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Adaptive Hyperactivity and Clinical and Laboratory Biomarker Search: The Case of Old Elders in the Blue Zone of Sardinia

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Abstract: Background/Objectives: Adaptive hyperactivity, characterized by increased activity levels and novelty-seeking traits without mood disorders, is prevalent among older adults in Sardinia's "blue zone," an area with high longevity. This study aims to evaluate the adaptive nature of hyperactivity concerning quality of life, social rhythms, and mood symptoms in individuals from this region, particularly among older adults over 80. Methods: This observational cross-sectional study included adults and older adults over 80 years from Sardinia's blue zone, recruited from the dermatology clinic at the University Hospital of Cagliari. Participants underwent psychiatric interviews and completed the Mood Disorder Questionnaire (MDQ), Patient Health Questionnaire (PHQ-9), SF-12, and Brief Social Rhythm Scale (BSRS). Data were compared with national and regional normative data. Results: Older adults in the blue zone demonstrated higher MDQ positivity (22.58%) compared to national averages (0.87%), without corresponding increases in dysregulated rhythms, depressive symptoms, or reduced quality of life. Younger elders (65-79 years) showed increased rhythm dysregulation (BSRS score: 20.64±7.02) compared to adults (17.40±6.09, p=0.040), but this trend was not observed in older elders (80+ years). No significant differences were found in CH3SH and (CH3)2S levels between groups. Conclusions: Hyperactivity observed in older adults from Sardinia's blue zone appears adaptive, not linked to social rhythm dysregulation, depressive symptoms, or diminished quality of life, suggesting resilience factors that may contribute to longevity. These findings support the potential classification of such hyperactivity as beneficial rather than pathological, warranting further research into biomarkers and psychoeducational interventions to prevent the onset of bipolar disorders in predisposed individuals.

Keywords: bipolar disorders; BD; laboratory medicine; applied biomedical technologies; bipolar spectrum; prevention; new technologies; hyperactive; blue zone; biomarker

1. Introduction

It has been found that older adults with hyperactivity and traits of novelty seeking, without mood disorders and a good level of social inclusion, show some genetic characteristics found commonly in bipolar disorders [1,2]. Starting from this evidence, attempts have been made to classify hyperactivity on a continuum from adaptive hyperactivity useful for overcoming challenging conditions [3], hyperactivity with stress and dysregulation of rhythms but without a precise psychiatric diagnosis ("DYMERS syndrome"), and, finally, pathological hyperactivity in the context of bipolar mania [4].

Another important aspect was the verification that the Mood Disorder Questionnaire, a tool created for the screening of bipolar disorder but considered not very accurate in recognizing cases diagnosed as bipolar disorder according to the current classifications [5–7], identified among the so-called "false positives" (i.e., positives without bipolar disorders) individuals with "non-pathological" hyperactivity but with traits of exploration and search for novelty [8], as in the case of migrants in Latin American megacities compared to the resident population in rural Europe [9,10], or people without a diagnosis of bipolar disorder but with dysregulation of rhythms, compromised quality of life or with DYMERS syndrome [11]. Thus, positives at M.D.Q. fell into a range from people with adaptive hyperactivity (i.e., hyperactivity well aimed at their own goals of life, with which they were satisfied) to people under stress. However, without a clear psychiatric diagnosis, stress manifested itself with dysregulation of social rhythms, symptoms of subthreshold anxiety-depression, and poor life satisfaction in people with frank bipolar disorder. In this study, the M.D.Q. is used to identify, in people without bipolar disorder, those who present traits of non-pathological hyperactivity [4].

This line of research began with hyperactive older adults. Perhaps it was inevitable since our group works in one of the so-called "blue zones". These are the five areas of the world where life expectancy is significantly higher than the world average. The study by Poulin et al. [12] found that central Sardinia is the area with the highest concentration of centenarians in the world. During this investigation, the researchers drew blue circles on a world map to identify the areas with the highest longevity, hence the term "blue zone." In addition to Sardinia, the "blue zones" identified were the island of Okinawa, Japan; Loma Linda, California, U.S.A.; the Nicoya Peninsula in Costa Rica; and, finally, the island of Icaria, Greece. That's why, for a group that deals with hyperactivity in Sardinia, it was inevitable to deal with the older adults. One of the causes of longevity in our blue zone is considered to be maintaining a high level of activity, even in leisure activities, despite the advancing years [13]. The present work aims to verify the state of hyperactivity concerning the evaluation of the quality of life, social rhythms, and mood symptoms (therefore evaluating the state of adaptivity) in a sample of people from the Sardinian blue zone with a strong representation of older adults and over-eighties, recruited as a control group for clinical research.

2. Methods

Design: Observational Cross-Sectional Study

Sample: The sample consists of controls recruited for a clinical study (Scano et al., in press) of people without a diagnosis of bipolar disorder according to DSM-5 [14] in order to verify the state of hyperactivity and well-being with particular attention to the elderly over 80 years of age. Recruitment was carried out on people who presented themselves to the dermatology clinic for routine examinations at the University Hospital of Cagliari over three days. After a detailed explanation of the objectives of the survey and the signing of the informed consent, the people who agreed to participate underwent a psychiatric interview and a general anamnesis and filled out the study instruments. The inclusion criteria for the control sample were age over 18 years without any exclusion by gender. In addition, for the specific interests of this study, we recruited people over 80 years of age from the central area of Sardinia (blue zone) on the same days and in the same outpatient dermatological facility.

Study tools: The hyperactivity level was measured using the Mood Disorder Questionnaire (M.D.Q.) [15]. The M.D.Q. was initially created as a screener for bipolar disorder. However, the

instrument's accuracy was poor, with the screening of an excess of false positives [5,6]. But, as mentioned above, recently, it was realized that the so-called false positives were people with traits of hyperactivity that fell into a range from people with adaptive hyperactivity (i.e., with hyperactivity well aimed at their own goals of life, with which they were satisfied) to people under stress. However, without a clear psychiatric diagnosis, stress manifests itself with dysregulation of social rhythms, symptoms of sub-threshold anxiety-depression, and poor life satisfaction in people with frank bipolar disorder [7]. In this study, the M.D.Q. is used to identify, in people without bipolar disorder, those who present traits of non-pathological hyperactivity [4].

The M.D.Q. includes items about behavior, mood, attitudes, and thoughts typical of bipolar disorder. A threshold for determining whether the proband has characteristics of the bipolar spectrum is to code positive for at least seven of the thirteen items on the questionnaire [4,16].

The measure of depressive symptoms (sub-threshold as the sample selection excluded those who had a lifetime psychiatric diagnosis) was the score obtained on the Items version of the Patient Health Questionnaire (PHQ9) [17,18] in the Italian version [19]. The overall score of the PHQ9 scale is the sum of the scores of each of the nine items of the tool. Each item inquires about one of the core symptoms useful for a diagnosis of a depressive episode according to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) [14]. Kroenke [17] found that a score higher than 9 identified people with clinically relevant features of depression. Due to the characteristics of our sample and the aims, we only compare the means of the scores between groups.

The SF-12 is a measure of perceived health-related quality of life. The instrument includes questions covering physical and mental health domains, investigating aspects of physical health and functioning, limitations in life due to physical and emotional health, presence of bodily pain, perception of general health, social functioning, vitality, and mental health [20]. The SF-12 has been used in various populations and countries with health and disease [21]. For this study, we use the comparison in total SF-12 scores and the presence in subgroups of the individuals below the mean and one standard deviation score of a representative sample of the Italian population [22,23].

The Brief Social Rhythm Scale (BSRS) [24] is a shortened and simplified tool derived from the Social Rhythm Metric (S.R.M.) [25]. BSRS aims to assess the (ir)regularity of activities in daily life (sleeping, eating, and having social contacts at work if people have a job and/or in leisure time). The tool consists of ten that inquired over the last week: a. Each Item/ activity is coded on a scale from 1 (maximum regularity) to 6 (maximum irregularity). Previous studies found that BSRS had excellent internal consistency in different languages. We adopted the Italian-validated version of the BSRS [26].

Analysis of VSCs: the breath of all subjects involved in this study was analyzed for three distinct sulfur volatile compounds (VSCs).The sampling was performed by inserting a sterile syringe up to the stopper into the oral cavity and holding the syringe between the front teeth, after the patient's lips were closed for 30 seconds, 1 mL of oral air was extracted. Following the draw, we promptly inserted the sample into the inlet of a portable gas chromatograph apparatus (Oral Chroma, ABI Medical, Abilit Corp., Osaka, Japan). After about eight minutes the amounts of: (i) Hydrogen Sulfide (H_2S), Methyl Mercaptan CH_3SH, and Dimethyl Sulfide $(CH_3)_2S$ were displayed by apparatus. An excessive amount of these metabolites proposes for a dysbiosis condition in the oral and gastric tissues. For example, oral dysbiosis was found to be more prevalent amongst subjects without regular habits, particularly patients with alimentary disorders or psychotic drug assumption, a condition often related with mood disorders [27].

Statistical Analysis: Data were collected anonymously using I.D. identification numbers. The ANOVA one-way measure was used to measure differences in mean and standard deviation scores of numerical data, and the Chi-square test (with Yates correction if needed) or Fisher's exact test was used to compare nominal data.

The scores at M.D.Q., SF-12, and PHQ9 of the study sample (subdivided into adults and elders) were compared with the mean and standard deviation of similar surveys concerning national M.D.Q. [8] and SF12 [23]) or regional samples [28].

Then, the scores of each subsample group (subdivided into "adults", "young elders", and "old elders") were compared according to all study tools.

The comparison of the frequency means scores at PHQ9, SF-12, and M.D.Q. positivity in our sample with the data of the general population could be conducted only considering the group of elderly people over 64 years of age because the frequency among old people is not reported among the results of the Italian study.

Ethical Aspects: Institutional Review Board Statement (IRB) approval was not required for this study because the data were de-identified and made available to the public.. The study was conducted according to the guidelines of the 1964 Helsinki Declaration. All the study participants signed a written informed consent form after receiving a detailed description of the study (aims, procedures, data protection), and they were aware of the possibility of terminating the study at any time.

3. Results

Table 1 illustrates the characteristics of the study sample divided into the sub-groups "adults" (18-64 years), young elders (65-79), old holders, the latter all coming from the blue zone (Central Sardinia). The three sub-samples do not present significant differences in distribution by sex despite a slightly lower presence of women in the sample of old holders, which, however, does not reach statistical significance. In the elderly population, the frequency of positives at M.D.Q. results (in the absence of psychiatric diagnoses) are significantly higher than the Italian normative average [22.58% vs. 0.87%, Chi-square, 1df=155.83, P<0.0001].

Table 1. Study Sample.

Item	Adults (N=33)	Young Olds (N=41)	Statistics	Old Olds from Blue Zone (N=21)
Age	13 (39.39%)	17 (41.46%)	Chi-square = 0.032 p=0.857	5 (23.80%)
Sex (Female)	43.41±18.77	72.59±8.73	ANOVA 1,72 df (Bonferroni) F=78.262 P<0.001	84.33±3.94

Table 2 compares the mean and standard deviation in the answer of the study sample (subdivided into adults and elders [>64 years old]) variable with available national (M.D.Q. and SF-12) or regional (PHQ9) normative data. The adult sample of the present study shows a frequency of depressive symptoms (PHQ9) and positive results on the M.D.Q. homogeneous concerning the normative reference samples. The frequency of SF12 scores is higher than the reference Italian population (36.14±5.28 vs. 38.61±6.33, ANOVA 1 way 1,653 df, with Bonferroni correction, F=4.954, P=0.026). The elderly in our sample are instead homogeneous to the normative samples concerning M.D.Q. and PHQ9 scores. In our study sample, no differences appear between the elderly and adults concerning the PHQ9 score, which aligns with what happens in the normative sample. The Italian normative sample shows adults a higher score on the SF-12 than the elderly (38.61±6.33 vs 34.32±7.20, ANOVA 1way, with Bonferroni correction, 1,2000 df; F=144.7; p<0.0001), but a similar difference does not emerge in our study sample where the SF-12 scores are homogeneous in the two age groups. The comparison of positive M.D.Q. results by age shows, in the normative sample, a lower frequency in the elderly compared to adults (0.87% vs. 3.57%, OR=0.24 CL95% 0.1-0.5) but in our sample, the ratio is inverted (22.58% vs. 6.06%, OR=4.52 CL95% 1.0-21.3).

Table 2. Comparison with normative data of the sample variables available national (M.D.Q. and SF-12) or regional (PHQ9) samples.

Item	Old (N=62)	Adults (N=33)	Statistics Old vs. Adults
SF12 Sample	33.41±6.06 (62)	36.14±5.28 (33)	ANOVA 1way (Bonferroni) 1,93 df; F=4.766; p=0.032
SF12 Italian	34.32±7.20 (379)	38.61±6.33 (1623)	ANOVA 1way (Bonferroni)

Community			1,2000 df; F=144.7; p<0.0001
Statistics Sample vs. Community	ANOVA 1,439 df (Bonferroni) F=0.887 P=0.347	ANOVA 1,653 df (Bonferroni) F=4.954 P=0.026	
MDQ+	14/62 (22.58%)	2/33 (6.06%)	Chi-square= 4.197 P=0.041 OR=4.52 CL95% (1.0-21.3)
M.D.Q. Italian Community	6/685 (0.87%)	97/2713 (3.57%)	Chi-square= 13.559 p<0.0001; OR=0.24; CL95% (0.1-0.5)
Statistics Sample vs. Community	Chi-square=155.83 p<0.0001	Chi-square=0.579 p=0.447	
PHQ9	4.01±3.50	3.49±2.89	ANOVA 1way (Bonferroni) 1,93 df; F=0.601, p=0.440
PHQ9 Italian Community	3.12±3.53 (190)	2.85±3.07 (530)	ANOVA 1,718 df (Bonferroni) F=0.997; p=0.318
	ANOVA 1,250 df (Bonferroni) F=2.984; p=0.088	ANOVA 1,261 df (Bonferroni) F=1.350; p=0.244	

Table 3 compares Oral Biomarkers (VSCs), well-being and/or impairment, and mood suffering within the sub-groups of the study sample. Once the sample of elderly people was divided into young elderly and older elderly people, it was noted that the positivity to the M.D.Q. increases in young adults compared to adults (but the difference does not reach statistical significance), the frequency is even higher in old elderly people, in this case, the difference compared to adults is statistically significant (28.57% vs. 6.45%, Fisher exact tests, P=0.031). In a specular opposite way, the BSRS score is higher in young, elderly people than in adults, indicating a dysregulation of rhythms (20.64±7.02 vs. 17.40± 6.09, ANOVA 1 way, 1.72 df with Bonferroni correction F=4.376, P=0.040) but the same score decreases in old elderly people, and no difference is detected with adults. A similar trend emerges from the frequency of people with an SF-12 score lower than the mean minus one standard deviation of the Italian normative value [22]; in this case, too, the frequency is higher among young-old people than among adults (31.70% vs. 12.1%, Fisher exact test, P=0.041). However, it decreased again with the old orders. In this case, any statistical significance is eliminated when comparing the scores of adults. The distribution of PHQ9 scores and volatile sulfur compounds in expired air do not show any statistically significant differences between groups; however, the distribution of $(CH_3)_2S$ shows a distribution profile between groups similar to that of the BSRS with an increase in young elderly and a decrease in old blue zone elderly.

Table 3. Comparison of Oral VSCs Biomarkers and/or impairment and mood suffering within sub-groups of the study sample.

Item	Adults N=33 (Pivot)	Young old >64; <80 N=41	ANOVA 1,72 df (Bonferroni)	Old Old ≥80 N=21	ANOVA 1,52 df (Bonferroni)
CH_3SH 24	14.98±15.33	12.52±9.67	F=0.707 P=0.404	12.7±14.57	F=0.480 P=0.491
$(CH_3)_2S$	15.61±23.64	24.13±31.26	F=1.677 P=0.199	18.95±25.52	F=0.241 P=0.626
BSRS	17.40±6.09	20.64±7.02	F=4.376 P=0.040	17.00±5.08	F=0.063 P=0.803
MDQ+	2 (6.45%)	8 (19.51%)	Fisher,	6 (28.57%)	Fisher,

			P=0.088		P=0.031
SF-12<31	4 (12.1%)	13 (31.70%)	Fisher P=0.041	5 (23.80%)	Fisher P=0.225
PHQ9	3.49±2.89	3.99±4.02	F=0.360 P=0.550	4.05±2.10	F=0.589 P=0.446

4. Discussion

Our study shows that a sample of old elders from the blue zone of Sardinia, the area with the highest density of centenarians in the world, have levels of hyperactivity, measured with the M.D.Q., paradoxically higher than those of the adults of the comparison sample the general trend is of a lowering of the score by increasing of age [22,23,29]. However, this high level of scoring and the increasing prevalence of positives do not correspond to the worsening in dysregulation of rhythms [30,31], the increase of the score on the PHQ9 (depressive symptoms) [32], and in volatile sulfides in the air breathed (Scano et al., in press), nor an impairment in the perception of quality of life and well-being as one would have expected in the case of an increase in the frequency of bipolar disorders [22,23,33].

The result of our study, therefore, supports the conclusion that hyperactivity identified in the old elderly from the Blue zone of Sardinia by a positive result to the M.D.Q. can be classified as adaptive. It is not associated with dysregulation of social rhythms as in the case of a positive result to the M.D.Q. in the so-called syndrome of dysregulation of social rhythms and disability [4,34] nor with an increase in "sub-threshold" depressive symptoms nor with a lowering of the perception of quality of life as often occurs in mania and mixed bipolar states also associated with M.D.Q. positivity.

The comparison of the frequency of M.D.Q. positivity in our sample in comparison with the data of the general Italian population could be conducted only considering the group of elderly people over 64 years of age, because the frequency among old older people is not reported among the results of the Italian study. Although this "dilutes" the frequency of our sample of old older people in that of the entire sample of elderly people, the result of the comparison is still exceptional; instead of a reduction of 1/4 of the risk of M.D.Q. positivity as found in the national sample, in the elderly people of our sample a risk of over four times, the frequency is observed even if the comparison with the markers clarifies that the highlighted condition is not at all pathological.

The result, therefore, indirectly confirms the theory according to which M.D.Q. positivity would define an area linked to the historical neo-Kraepelinian concept of the bipolar spectrum [35,36], which includes people with adaptive hyperactivity, syndromes of dysregulation of rhythms linked to chronic stress, and cases of frank bipolar pathology [4,34].

Despite the limitations of a small sample selected among those who had to undergo a routine dermatological visit, the study lays the foundation for future research studies on biomarkers of adaptive hyperactivity. This may have important consequences in the geriatric field and psychiatry in the prevention of bipolar disorder. The study of how hyperactive elderly people from the blue zone have addressed their hyperactive attitudes could, in fact, suggest important elements for developing psychoeducational training for the prevention of the onset of bipolar disorder in individuals with these "basic" characteristics.

A first element that must be underlined is the concomitance between hyperactivity (positive to the M.D.Q.) and good regulation of rhythms (such as sleep, eating, and meeting friends), which seems, in fact, to be the key element. In fact, both in the recently described DYMERS syndrome and in frank mania, a close relationship between suffering and dysregulation of rhythms emerges. Although now this element has a merely heuristic value, given the relevance in terms of public health, the study suggests verifying the link between adaptive hyperactivity and good regulation of biorhythms and social rhythms through the conduction of ad hoc studies better equipped in terms of samples examined and with robust methodologies adopted.

Other limits of the study are, firstly, that the study, given its preliminary nature, could not provide a truly representative sample of the general population of the blue zone and an adequate

control sample. Furthermore, the comparison of the frequency means scores at PHQ9, SF-12, and M.D.Q. positivity in our sample with the data of the general population could be conducted only considering the group of elderly people over 64 years of age because the frequency among old older people is not reported among the results of the Italian study. It can be considered that this "dilutes" the frequency of our sample of old older people in that of the entire sample of elderly people.

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