive avoidance symptoms in our conceptualization of child and adolescent PTSD. The four-factor Dysphoria model provided a good fit and the Dysphoria model performed slightly better than the DSM-IV model and its fit was roughly comparable to that of the four factor Numbing model.

Moreover, one more interesting study[27] concluded that the CTSQ-HR was better than the CTSQ alone or HR alone at identifying children likely to develop PTSD symptoms suggesting that the CTSQ-HR screen may increase identification of children who are at risk to develop PTSD symptoms, enabling deployment of targeted prevention programs. Furthermore, Enlow et al[30] managed to create the CSDC-SF, a very short, reliable and valid measure that assesses risk for PTSD in youth following a medical trauma that was derived from the 36-item CSDC. It should be emphasized that the CSDC-SF, due to the ease use has potential for more widespread broad application and future studies should further explore the psychometric properties of this measure so that its validity in diverse settings among different populations may be established.

One more assessment tool that approved valid was the PTSD-AA excluding Criterion C3 which was used to identify children and adolescents following PICU admission who are in great danger of developing PTSD.[32] For one more time DSM-IV PTSD lagged in relation to other tools, as PTSD-AA found to be superior to DSM-IV PTSD in young children, was more diagnostically valid in older children and was more sensitive identifying children with functional impairment.

Last but not least, the results of Stoddard's et al study[38] may offer clues to current diagnoses of PTSD in young children, because PTSDSSI diagnosis is strongly linked to the diagnostic and statistical manual-5 (DSM-5) criteria for "PTSD in children 6 years and younger".

Limitations

Some limitations of this review should be acknowledged. The greatest limitation - but also significant finding - of this review is the scarceness of published studies on this topic. The participation rate was low in the majority of including studies leading to reduction of generalizability of the results of those studies. Accordingly, the generalization of the findings of the present review should be interpreted with caution.

Conclusions

This review concluded that there is a variety of aggravating factors associated with the development of PTSD in children after hospitalization that all the healthcare workers should know in order to take the necessary precautionary measures to reduce the risk of developing PTSD. Assessment tools should provide a quick and reliable screening to identify immediately the children who are likely to or have already developed PTSD or PTSS.

Επιβαρυντικοί παράγοντες και εργαλεία αξιολόγησης της Διαταραχής Μετατραυματικού Στρες στα παιδιά μετά από νοσηλεία

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Η Διαταραχή Μετατραυματικού Στρες (ΔΜΤΣ) είναι μια ψυχική διαταραχή, η οποία προκαλείται από ποικίλα συμβάντα που σχετίζονται με ψυχοτραυματισμό. Είναι πολύ συχνή στην παιδική ηλικία και η μη έγκαιρη αντιμετώπιση των συμπτωμάτων της ΔΜΤΣ σε παιδιά και εφήβους συχνά οδηγεί σε δυσμενείς συνέπειες για την ανάπτυξή τους, με αυξημένο κίνδυνο για ποικίλες σωματικές και ψυχικές διαταραχές. Πολλές μελέτες έχουν καταλήξει στο συμπέρασμα ότι τα συμπτώματα της ΔΜΤΣ υποχωρούν μόλις εφαρμοστούν οι κατάλληλες θεραπευτικές παρεμβάσεις. Ο σκοπός της παρούσας ανασκόπησης ήταν να συνοψίσει τη διαθέσιμη βιβλιογραφία σχετικά με τους επιβαρυντικούς παράγοντες που σχετίζονται με την ανάπτυξη της ΔΜΤΣ σε παιδιά μετά από νοσηλεία και των εργαλείων αξιολόγησης τα οποία συμβάλλουν στον γρήγορο και αξιόπιστο εντοπισμό των παιδιών που κινδυνεύουν να αναπτύξουν ΔΜΤΣ. Η βιβλιογραφική ανασκόπηση των δημοσιευμένων μελετών διεξήχθη μέχρι τις 10 Απριλίου του 2019 με σκοπό τον εντοπισμό δημοσιευμένων μελετών στην αγγλική, γερμανική ή ελληνική γλώσσα, οι οποίες αναφέρονται στους επιβαρυντικούς παράγοντες και στα εργαλεία αξιολόγησης της ΔΜΤΣ σε παιδιά μετά από νοσηλεία. Η αναζήτηση πραγματοποιήθηκε στη διεθνή ηλεκτρονική βάση δεδομένων PubMed με τον ακόλουθο συνδυασμό λέξεων-κλειδιών: «ΔΜΤΣ» και «παιδιά» και «νοσηλεία», χρησιμοποιώντας τα φίλτρα «άνθρωποι» και «Ημερομηνία δημοσίευσης των άρθρων από 30/11/2007 έως και 09/04/2019» και επιλέγοντας «όλα τα πεδία» στη μηχανή δημιουργίας σύνθετης αναζήτησης της PubMed. Από τα 115 άρθρα που ανασκοπήθηκαν, 16 σχετικά άρθρα συμπεριλήφθηκαν στην παρούσα μελέτη, από τα οποία 10 αναφέρονται στους επιβαρυντικούς παράγοντες και τα υπόλοιπα 6 αφορούσαν στα εργαλεία αξιολόγησης. Σημαντικοί επιβαρυντικοί παράγοντες που σχετίζονται με την ανάπτυξη της ΔΜΤΣ ήταν: η εισαγωγή στο νοσοκομείο που σχετίζεται με τραυματισμό ή παθολογική κατάσταση, το ιστορικό προβλημάτων υγείας, η νοσηλεία σε Μονάδα Εντατικής Θεραπείας Παιδιών, η νοσηλεία των παιδιών σε ψυχιατρική μονάδα παιδιών και εφήβων, το θηλυκό γένος και τα αρχικά έντονα συμπτώματα μετατραυματικού στρες στους γονείς. Όσον αφορά τα εργαλεία αξιολόγησης, παρατηρήθηκε ότι ο συνδυασμός του Ερωτηματολογίου Ελέγχου Τραύματος στα Παιδιά [Child Trauma Screening Questionnaire (CTSQ)] με την καρδιακή συχνότητα (CTSQ-HR), ο εναλλακτικός αλγόριθμος της ΔΜΤΣ [(alternative PTSD algorithm (PTSD-AA)], η Σύντομη Έκδοση της Κλίμακας Αξιολόγησης Διαταραχών Στρες στα Παιδιά [Child Stress Disorders Checklist-Short Form (CSDC-SF)], το Διαγνωστικό και Στατιστικό Εγχειρίδιο Ψυχικών Διαταραχών, Τέταρτη Έκδοση (DSM-IV) για τις κατηγορίες συμπτωμάτων της ΔΜΤΣ, η Ημιδομημένη Συνέντευξη για το ΔΜΤΣ [The Posttraumatic Stress Disorder Semistructured Interview (PTSDSSI)], η Κλίμακα Αξιολόγησης του Στρες Παιδιών Προσχολικής Ηλικίας [The Preschool Children's Assessment of Stress Scale (PCASS)] και η διαγνωστική συνέντευξη για παιδιά και εφήβους [the diagnostic interview for children and adolescents (DICA-P)] οδήγησαν στον εντοπισμό περισσότερων παιδιών που ήταν πιθανόν να αναπτύξουν ή έχουν ήδη αναπτύξει συμπτώματα ΔΜΤΣ στον εκάστοτε πληθυσμό που

εφαρμόστηκαν. Ο κυριότερος περιορισμός αλλά παράλληλα σημαντικό εύρημα της παρούσας ανασκόπησης είναι ο μικρός αριθμός δημοσιευμένων μελετών που αφορούν στο συγκεκριμένο θέμα. Συμπερασματικά, υπάρχει μια ποικιλία επιβαρυντικών παραγόντων που συνδέονται με την ανάπτυξη της ΔΜΤΣ στα παιδιά μετά από νοσηλεία. Τα εργαλεία αξιολόγησης θα πρέπει να είναι σε θέση να εντοπίζουν αμέσως τα παιδιά που ενδέχεται να έχουν ή έχουν ήδη αναπτύξει συμπτώματα ΔΜΤΣ.

Λέξεις ευρετηρίου: Διαταραχή Μετατραυματικού Στρες (ΔΜΤΣ), παιδιά, επιβαρυντικοί παράγοντες, εργαλεία αξιολόγησης, νοσηλεία.

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