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Research

Children with Dyslexia - Special Language Impairment and Kinetic Skills

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Abstract

The present research aims to investigate the kinetic profile of Greek school children (6-12 years old) with Dyslexia & Specific Language Impairment (SLI) using the Movement Assessment Battery for Children, MABC-2, and tool as compared with children in formal education and assess any differences in kinetic profile among subgroups of such children. Participants were two groups of children of which 36 comprised the first group and were diagnosed, either by a Center for Differential Diagnosis, Diagnosis and Support (KE.D.D.Y.) or Psychodiagnostic Centers for Special Educational Needs, as children with Dyslexia & Specific Language Impairment (SLI) (average age: 112.05 months). The second group comprised 51 children of the same sex and age without any developmental disorder (average age: 114.55 months). The research was conducted individually at the Center for Differential Diagnosis, Diagnosis and Support (KE.D.D.Y.) Thessaloniki II, as well as in Primary and Secondary Schools in the Prefecture of Serres. Statistical analysis was performed by means of two-way analysis of variance (ANOVA) and the results established statistically significant differences in the general motor score of Movement Assessment Battery for Children (MABC-2) between the group of children with Dyslexia & Specific Language Impairment (SLI) and the group of children in formal education. In addition, ANOVA established significant differences in hand dexterity, ball skills and balance between the two groups of children with dyslexia & Specific Language Impairment (SLI) and the group of children in formal education. Further analysis established that no significant differences in the general motor score of the test were exhibited among children with Dyslexia & Specific Language Impairment (SLI). Specifically, the group of children with Dyslexia & SLI in our research exhibits Developmental coordination disorder (DCD) at a rate (44%) as opposed to children of typical development who exhibit a much lower percentage (12%). Even within the group of Dyslexia & SLI exhibits a DCD, a percentage of children exhibit a DCD risk (22%) while the remainder (33%) does not exhibit any difficulties. On the contrary, children of atypical development exhibit much lower rates, i.e. there is a DCD risk percentage (12%) and another (78%) exhibiting no DCD at all. Within this research framework, the view supported by the contemporary international literature that movement disorders often coexist with Specific Learning Difficulties is established.

Keywords: Kinetic coordination, developmental disorders, specific learning difficulties

INTRODUCTION

Movement provides people freedom, the right of choice and participation in simple and complex daily life activities. When movement suffers, then the involvement of children in activities both inside and outside of the school environment is seriously disturbed, with negative side effects on both physical and mental health [1].

Developmental Coordination Disorder Kinetic (DCD) is a disorder of which the percentage is growing constantly and is one of the most frequent to teachers of all levels within the school environment [2]. «Developmental coordination disorder is a situation where, given the age, children with normal mental and physical development and no apparent neurological disease have difficulties in carrying out culturally typical motor skills, including activities of daily life and school [3, 4].» For a specific description of the problem, there are difficulties because there is a clearly defined pattern of behavior. Children with DCD face lots of operational difficulties associated with movement skills, skills of playing, leisure activities and recreation. [5] The last 100 years, children who have difficulties in movement, is generally accepted those face growth problems as well [2]. Moving activity and coordination of movements are necessary functions for the total development and SLI of the individual. This is about features which are developing gradually, following the pace of gradual maturation of the nervous system and the conquest of sensory processing capacity (visual and tactile) stimuli [6].

The principle for the acquisition of movement skills is physical education [7]. The term movement skills refer to the development of moving control, the accuracy and correctness of execution of the basic and specialized movements. The gradual SLI of movement skills is crucial while insufficient development often leads children to frustration and failure during adolescence and adulthood [7]. The psychosocial and psycho-motor development of the child occurs through the participation in physical activities in the form of free play and active participation in organized sports activities. A fairly significant percentage of children experiencing moving disorders without any neurological, mental or musculoskeletal problems are characterized as children with physical awkwardness [8]. The moving clumsiness

today which is defined by the term Developmental Coordination Disorder Kinetic (DCD) is presented as a heterogeneous, having some of the children with difficulty only in fine moving skills, others having only rough moving skills, or others in both cases (9). The diagnosis is based primarily on moving skills tests (9). In order to diagnose if a child displays DCD, the numbers of the results must be outside the normal range, as set by the above procedure.

Children classified as «clumsy» fall into two broad categories [10]. Experts dealing with these children, rank in the first category those for which there is no apparent reason for their difficulties. These children do not have anatomical malformations; biochemical and sensory functions are normal, no neurological disorder marked and has a good mental level. Nevertheless, they face considerable difficulties in obtaining appropriate to their age, moving skills [10]. This category of children has attracted the interest of scientists in recent years both in the field of good assessment and on effective intervention. For the second category of children with disabilities, the moving clumsiness is a symptom of a medical disease or a psychological condition in which primary importance have the facts which are related to the organ that is diseased and as a result has the appearance of moving dysfunctions. In addition, in this category, there are children with hyperactivity, dyslexia, or specific speech problems. Another closer examination may reveal the moving coordination disorder as a minor problem (10). This kinetic disorder affects their daily life in a significant way and not due to a neurological disorder or delay of cognitive development (8). The recognition of this disorder is crucial. For someone who does not have the proper training, these difficulties are often interpreted as a result of immature behavior, laziness and lack of willingness to cooperate, as reported [11, 12]. Although in the past, researchers believed that children with DCD sometime would overcome these kinetic disorders, research has demonstrated that these problems remain both in adolescence and in adulthood [13]. Children with DCD fail to meet the environmental requirements while parents believe that the problem will be overcome as the child grows [14] highlighted that many difficulties at the age of six years remain even at 16. If DCD's difficulties accompanied by

socio-affective disorders, then it is more likely that the situation will remain after the end of the school life and studies have shown that the appearance of DCD at younger ages, it is very likely to lead to other learning difficulties [15, 16]. As time goes by, the reflections in science become more and more intense about the diagnosis and treatment of developmental disorders seen in childhood [17]. Researchers have shown that DCD coexists with learning difficulties as well as difficulties in articulation, the delay in language development and also with attention difficulties and social interaction [18].

Some children of formal development, on their entry into primary education, meet great difficulty with DCD and writing. These children are characterized by children with Specific Learning Difficulties (SLI) [18]. Some others systematically fail to perform simple every day moving skills at school or at home, that is a distinct developmental disorder in the assembly of their movement. Although often one of these characteristics prevails in relation to the other, the problem is rarely isolated. Most of the times children with Specific Learning Difficulties have difficulty in assembly of their movement to a greater or lesser extent. The kinetic disorder significantly affects their daily life and it is not due to a neurological disorder or delay of cognitive development [8]. The recognition of this disorder is crucial. For someone who does not have the proper training, these difficulties are often interpreted as a result of immature behavior, laziness and lack of willingness to cooperate, as reported [19] [12].

Research has shown that the frequency at which coincide Specific Learning Difficulties (SLI) and disturbances in moving coordination (DCD) is approximately 50% [20, 21, and 22]. In Greece, according to the results of a few studies, it has been confirmed that the phenomenon of impaired locomotor coordination occurs at a rate of 5-10% [23]. Also, very few studies in Greek bibliography have dealt so far with the coexistence of disorder of moving coordination and the Specific Learning Disorders, and as a result, there are not sufficient data for the Greek educational space [24].

The Specific Learning Difficulties are a heterogeneous group of disorders (National Joint Committee of Learning Difficulties / NJCLD, 1988). Both the way they occur and possible etiology

appear particularly differentiated to an SLI that is difficult to identify some common features for all children. «The Specific Learning Difficulties» (SLI) is a generalized term that describes a large group of diverse difficulties, which are manifested in a wide range of linguistic processes and refers to the operation and learning of speaking, DCD, writing, understanding DCD and writing and mathematics. Along with SLI problems of self-regulation of behavior, social perception and social interaction may coexist, which, however, do not identify a learning disability. Also SLI can occur simultaneously with other problems (eg functional impairment of consciousness, mental retardation, serious emotional disturbance) or with extrinsic influences (e.g. cultural differences, language deprived environment, insufficient or inadequate education), but it is not a result of these conditions or influences (National Joint Committee of Learning Difficulties / NJCLD, 1988). The above definition is the one the Joint National Committee on Learning Disabilities has formulated (National Joint Committee of Learning Difficulties / NJCLD) of the USA in 1988. It is considered vague and simultaneously the most concise definition relied on the wording of, all the contradiction about who can be regarded as SLI and who is not. The intrinsic nature of SLI must be emphasized which comes through the term «minimal brain dysfunction» [25] and is based on the assumption that there is a neurological dysfunction, thus excluding all those external factors that cannot be considered a cause for SLI such as family, economic, cultural, social problems. Note, of course, that it is possible the aforementioned factors to coexist and exert influence, but are not responsible for the appearance of SLI [26]. These problems are inherent to the person, deemed to exist because of the dysfunction of the central nervous system and may occur throughout [27].

The coexistence of SLI and particularly dyslexia and specific language impairment and DCD has been studied worldwide [21, 27, 28, 29, 30, 31, and 32]. More specifically, [33] on the results of the survey, highlights that children with DCD have problems in writing at 87%, in DCD at 70%, compared to typical development children (15% and 14% respectively). Concluded that if SLI accompanies DCD the difficulty encountered by these children in performing perceptual-moving skills is greater [34]. Accord-

ing to the researchers, the performance of children with DCD and SLI in moving skills, it was clearly lower than in groups who had only SLI or only DCD and moreover children SLI attributed significantly lower moving skills compared to their peers without SLI [35, 36]. Due to the reduced moving coordination, these children experience frustration at school, as well as in sports and recreational activities. Kinetic difficulties that children face, based on the theories of motivation, as the researchers claim, create kinetic syndrome clumsiness [37].

The coexistence SLI and DCD is a reality, so it would be important in our country to provide training to those involved in education and diagnosis of children and informing their families, aimed to early diagnosis and support of children. Early diagnosis could be strengthened with the appropriate supportive and therapeutic framework which would result in great improvement of the motor skills of children and change of the development of the disorder.

METHODOLOGY

Participants

The survey involved 36 schoolchildren aged 6-12 years from schools of Western Thessaloniki who have passed the diagnostic procedure of B' KEDDY of Thessaloniki and have been diagnosed with dyslexia or SLI. Out of the 36 children, 11 were diagnosed with dyslexia and 25 were diagnosed with SLI. Out of the 11 children with Dyslexia (Specific Disorder of Learning) the vast majority, 72.8% (8 children) belonged to the age group of 7-11 years. 27% (3 children) belonged to the age group of 3-6 years old, while there is not a representative sample for the age group of 12-16 years. Out of all the children with dyslexia and SLI, the vast majority, 60% (15 children) belonged to the age group of 7-11 year, 28% (7 children) belonged to the age group of 12-16 years, while 12 % (3 children) belonged to the age group of 3-6 years old.

The group of children with formal education consisted of 50 children with the same school age, from the typical population of Serres without developmental disorder in learning or motor

coordination. Out of all the children with formal development (50 children), 23 are boys (48%) and 27 are girls (52%). As far as the age groups concerns, children are allocated to the following percentages: the majority, 82% (32 children) belongs to ages of 7-11, 12% (8 children) at ages of 3-6, and the rest 6% (6 children) belongs to the age group of 12-16 years.

Data Collection Tool

As data collection tool to evaluate the motor performance of children was used the kinetic evaluation package «Movement Assessment Battery for Children» (MABC-2), [37] which has been created to detect disabilities and is the upgraded form of the Movement Assessment Battery for Children (MABC). This tool has been designed to identify and describe disorders in motor performance of children and adolescents of ages from 3 to 16 years. The MABC-2 consists of 3 parts: a) the kinetic assay which is applied individually and requires from each child to perform certain skills, b) a checklist which is completed by parents, teachers, psychologists and experts therapists, c) a Manual with instructions and interventions for children with disabilities. The kinetic assay MABC-2 [37] is an evaluation instrument based on norms. The norms of the upgraded version cover the ages between 3 to 16 years. The final score shows the level at which each child is, depending on its age. It consists of 32 exercises organized in four sets (eight exercises per set). Each set is addressed in one of the three age categories: Category 1 (ages 3-6), Category 2 (ages 7-11) and category 3 (ages 11-16). The characteristics of the exercises are the same for each category. We used exercises of all categories to evaluate the students. Depending on the performance of each exercise the child receives a corresponding motor score. The scores of exercises that constitute on the field of hand dexterity are summed up and give the final score for this sector. The same procedure is followed both for the ball and balance exercises. In the end, the scores of all three sectors are an SLI related and it gives the total motor score which may range from 0 (for a child with no difficulty) to 40 (for a child with severe difficulties in movement). The kinetic assay takes 20 to 30 minutes and depends on the age of the child, the SLI of the movement difficulties but also

the conditions under which the measurement is made.

A child, who has a total motor score of less than 10, shows no problem. A child who has a total motor score of 10 to 13.5, shows moderate difficulties, while a child who has a total motor score over than 14, indicates severe disabilities. The test has been designed to differentiate the children on the motor performance and the modulation levels are between 15 and the 5 (as the lowest percentage level). As a result of a child whose kinetic performance drops below the 15th percent position compared to the norms which are set for his age, is in a limited state, having some mobility problems. If the motor performance falls below the lowest 5th percent position is severely disabled. The reliability and validity of MABC are satisfactory and described in detail in the instruction book of the test [37].

In a survey in Greece [39] in a sample of 82 children who were measured three different times, found that the correlation coefficient between the measurements was satisfactory (ICC = .78), the fact that indicates a high SLI of reliability. Moreover, as far as validity concerns, an investigation in Greece (40), showed that the kinetic tests Movement Assessment Battery for Children-2 has good construct validity and displays a satisfactory level of reliability and internal consistency.

Data Collection Process

The data collection process took place in two ways: Firstly verbally or over the phone interviews with the parents of children who had received a diagnosis SLI or dyslexia by their near KEDDY, in order to ensure their consensus and acceptance for the participation of children in research. In case of agreement, the parents signed a solemn declaration of acceptance. In a second time, we held an individual evaluation of children's motor skills after an appointment with their parents on a specified time at KEDDY. Each student has been evaluated individually by the researcher in days and hours agreed with their parents. The exercises of the tests had been conducted in accordance with the manual instructions. Data collection for the standard population children occurred after personal contact, information and consultation with the Director of each school who expressed

the will to take part in research, the permission of the teachers' association and the written consent of the parents who wanted their children to participate in our survey. So the fitness rooms of each school had been suitably shaped, according to the instructions of the manual and we performed the kinetic evaluation of children.

Statistical analysis

For the statistical analysis of empirical research data, we originally used the descriptive statistics for calculating the percentage incidence of the disorder of motor coordination in children with dyslexia and SLI and distribution-differentiation of children in accordance with the norms of MABC-2 fields: fine mobility, ball skills, static and dynamic balance. Then, the analysis of variance has been used to detect any differences between the experimental and the control group in the general motor score of the MABC-2 motor test.

- Among the group of children with dyslexia and SLI and the group of children TE, the three areas of motor MABC (hand dexterity, ball skills, static and dynamic balance).
- Among the group of children with dyslexia and SLI and the group of children TE, the score motor test MABC-2
- Among children with dyslexia and children with SLI the score of the MABC-2 motor test. Differences at .05 were considered statistically significant

RESULTS

The study involved 36 children who had dyslexia and SLI from KEDDY and 51 children from formal education schools. The following results refer to the performance of both groups of children (dyslexia - SLI and children T.E.) in the MABC-2 kinetic test and the norms that provide the test.

Comparison of the two groups of children (dyslexia- SLI and T.E.children) to the subcategories of the MABC

The mean values in the three mobile areas of MABC were then investigated. The fluctuation analysis revealed statistically significant differences with respect to the individual kinetic sectors.

Table 1: Hand Skill, Ball Skills, Overall Performance

Performance / Pupils	Typical Performance	Dyslexia	SLI
	Performance	Performance	Performance
Handskill	19.82 (5.27)	16.54 (4.48)	17.28 (5.38)
Ballskills	32.98 (8.65)	22.09 (9.75)	22.28 (10.27)
Total	75.21 (14.06) _{a,b}	54.90 (17.60) ^a	58.40 (19.41) ^b

a= statistically significant differences between TE children and children with Dyslexia

b = statistically significant differences between TE children and children of SLI

The relationship between MABC-based ranking and learning difficulties (dyslexia-SLI).

In order to examine the relationship between the MABC ranking and the specific learning difficulty, the x2 test was applied. A total of two analyzes were made, the first one looking at the relationship between the group of children with dyslexia and the SLI in relation to the children of the typical population in the MABC-2 kinetic test score, while the second focuses on the relationship between groups of children with dyslexia with children with SLI in the MABC-2 kinetic test score.

Table 2: Comparison of Teenage Children and children with dyslexia - SLI.

	Normal	>15%	>5%
T.E.	38	9	4
dyslexia-SLI	12	6	18

Table 3: Comparison of the performance of children with Dyslexia & Special Linguistic Impairment (SLI) and Children of Standard Performance

MABC / Groups	studentswithDyslexia& SLI		Students with Typical Education (T.E.)	
	N	%	N	%
Standard Performance	12	33	39	79
At risk	8	22	6	12
SLI	16	44	6	12

In this Table, we observe that the comparison of the two groups reveals significant differences between children with dyslexia and SLI compared to standard development children. In particular, the group of children with dyslexia and SLI shows DCD (44%) as opposed to typical development children with a much lower percentage (12%). Still, dyslexia and SLI group have a percentage of children at risk of having DCD in the(22%) and the rest (33%) has no difficulty. In contrast, children in formal development have much lower rates, ie one (12%) is at risk of having DCD and a percentage (78%) does not show DCD and one (12%) is at risk

Results of comparing motor skills classification among children with Dyslexia and SLI.

Table 4: Comparison of children with dyslexia -SLI

	Normal	>15%	>5%
Dyslexia	9	9	18
S.L.I.	12	7	17

Table 5: Comparing Performance of Children with Dyslexia and Children with Special Language Impairment (SLI)

MABC/ groups	Students with Dyslexia		Students with SLI	
	N	%	N	%
Standard Perfor- mance	3	27	9	36
At risk	3	27	5	20
D.C.D.	5	45	11	44

As shown in the diagram above, which shows the comparison of the overall score among children with dyslexia and children with SLI we can see that the children of both teams with DCD and those in the risk zone do not differ significantly from each other. However, we can observe that children with dyslexia have a slightly higher percentage (27%) at risk of having DCD while children with SLI with a percentage (20%). Yet another percentage of children with SLI around (20%) do not seem to be at risk of having DCD in relation to children with dyslexia whose percentage reaches (27%). Children with dyslexia have (27%) the possibility of having no motoric difficulties, as opposed to children with SLI where their share reaches (36%).

DISCUSSION

This work was designed to investigate the motor profile of children with dyslexia and DCD (6-12 years old) by using the MABC-2 tool [37] in the Greek population and controlling the differences, if any, among the subgroups of these children. From the results of this research, it was realized that there is a large percentage of DCD existence children with dyslexia and

DCD (44%) confirming our initial hypothesis as assessed by the Movement Assessment Battery for Children (1992).

The results of this research on the incidence of motor problems at school showed that (24%) of them after their assessment with ABC-2 appeared to have mobility difficulties. Twelve percent of children were in the red zone with severe motor problems, while 12.0% were in the danger zone for the onset of the disorder. In the international literature, there are large fluctuations in the declared prevalence rates of the disorder. According to the American Psychiatric Society (APA), rates range from 5%-6% of the school population, while 10% -15% are likely to be in the risk zone according to [38].

A high percentage of 19%, however, was found in Greece in a survey [41], while a very small percentage was found [24], with only 1.6% of children being treated with ADHD of this research was found to be consistent with the above bibliographic references. The percentage of children in the risk zone seems to be consistent with the rates of the research, (2006)[38]. Therefore, the overall percentage and for the above reasons can be compared and agreed with other surveys. Further research seems to be necessary, with greater participation of children, where it will show exact percentages in the Greek territory.

The selection of the age of the participants was based on the fact that at this age there were significant changes in the development and improvement of the basic motor skills of children [42]. In such studies the sample was children with special learning difficulties, the age of the participants ranged from 5 to 12 years, confirming the age of the participants [42]. In addition, it is considered that if there is no interference until the age of 12 in order to reduce the mobility difficulties before the child's admission to adolescence, then any intervention may have no effect [40]. Of course, the sooner the diagnosis of the kinetic difficulties is made, the better the intervention and the treatment can be designed [21]. The sample of the group of children with dyslexia and S.L.I. was collected from an urban area while the children of the Department of SLI (T.E.) who took part in the survey came from urban semi-urban and rural areas. The socio-economic situation of the parents was not taken into account. In addition, none of the above factors affect the perfor-

mance of children [37].

A remarkable contribution of this research to the literature lies in the fact that children with dyslexia and DCD are examined as a group in relation to motor dexterity and not as separate subgroups as is the case in most investigations.

Regarding the first research question, the results of the study showed that children with dyslexia and SLI have a markedly higher percentage of motoric hardship than the typical population. «Poor motor skills very often coexist with dyslexia.»[43]

This has been reported since the 1930s when children with dyslexia were first characterized as motorically clumsy [43]. Dyslexia was thought to be related to problems in motor development and coordination. Children with dyslexia are characterized by «a difficulty in rough and thin mobility that is not in keeping with age and stage of development» [43] Previous research estimates that 60% of children with learning disabilities have DCD and other problems with motor skills[44, 21].

This has led to the question of whether poor motor skills and dyslexia are only a problem of co-morbidity, or whether both developmental disorders are simply caused by a generalization problem. However, the incidence of motor symptoms in groups of children with dyslexia is variable in many studies. The research found that in 59% of cases a kinetic problem was found in a group of 22 children with dyslexia aged between 8 and 12 years old[45, 21], in their research, found that 63% of children with DCD they also had dyslexia. This variability, however, may be related to the methods for evaluating these disorders.

At the same time, it is necessary not to generalize about the mobility difficulties experienced by children with SLI and to talk about specific difficulties in terms of rough and fine mobility.

In the case of children with DCD, it has been reported by different researchers that they usually have fewer motor skills in some areas than their typically developing peers [46, 47, 48], although in some areas there is a spectacular improvement in their performance if an intervention program of their motor skills is implemented[39, 30].

Some studies done using MABC, [49] have confirmed the above theories. Thus, although the research data is not much, it seems that the subgroups of children with DCD[39] may have difficulties in visual-spatial and motor skills, a finding that may require further detailed research [46] reports that children with SLI they resembled them with DCD. This percentage is consistent with the 50%, rate of coexistence of the two disorders, which they reached using the same measurement tool (MABC) and other researchers[21, 49].

The relationship between the SLI and motor problems should be examined with detailed descriptions and comparisons of these disorders. Taking into account the rates of occurrence of the SLI at 5-7% [50] and DCD in 6% (APA, 1994), and their increased incidence in other neurodevelopmental disorders, there is an urgent need for further understanding of the difficulties encountered in these disorders. A large number of this overlaps SLI the possibility of a single underlying reasoning.

In contrast, it has been appreciated that with regard to precision in motor skills, children with DCD[48,51]. Despite the difficulties associated with the research of neurodevelopmental disorders in relation to the development of motor skills, research to understand this relationship needs to be developed. In short, it is clear that motor dexterity is characteristic of children with dyslexia and SLI.

According to the above, our research confirms the results of other previous studies from the international literature and is particularly important for the evaluation and treatment of developmental disorders.

From the results of the research on the second research question, it was realized that school-age children with dyslexia and SLI are more likely to have motor problems than children in the typical population. These two disorders have been highlighted by many studies that they burden the development of children not only at the motor and learning levels but at social, emotional and academic levels[30].

From the comparisons between the two groups of children in our research, as far as the three individual areas of the test (hand skills, ball skills, and dynamic static balance) are con-

cerned, children with dyslexia and SLI recorded significantly lower performance. Compared with the children's TE group, the group of children with dyslexia and DCD had serious difficulties in hand skills, and in particular the ability to perform repetitive movements that required precision. Important difficulties were presented by the group of children with dyslexia and SLI in the ball skills and minimal in the static and dynamic balance.

The results of this work are consistent with previous studies [51,52,53] that children with dyslexia and SLI encountered significant problems in hand skills and balance skills, with hand skills as the most difficult sector, but there are also differences in literature research. Other research, of course, SLI that there was no difference in ballistic skills among the experimental and control [52, 53], and there was a statistically significant difference.

The weakness in skills that mainly concerned hand skills reveal that many children with dyslexia and DCD encounter significant difficulties in grapho-kinetic co-ordination, ie in writing, which means they have limited skill in the hands. This may have a direct impact on the academic development of the child, so appropriate and specialized intervention is required to improve their visual and emotional coordination. Early diagnosis of motor coordination disorders offers more opportunities for recognition, intervention and coping with both the disorder itself and specific learning difficulties.

Researchers report that there is no golden rule for the assessment of motor skills and extensions for recognizing the disorder of motor coordination [10]. Even weighted tools do not recognize the whole range of motor problems because the assessment uses limited skills but also why the quality of the movement is difficult to evaluate [11]. Another problem is that there is no agreement on how severe the disorder should be to qualify as a child with DCD[54].

The kinetic profile of children with dyslexia and special language in our third research question seems to be different from that of the children of the typical population. Thus, the percentage of children in the typical population who presented DCD

ranged in (12%) while children with dyslexia and DCD had a percentage (44%).

In a survey conducted in Greece [55], the results regarding the incidence of motor problems at school showed that (41.3%) of the children who participated after their assessment with MABC-2 appeared to have motoric difficulties. A proportion of 28.3% of the children was in the red zone with severe motor problems, while 13.0% were in the risk zone for the onset of the disorder.

In the international literature, there are also large fluctuations in the reported prevalence rates, while according to [38] a 10% -15% is likely to be in the risk zone. A high percentage of 19%, however, was found in Greece in a survey [39], while a very small percentage was found [24], with only 1.6% of children facing DCD. Perhaps a possible explanation, is the fact that the results of the assessment with Movement Assessment Battery for Children [37] for equilibrium skills as age grows, show unusually high scores, resulting in many children feeling motorically awkward because of their failure to do so[37].

This contrasts our own findings where, in the field of balance, no significant differences between the two groups of children were observed. An older survey conducted in our country in children aged 7-12 years, where the results showed that as the age of children grows, the more the difficulties in equilibrium skill in MABC [40].

The percentage of typical development children in our research who have DCD is 12%, as well as the percentage of children in the danger zone (12%). While children belonging to the typical development team are in (76%). On the contrary, the percentage of children in the risk zone seems to be in line with the rates from the [38]. From the group of children with dyslexia and DCD who participated in the present study, they exhibited kinetic behavior with severe motor problems (44%), while fewer children (22%) were found within the limits of motor coordination disorder.

The sample of the group of children with dyslexia and SLI was not homogeneous in terms of gender to see if the boys, according to some surveys, are the majority of children with ID[53].

Further research involving a larger number of children and covering the entire territory of Greece seems to be necessary. If motor problems are identified at an early age, parent educators and other specialists should be prepared for the possibility of gradual occurrence of other developmental disorders [53]. Therefore, the overall percentage and for the above reasons cannot be compared and agreed with other investigations.

The kinetic profile of the two groups of children, i.e. dyslexia and children with SLI in our fourth research question did not seem to differentiate between each of the three areas assessed (hand skills, ball skills, and dynamic static equilibrium). Thus, our rates show that children with dyslexia who have DCD they are (45%), they are at risk (27%), and without mobility difficulties they are (27%), and children with DCD who have SLI are (44%), at risk (20%), and without mobility difficulties (36%). These rates, of course, are much smaller than other surveys [55], where about 60% of pupils with special learning difficulties who participated in the research showed kinetic behavior with serious motor problems. On the contrary, the percentage (50%), the coexistence frequency of the two disturbances, and other researchers [56]. In our research, we did not examine the gender of the children involved because, unlike what they previously believed, kinetic clumsiness was more common in boys than in girls [25]. Current research data do not confirm [21, 30, and 53]. They believe that the previous view emerged from the boys' predominance among the experimental group participants because the boys' supremacy in sports activities was more.

From the results of this research, it was realized that there is a large percentage of SLI coexistence among children with dyslexia and children with SLI as assessed by the Movement Assessment Battery for Children [37]. Early diagnosis of motor coordination disorders offers more opportunities for recognition, intervention and coping with both the disorder itself and specific learning difficulties. The only guaranteed conclusion at present that we can export is that the difficulties of children with dyslexia and SLI not specifically related to language. Although the information that has so far is minimal and unclear, it is indicative of overlap, should not be treated as separate

disorders and should, therefore, be considered as being aware of the risk and knowing that linguistic delay is associated with mobility problems [46]. On the basis of the data considered, it is reasonable that while the underlying cause of these disorders is the same, the behavioral expressions of the disorders are different and are due to various factors, such as age, the severity of the disorder and brain development [43, 21]. Researchers report that there is no golden rule for the assessment of motor skills and extensions for recognizing the disorder of motor [10].

We, therefore, need far more time to understand the relationship between neurodevelopment language and movement disorders. After reviewing the literature and despite the fact that this review was not exhaustive, it can be seen clearly that there is considerable co-morbidity between dyslexia and the SLI and poor motor skills, as well as those kinetic difficulties in children with dyslexia and SLI, are similar to those seen in other neurodevelopment disorders, such as DCD.

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(Summer) Time for murder: Is there a link between increased temperature and homicides?

Research

(Summer) Time for murder: Is there a link between increased temperature and homicides?

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Abstract

A number of studies investigating the link between weather and homicides indicate that weather has an effect on the occurrence of murder. These studies argue that the weather and its changes can act as stressors, especially for individuals who are highly sensitive to stress and thus the weather can have both physiological and psychological effects on human behaviour. The aim of the present study is to examine the relationship between temperature (daily Tmean and Tmax) and the incidents of homicides in Central and Northern Greece. A total of 137 homicides were registered in the investigated area between 1995 and 2004. The results revealed that more than 30% of the registered homicides occurred on a day with a Tmean > 25° C and that about 45% of the registered homicides occurred on a day with a Tmax > 25° C while half of them were committed with a Tmax > 30° C. The results showed a higher correlation of the number of homicides with Tmax than with Tmin. Our findings are in accordance with other studies, which showed an association between crime and increased temperature, as well as with theories of criminality, according to which negative affect and violent acts increase as temperature rise.

Keywords: Homicides, temperature, summer, environment, mental health

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Introduction

A comparison between Greece and other European countries, as well as the US, revealed similar decreasing trends in the number of homicides [1]. According to the statistics of the Greek Police (www.astynomia.gr), in 2015 there was a 18% decrease of the reported homicides compared to 2014. More precisely, 86 homicide cases were recorded, out of which 16 were motivated by robbery. In addition, there were 169 homicide attempts, compared to 155 recorded in 2014 (increase of 9.03% in attempts). In 2016, further decrease in homicide cases was recorded by the Greek police (www.astynomia.gr) compared to 2015. There were 81 cases of homicides, out of which 9 were motivated by robbery and 132 homicide attempts were recorded (21,9% less than in 2015). The statistical data may not be entirely accurate and despite the technological progress (use of new statistical programs, full computerization in the work of authorities, electronic interconnection between authorities), there is still insufficient evidence with respect to crimes and perpetrators. Crime trends depend on the coverage and reports of authorities, measurement rules, redrafting of criminal provisions and criminalization and decriminalization of behaviour. Besides, the overall downward trend in the number of crimes against life in recent years in Greece is only one aspect of the criminality phenomenon, compared to intentional manslaughter, where there is a general trend upward trend [2].

Among the factors that affect the incidence of homicides, weather is of particular interest, due to the observed association between crime and temperature. Most homicides take place between 30° North to 30° South latitudes, and therefore in the warmest regions of the world [3]. Crime maps in the US presenting the amount of violent crime per capita by state confirm that in general the South is particularly violent with regards to murder, aggravated assault and property crimes, in contrast to the North [4]. A number of studies investigating the link between weather and homicides indicate that weather has an effect on the occurrence of murder. These studies argue that the weather and its changes can act as stressors, especially for individuals highly sensitive to stress. Thus, the weather can have both physiological and psychological effects on human behaviour [3]. According to Gary Becker's [5] **Canonical Model**

of Crime, individuals act in a rational way even when committing criminal acts, since they calculate costs and benefits. The benefits of their actions have to outweigh the costs, in order to be carried out. Therefore, the weather can be a predictor of crime, since it has an impact on its successful completion, as well as on the probability of being sanctioned afterwards [6]. According to the **Social Interaction Theory of Crime**, the commitment of a deviant act is influenced by social interactions taking place on a daily basis [7, 8]. Taken a step further, the conditions under which social interactions take place (e.g. weather) could lead to an increased crime rate. Anderson et al. (1995) [9] postulate in their **General Affective Aggression Model** that a person's arousal, state of affect and cognitions are determined by various personal and situational variables. In this model, temperature predicts violence in a steady and linear relationship [4]. The **Routine Activity Theory** of Cohen and Felson (1979) [10] states that a crime occurs if a suitable target is available, there is no guardian to prevent the crime and there is a motivated offender. According to this theory, during the warmer months people leave their homes to travel to public places. Within these places, the interactions with many others often lead to victimizations. This theory also considers the increase in violence as a linear function of increases in temperature [4]. Another theory relating temperature to violent acts is the **Negative Affect Escape Model** [11, 12]. According to this model, negative affect (feelings of irritation, annoyance, or discomfort) and violent acts increase as temperature rises, but this happens up to a certain inflection point. After reaching this point, there will be a decrease in violence as temperature increases because it will be more important for a person to escape the heat and engage in activities that reduce discomfort, instead of pursuing aggressive motives [13]. Therefore, this model hypothesizes a curvilinear relationship. The same holds true for the **Social Escape / Avoidance Theory** of Cohn et al. (2004) [14], which is closely related to the Negative Affect Escape Model. It argues that people will try to avoid conditions that could have negative affect as a consequence. Therefore, on days with extreme temperatures (both hot and cold) people will have less social interaction, which in turn leads to decreased opportunities for the occurrence of violent crime [13].

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Moreover, theories on external conditions argue that these can impact human judgment in a way that increases aggression and loss of control [15, 16]. In addition, the literature indicates that climatic conditions affect mental health conditions [17, 18]. A number of studies which have explored this link have not found a significant correlation between homicide rates and meteorological variables. The findings of Michael and Zumpe (1983) [19] did not indicate clear links between temperature and monthly number of homicides in different geographic locations of the US and neither did Maes et al (1993) [20], when they assessed the effect of weather variables on homicides levels. In a study conducted in Belgium for the period 1979-1987, Maes (1993) [21] reported significant seasonality in suicide but not in homicide [22]. Cheatwood (1995) [23] assessed the effect of the number of previous days (i.e. before a homicide) in a row in which the discomfort index (a combined measure of temperature and humidity used to analyze the relationship of heat and violence) has been over the physiologically relevant level over an 8-year span of time. He concluded that in all cases the variance explained was quite small [13]. The same insignificance for homicides was shown by the findings of Yan (2000) [24] on seasonality of suicides in Hong Kong. Rotton and Cohn (2003) [25] used cross-sectional and time series analyses and showed that temperature is associated to various violent crimes, such as assault or rape but the effect of temperature was not verified for cases of homicide. Nakaji et al (2004) [26] evaluated the seasonal changes in mortality rates from main causes of death in Japan (for the time period 1970–1999) and found that homicides were “*little or not at all influenced by seasonality*”. Similarly, Butke and Sheridan (2010) [13] analysed data between 1999 and 2004 for the city of Cleveland, Ohio and found that while higher temperatures are related to higher amounts of aggressive crime they do not have an effect on homicides. In addition, Talaei et al. (2014) [27] examined various meteorological elements (daily mean air temperature, minimum & maximum relative humidity, minimum & maximum daily air pressure) in the city of Mashhad, in the northeast of Iran, between March 2009 to February 2010 and their findings indicate that homicide and suicide rates do not correlate with any meteorological variables.

In contrast, other empirical results suggest that high temperature is related to increases in homicides, as well as the hit-and-run deaths in Tokyo [13]. Various studies support a linear relationship between temperature and violent crime [9]. DeFronzo (1984) [28] also found a significant relationship between homicide data and the number of ‘Hot Days’ in his study. According to the results of Harries and Standler (1988) [29] there is no curvilinear effect between temperature and aggression, even under conditions of extreme heat [3]. Anderson (1987) [9] showed that on hotter quarters of the year there was an increase in violent crimes. However, a number of studies suggest that there exists a curvilinear, inverted-U shaped relationship between temperature and crime [4]. It is therefore possible that after temperature reaches a threshold the behaviour changes and becomes less aggressive [22]. The findings of Cohn and Rotton (1997) [8] considering assaults and domestic violence in Minneapolis and assaults in Dallas indicate the existence of an inverted-U relationship [4]. The results of Jacob et al., (2007) [6] show an impact of short term weather changes on weekly or daily rates of criminal activity, however it was indicated that in the long run this correlation is not linear. A series of experiments conducted by Baron and Bell [12] in the 70s which examined the influence of high ambient temperature on aggressive behaviour showed a curvilinear relationship between aggression and heat. In their experiments they used two temperature conditions (34°C for heat and 23°C for <cool>) and two arousal conditions. The findings indicated that aggressive behaviour increases until the temperature reaches the threshold of 29°C, and then decreases. It was concluded that high ambient temperatures, particularly when other sources of irritation or discomfort coexist, may become so annoying that aggression is no longer being enhanced and can well be reduced. These results led to the conceptualization of the negative affect escape model. Anderson and Anderson et al (2000) [30] draw the attention to the fact that the indicated curvilinear effect could be an experimental artefact, since the temperature manipulations were extremely obvious to the subjects [3]. Similarly to Baron and Bell [12], a study by Gamble and Hess (2012) [4] examining the effects of temperature on violent crime in Dallas from 1993 to 1999 found a curvilinear relationship between daily mean temperature and daily rates

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of violent crime. Beyond the threshold of 26.6°C increases in temperature lead in rises in crime. Upon this threshold and for temperatures up to 32.2°C the relationship becomes negative. While the relationship between climatic conditions and homicides is of great interest, it has not been examined sufficiently. Having in mind the above data, the aim of the current study is to examine the association between temperature (daily T_{mean} and daily T_{max}) and homicide incidents (attempted and accomplished) in Central and Northern Greece. In Greece there is no previous study exploring results by region and/or frequency per time period (e.g. months or seasons).

Method

Temperature determines weather conditions and most studies which examine the relationship between weather and crime are based on the variability pattern of temperature. The temperature data (daily T_{mean} and daily T_{max} in Celsius degrees) were obtained from the European Climate Assessment & Dataset (ECA & D) [31] which "consists of daily station series obtained from climatological divisions of the National Meteorological and Hydrological Services and stations series maintained by observatories and research centres throughout Europe and the Mediterranean". Table 1 presents the data used for the purpose of this study and in Figure 1 the location of the meteorological stations is displayed.

Table 1: Temperature data for the time period 1995-2004

Region – Prefecture	T_{mean}	T_{max}
Epirus	Ioannina (1998-2004)	Ioannina (1998-2004)
	Corfu (1995-1998)	Corfu (1995-1998)

Western Macedonia	Kozani (1998-2004)	Kozani (1998-2004)
	Hellinikon (1995-1998)	Lamia (1995-1998)
Central Greece	Tanagra (2001-2004)	Tanagra (1995-2004)
	Agrinio (1998-2001)	
	Hellinikon (1995-1998)	
North Aegean	Samos (1995-2004)	Samos (1995-2004)
Larissa	Larissa (1995-2004)	Larissa (1995-2004)
Trikala	Larissa (1995-2004)	Larissa (1995-2004)

Figure 1: presents the location of the meteorological stations which are included in the ECA dataset.



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Not all meteorological stations in the investigated area could provide the required time period data and therefore some stations had to be combined. Although Lamia is located in the northern part of Central Greece it was included in the region of Western Macedonia. In addition, the area of Hellinicon which is not located within the investigated area was included in the Periphery of Central Greece and Western Macedonia. Since data from different stations were used, in some cases T_{mean} equals T_{max} (see Fig. 3).

Figure 2: Geographical coverage of available data

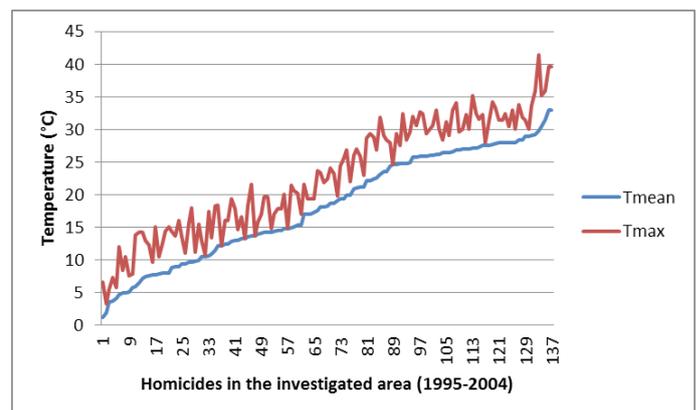


Data for homicides in the years between 1995 and 2004 were collected by the regional and local police departments and include both attempted and accomplished homicides. In the present study data from the regions of Epirus, Western Macedonia, Central Greece (Continental Greek Region) and North Aegean were analysed. In addition, data from the Prefectures of Larissa and Trikala (region of Thessaly) have been evaluated. The mentioned areas represent in total 16.5% of the Greek population (investigated area: 1.789.538 - total: 10.815.197) and 35.5% of the Greek geographical area (investigated area: 46.804 km² – total: 131.957 km²). Figure 2 presents the geographical coverage of the available data.

Results

A total of 137 homicides were registered in the investigated area between 1995 and 2004 ($M = 14$, $SD = 3$). The minimum number of homicides per year was 9 (in 1998) and the maximum was 17 (in the years 1999 and 2002). A monthly and a seasonal analysis were conducted. Linear and exponential regression analyses for the number of homicides within the selected temperature ranges were performed (intervals of 5°C or above a certain temperature value). The results show that 43 (31.4%) of the registered homicides occurred on a day when $T_{\text{mean}} > 25$ °C and that 61 (44.5%) were conducted on a day when $T_{\text{max}} > 25$ °C (31 of which when $T_{\text{max}} > 30$ °C).

Figure 3: Homicides in the investigated area and daily values of T_{mean} and T_{max}

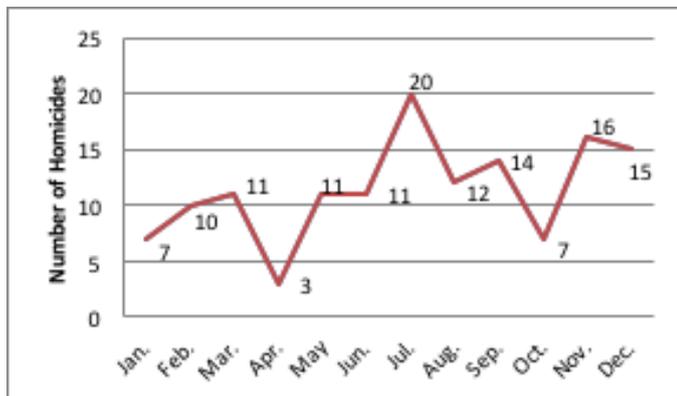


According to the monthly analysis, in the time period 1995 to 2004 only 3 homicides occurred in April (see Fig. 4), whereas 20 occurred in July ($M = 11$ per month, $SD = 5$). Although the highest number of homicides occurred in July, November and December follow as months with the highest number of homicides (16 and 15 respectively). The number of homicides for June and August (a month in which temperature reaches 35°C to 40°C) are close to the average with 11 and 12 homicides respectively. Spring is the only season during which the number of homicides per month is lower than the monthly average.

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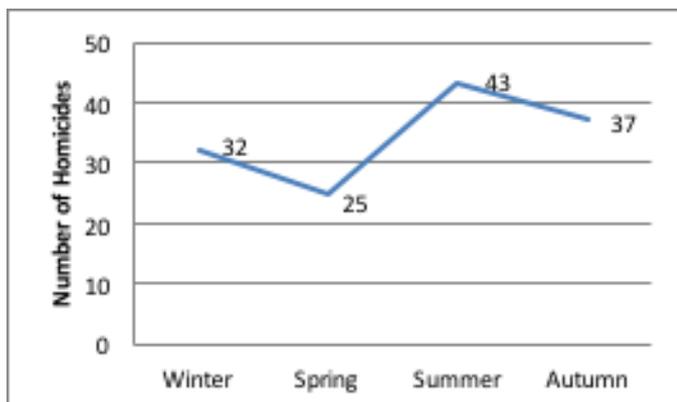
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Figure 4: Monthly analysis for homicides and temperature data (1995 – 2004)



The seasonal analysis (see Fig. 5) shows that most homicides occurred during summer (31%), followed by autumn (27%), winter (23%) and spring (18%). The number of homicides in the summer period is 72% higher than in the spring.

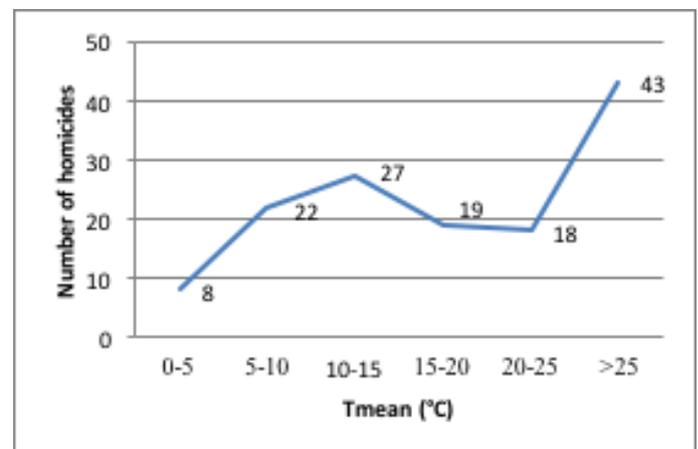
Figure 5: Seasonal analysis for homicides and temperature data (1995 – 2004)



Daily T_{mean} values for registered homicides ranged from 1.2 to 33.0°C. This range of daily mean temperature was divided into the six following groups: Group 1: 0 to < 5°C, Group 2: 5 to < 10°C, Group 3: 10 to < 20°C, Group 4: 15 to < 20°C, Group 5: 20 to < 25°C, Group 6: > 25°C. The number of homicides per temperature group for T_{mean} is presented in Figure 6. The lowest

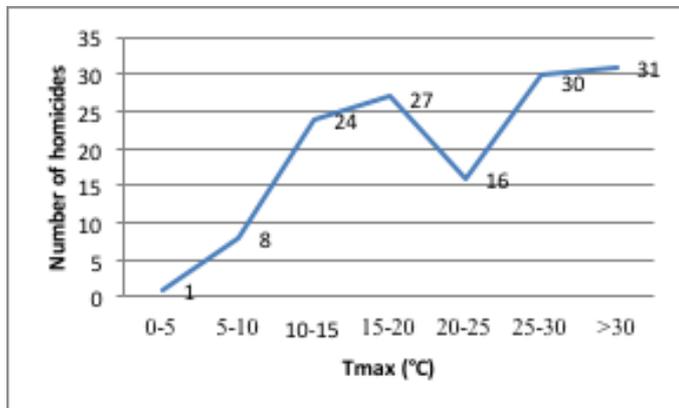
number of homicides (5.8%) occurred when the daily T_{mean} was lower than 5°C, while the highest number of homicides (31.4%) occurred when the daily T_{mean} was higher than 25°C. The number of homicides per temperature group for T_{mean} is rising between groups 1 and 3, is decreasing in the next two groups and is increasing again in the last group.

Figure 6: Number of homicides per temperature group (T_{mean})



Daily T_{max} values for registered homicides ranged from 3.2 to 41.4 °C. This spectrum of daily maximum temperature was divided into the seven following groups: Group 1: 0 to < 5°C, Group 2: 5 to < 10°C, Group 3: 10 to < 20°C, Group 4: 15 to < 20°C, Group 5: 20 to < 25°C, Group 6: 25 to < 30°C, Group 7: > 30°C. The number of homicides per temperature group for T_{max} is presented in Figure 7. The lowest number of homicides (0.01%) occurred when the daily T_{max} was lower than 5°C, while the highest number of homicides (22.6%) occurred when the daily T_{max} was higher than 30°C. The number of homicides per temperature group for T_{max} is rising between groups 1 and 4, decreasing in group 5 and finally increasing again in the last two groups.

Figure 7: Number of homicides per temperature range (T_{max})



The results of the linear and exponential regression analysis that were performed for the number of homicides per temperature group are presented in Table 2.

Table 2: Regression analyses of temperature range of reported homicides for years 1995–2004

Element	Analysis	b	R	R ²	R ² _{adj.}
T _{mean}	Linear	4.429	0.709	0.503	0.379
	Exponential	0.213	0.719	0.517	0.396
T _{max}	Linear	4.500	0.839	0.704	0.645
	Exponential	0.448	0.780	0.609	0.531

For T_{mean} in the linear regression R² = .503 and in the exponential regression R² = .517 and for T_{max} R² = .704 in the linear regression and R² = .609 in the exponential regression. In the linear regression analysis the value of b was similar for T_{mean} (b = 4.42) and T_{max} (b = 4.50). In contrast, in the exponential regression analysis for T_{mean} the value of b was much lower (b = .21) than the one for T_{max} (b = .44). The results indicate a stronger correlation of homicides with T_{max} than with T_{mean}.

Discussion

The present study indicates a stronger correlation of homicides with T_{max} than with T_{mean}. This finding is in accordance with the *Negative Affect Escape Model* [11, 12], according to which negative affect, such as feelings of irritation or discomfort, and violent acts increase as temperature rises. However, the findings of the monthly analysis, according to which most homicides occur in July, even though the warmest days usually include the first week of August, could indicate that there is a threshold of temperature beyond which aggression decreases. In our study only 2 homicides were reported at T_{mean} > 32°C. On the other hand, it could be possible that after the second week of August the temperatures begin to decrease. The different results of the studies indicating a linear or curvilinear relationship between weather and crime can be partly traced back to the different measurements. While a number of studies focus on the measurement of the short-term relationship between these variables using hourly, daily, or weekly microdata, other studies concentrate on the measurement of the same relationship by using aggregate annual data.

We found that most homicides occurred when T_{mean} was higher than 25°C and T_{max} was higher than 30°C and in addition most murders occurred in summer followed by autumn and therefore the results support *Routine Activity Theory* [10]. It is therefore likely that homicides in Central and Northern Greece occur mostly during vacations (i.e. summer / early autumn). If this explanation holds true, it would mean that the increased number of homicides in the summer and autumn is more strongly related to variations in people's activity patterns and the greater risk of victimization when being outside, than to changes in weather conditions. The findings of a study conducted by Copus and Laqueur [32] in 2014 showed that during large scale sporting events there was a decrease in crime rates in Chicago. According to the authors this drop can be traced back to the fact that people watch the games at home and that there are therefore less people in public spaces. The decrease in crimes of 25% in Chicago during the Super Bowl supported this view [32]. As the climate becomes warmer worldwide it is essential to conduct further studies on the relationship be-

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tween temperature and homicides, as well as on the question if this relationship is linear or curvilinear. In particular if the relationship is linear, substantial increases in homicides may be a consequence. This could impact law enforcement and its resources. In addition, the examination of this relationship could enable prediction and prevention activities [4]. There is an annual increase in temperature of about 0.4°C to 0.6°C since the 1990 in Greece. According to the Ministry of Environment, Energy and Climate Change (2014) this increase is mostly due to a steady rise of temperature during the summer period.

A limitation of our study is that we have not used microdata, as in the study by Jacob et al (2007) [6], which showed that crime rates are increasing during hot weeks. Moreover, we can suggest that the positive serial correlation in crime commonly reported is not an endogenous process driven by the optimization of offenders, but probably reflects persistence of unobserved factors that influence of criminal activity [6, 33]. The link between poverty, unemployment and economic downturns and increases in crime rates has long been the subject of social science study. For example, in our previous studies we examined if the recent financial crisis in Greece has coincided with an increase in crime, analyzing crime rates since the start of the financial crisis and over an extensive time period (7 years). Our results are in agreement with the results of previous broader studies as well as with criminological theories, according to which in times of economic stress an increase in both property crimes and violent crimes is expected [34, 35].

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Research

“ACTIVAGE project: European Multi Centric Large Scale Pilot on Smart Living Environments. Case Study of the GLOCAL evaluation framework in Central Greece”

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Abstract

ACTIVAGE Project is an initiative that has received funding from the European Union’s Horizon 2020 research and innovation program (grand agreement No.732679) and focuses in meeting the challenges posed by the ageing of the population via solutions entailing the use of the Internet of Things, a digital interconnection-based concept that will make it possible to make older persons safer, contributing to their staying independent and having an active social life, as well as reducing the negative impact involved in chronic disorders and degeneration.

It has the support of 49 organisations, 10 of which are industrial, 14 leading research institutes or universities, 11 major corporations plus 15 highly innovative small and medium-sized enterprises and is coordinated by Medtronic Ibérica co-funded from the European Union’s Horizon 2020 research and innovation programme"

This article mainly focuses in presenting the Central Greece use case and expected results as well as the multidimensional evaluation framework of the project “GLOCAL”.

Key-words: Ageing population, Active and Health Ageing , IoT services, quality of life, Health Related Quality of Life, Health Technology Assessment, GLOCAL evaluation framework, Open data base

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Introduction

Throughout Europe and all around the world, mortality rates have fallen significantly over the past decades leading to considerable changes in the age distribution of societies. In this context, people aged 60 are now expected to survive an additional 18.5 to 21.6 years and soon the world will have a higher number of older adults than children. This transformation is expected to continue, with the age group of elders (65+) growing from 18% to 28% of the EU population by the year 2060. Furthermore, according to the 2015 Ageing Report¹, one in three Europeans will be over 65 with a ratio of «working» to «inactive» population of 2 to 1, this representing a heavy impact on health and social care systems. Indeed, population ageing creates a common challenge for European countries as they must find ways to do more with less. Therefore, citizen empowerment and incitation to self-equip is one of the explored options.

ACTIVAGE Project is an initiative that has received funding from the European Union's Horizon 2020 research and innovation program (grand agreement No. 732679) and focuses in meeting the challenges posed by the ageing of the population via solutions entailing the use of the Internet of Things (IoT), a digital interconnection-based concept that will make it possible to make older persons safer, contributing to their staying independent and having an active social life, as well as reducing the negative impact involved in chronic disorders and degeneration.

This large-scale pilot scheme will be carried out for three and a half years actively involving nearly 10,000 older persons in seven different European Union countries. The pilot is implemented in Spain (Madrid), Italy, Greece (Attica, Central Greece and Macedonia), France (Grenoble), Germany (Woquaz, Region of Hessen), United Kingdom (Leeds) and Finland.

Nine different use cases that deal with the elderly everyday needs are deployed across Europe using the Internet of Things. Within the Use Cases focused on IoT supported independent living for elderly users, the Greek cluster is currently implementing 150 smart homes on Municipality of Metamorfosis, 150 smart homes on Municipality of Pylaia-Hortiati and 150

smart homes on the 10 Municipalities of Central Greece that are members of CitiesNet S.A.

Central Greece pilot mainly focuses in supporting elderly users in prevention of frailty. The main objectives are to promote the autonomy of the elderly living in their own homes by supporting demand driven solutions through high quality and yet sustainable welfare systems, to pursue Silver Economy policy initiatives, to allow the elderly to have a healthy and active everyday life while staying at home for as long as possible via a smart house service that offers better prevention, innovative home care services and community base solutions and finally to boost innovation by accelerating the development of ICT services.

The users involved in the pilot are elderly people (+65) that live alone, professional caregivers or relatives that have the role of the informal carers, health care providers e.g. service providers or health centers, smart living –AAL (Active and Assisted Living) ecosystem and integrated care in general.

The everyday needs are addressed via a number of services such as daily activity behavior monitoring at home for formal and informal carers' support and follow up, health tele-monitoring and tele-care services for increasing efficiency and fast response times as well as outdoor monitoring services to increase mobility and prevent social isolation.

All smart homes are using a number of sensors (motion Sensor, door/window sensor, panic button) that are installed to the elderly's home. All sensors send daily indications and/or alarms both to the ACTIVAGE platform that the appointed health personnel monitors as well as to the informal caregiver via an email service.

Methods

One of the most important objectives of ACTIVAGE is the implementation of a reference evaluation framework for Smart Living for aging well solutions. Particular attention has been dedicated to raise specific indicators related not only to QoL (Quality of Life), Economic, Acceptability and Usability but also

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to deployment scale and service model achieved during the pilots. The evaluation framework reports together with the analysis of enabling factors and potential barriers, will show the EVIDENCE to motivate the mobilization of the investment at public and private levels, not only in Europe but also world wide, in order to start the way for massive adoption of IoT solutions with a clear European leadership. ACTIVAGE does not reinvent methods and approaches but rather builds on top of existing best practices and experiences.

ACTIVAGE points out the importance for each partner to organize the Key Performance Indicators (KPIs) to be used to measure and evaluate outcomes of the piloting phase and to support the scaling up of ACTIVAGE LSP (Long-Scale Pilot).

This need will be covered through the ACTIVAGE “GLOCAL” evaluation framework. One key aspect of the ACTIVAGE approach is the multilayer and multi-dimensional evaluation strategy, which is able to catch and integrate Global and Local specific features (GLOCAL approach). Each pilot site will measure not only global indicators related to domain standard reference parameters able to contribute to demonstrate effectiveness of the implemented solution (impact on citizens’ QoL, sustainability, innovation), but also to local socio-economic indicators that will attract the mobilization of investment by public and private entities in each site according to the actual socio-economic context.

ACTIVAGE will apply different evaluation strategies in the different use cases in order to make an overall assessment that will allow to constitute a coherent and structured evaluation framework. On such basis it will be possible to properly correlate and compare outcomes of the same use case scenario implemented in different pilot sites and assess the relevance of global and local specific indicators.

The GLOCAL evaluation framework is based on three main evaluation categories referring to the main Triple Win indicators of the EIPonAHA: impact on QoL, Sustainability, Innovation & Growth. Every category is composed of sub-criteria focused on specific aspects. Both global and local indicators will be detailed in terms of measurement tool, target and reference methodology.

Finally, GLOCAL will seek synergies with MAFEIP, ASSIST) and MAST (Kidholm et al.,2012) evaluation frameworks².

The results and lessons that will derive from this evaluation framework will be communicated in the best possible way to various stakeholders via a global data-repository called “ACTIVAGE Evidence Open Data Base”: This repository has three different user interfaces (views) that access it:

The LSP-Dashboard: A user interface to be accessed by partners of the project in order to access in real time the information that is being captured by each deployment site.

The “ACTIVAGE Public Evidence website”: A user interface to be accessed openly by any person or professional interested in accessing the underlying ACTIVAGE Evidence Open Data Base. This tool is foreseen to remain active and available after project ends in order to offer a rich interface to the whole ACTIVAGE evidence.

The “AHA-ADVISOR”: An interface that will provide a reference web-based ICT multi modal platform for people interested to know about IT solution for aging well, with broad range of services and benefits in the domain of Smart Living and self-monitoring devices for aging well.

Results

The central Greek pilot has established a concrete evaluation schema when it comes in measuring the local KPIs. The ACTIVAGE smart home environment is evaluated (Table 1) in terms of impact on QoL and well-being (for both the elderly end user and the informal caregiver) and on sustainability, reliability, scalability, acceptability and innovation of the ACTIVAGE services.

There will be three evaluation periods (baseline, intermediate and final) during the one-year pilot and the evaluation tools used are the following:

CarerQoL-7D to measure the impact on quality of life of the caregiver³

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EQ5D-3L to measure the impact on quality of life of the elderly end user⁴

UT-AUT to evaluate the end user’s acceptance of the service⁵

Global Questionnaire which is a common evaluation tool designed for all 9 Deployment sites that will provide input on QoL and Acceptability of ACTIVAGE IoT platform by users

ADL and IADL to measure the end users’ level of independency on everyday chores^{6&7}

UEQ to measure the end users’ level of empowerment⁸

UCLA to measure the end users’ level of isolation and loneliness⁹

FES-1 to evaluate the end users fear of fall¹⁰

Decrease social isolation	Impact on QoL	UCLA LONELINESS SCALE
Increase the patient empowerment	Impact on QoL	User Experience Questionnaire (UEQ)
Enhancement of usability and acceptance of provided personalized services by the elderly	Sustainability	UT-AUT
Share of main users wanting to continue using service	Sustainability	Nr of implemented technologies/ services offered
Enable new IoT based services and increase the number of services provided to elderly people	Innovation	Number of IoT supported users
«Creation of business case for use of IoT solutions for healthy ageing»	Innovation	Business Plan
Global ACTIVAGE Questionnaire		Input on QoL and Acceptability of ACTIVAGE IoT platform by users
Reduce the fear of fall	Impact on QoL	FES-I

Table 1. “Central Greece ACTIVAGE Deployment Site KPIs”

Improvements in the elderly Health Related Quality of Life that are actively ageing, independent living via IoT supported services	Impact on QoL	EQ-5D- 3I
Independent Living of elderly via IoT supported services promoting AHA	Impact on QoL	User Experience Questionnaire (ADL & IADL)
Informal caregivers of elderly expected to experience a decrease in care burden and feel comfortable living of their elderly at home via IoT services	Impact on QoL	CarerQoI-7D

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So far 16 smart homes have been installed, thus 18 elderly end users and 12 relatives/informal caregivers have gone through baseline evaluation. All 150 smart homes are expected to be installed and in full operation in January 2019.

During this small pilot baseline evaluation, the following questionnaires were distributed:

CarerQoL-7D to measure the impact on quality of life of the caregiver

EQ5D-3L to measure the impact on quality of life of the elderly end user

Global Questionnaire which is a common evaluation tool designed for all 9 Deployment sites that will provide input on QoL and Acceptability of ACTIVAGE IoT platform by users

ADL and IADL to measure the end users' level of independency on everyday chores

UEQ to measure the end users' level of empowerment

UCLA to measure the end users' level of isolation and loneliness

FES-1 to evaluate the end users fear of fall

Discussion

The emergence of remote IoT telemedicine services has motivated the need in measuring the impact and evidence of the benefits of these relatively modern practices in the health sector. Some of them are focused on specific application domains (e.g. telemedicine), others are related to specific aspects (e.g. technology user acceptance, socio-economic impact). Apart from GLOCAL, other specific selected methodologies have been developed with relatively different focus (e.g. MAFEIP Monitoring and Assessment Framework for the European Innovation Partnership on Active and Healthy Ageing services (EIPonAHA) [11], ASSIST Assessment and Evaluation Tools for Telemedicine and MAST [2]).

These methodologies have proved their reliability and sci-

entific-based approach to help decision makers about future investments in the Smart Living and telemedicine domains, which have a strong parallelism with the IoT technologies for active and healthy ageing. For example, MAST has been already used in integrated care pilots with large number of users (BEYOND SILOS, SMARTCARE, MASTERMIND, RENEWING-HEALTH, etc.). MAST is very much focused in the assessment of the outcomes of telemedicine solutions, and may be more clinically oriented when compared to other contexts of IoT for ageing well.

Conclusions

ACTIVAGE mainly focuses in overcoming the fragmentation of vertically-oriented closed systems, architectures by investing towards open systems and integrated environments across different domains and creating a unified framework for the integration of different IoT technologies and AHA approaches.

During these 3,5 years project a variety of IoT technologies will be implemented in large scale pilots across Europe and evaluated in terms of their socio-economic, technological & business impact on a local and global level. Among these large-scale pilots, interoperability of different layers should be accomplished among various heterogeneous platforms so as to build local IoT ecosystems on top of legacy open or proprietary IoT platforms.

Lastly, the Global+Local (GLOCAL) evaluation framework is expected to help identify, measure, understand and predict the demands and real everyday needs of the elderly and promote market growth and sustainability of the final system.

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Special article

The mapping of women's physical attractiveness onto mate value: a proposed method of derivation

Antonios Vakirtzis

Abstract

Though female attractiveness is one of the most widely studied variables in the human mating literature, there has been no attempt to quantify its relation with female mate value. I propose that the possibility of mapping female attractiveness onto mate value in the form of a curve should be explored. The curve will differ for short and long-term mating contexts and across individual males. The area under each curve could be used as a concise and global measure of male choosiness. I suggest a possible method of empirically deriving this curve, whereby male participants make forced choices between sets of female stimuli.

Keywords: female attractiveness, mate value, short-term mating, long-term mating, mate choice.

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The mapping of women's physical attractiveness onto mate value: a proposed method of derivation

Introduction. Female attractiveness and male choice.

The centrality of female physical attractiveness in men's mating desires and choices can scarcely be exaggerated. Decades' worth of experimental, observational, sociological, cross-cultural and neuroscientific data support the thesis that attractiveness is generally the most important determinant of female mate value, and the primary consideration underlying men's choices (1-5). Indeed, physical attractiveness (both female and male) is by far the most studied and manipulated variable in contemporary mate choice studies (6-8).

To date the evolutionary psychological literature has approached the relationship between female attractiveness and mate value in a largely particularistic, contextual or piecemeal manner. Research questions are often framed as between-groups' comparisons of means, e.g. "how do two treatment groups of men x and y differ in regard to their preference for attractive female faces?" Alternatively, correlational designs are used to test for the relationship between the mate value men derive from women and some third variable, e.g. "what is the minimum level of female attractiveness that a man will settle for given systematic manipulation of independent variable z?" or something along those lines. Invaluable as such research clearly is, there has been to my knowledge no attempt to quantify the relationship between the various levels of female attractiveness and the mate value these provide to men, stripped of complicating factors and third variables. By "quantify" I simply mean treating mate value as a function of female attractiveness, and attempting to derive this function.

But is it reasonable to even attempt this, to start putting numbers on women's mate value? Can we possibly hope to treat mate value as a scalar quantity and start making statements to the effect that, say, the mate value of one woman in the top percentile of female attractiveness equals that of ten women in the twentieth percentile? Only empirical research can eventually settle the matter, but a task analysis of the human motivational system by Tooby, Cosmides and Barrett suggests this is almost an inevitability:

"In order to make choices in a way that usually promotes fitness, our [psychological] architectures need to be able to discriminate alternative courses of action on the basis of computed indices of their probable fitness consequences. To serve this purpose, the minimum valuation-proprietary form of content is therefore a form of representational tagging with computed scalar utilities (or their equivalent) assigned to whatever representational parsing there is of goals, plans, situations, outcomes or experiences [...] Although the motivational system is far richer than just a utility computing system, we know this unidimensional neural currency must exist as one aspect of the motivational system, or the system could not be designed to make mutually exclusive choices nonreflexively in a way that tracked higher fitness payoffs. *This form of payoff representation must be scalar so that magnitudes can be ordered, and should in addition have properties of a ratio scale so the computational system can arbitrate competing goals under different probability distributions.*" (9:320; emphasis added).

Viewed this way, mate value would simply be one expression of this "unidimensional neural currency". And just as this mate value would need to be compared against the value derived from other resources (unrelated to mating), so too must the value derived from different individual women be directly comparable to each other.

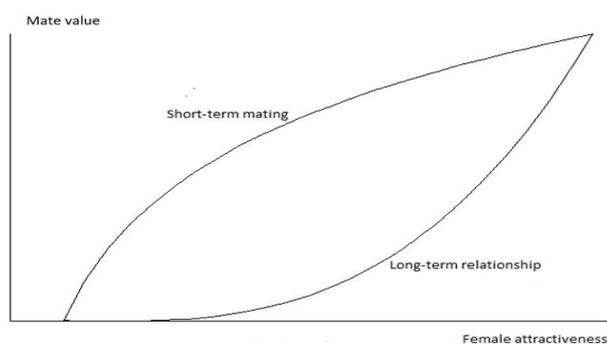
The mate value curve: Long and short-term functions.

It is assumed that the relationship between female attractiveness and the mate value this represents to men can be modelled by a continuous function with domain from the lowest to the highest value of female attractiveness. We can safely assume that this function's curve will be increasing, so that a man will derive larger mate value from higher levels of female attractiveness. Other than this we cannot say much with certainty, but *a priori* it is likely that the shape of the curve will change depending on the level of male involvement. Here I will consider the curve at two extremes, the short-term and long-term mating contexts (2,10). The human literature supports Trivers'

suggestion of males being more indiscriminate when pursuing low parental investment relationships and becoming progressively choosier as their level of investment increases (11). It has been found that men lower their minimum standards of what is acceptable in a woman when pursuing short-term matings and progressively raise them with increasing levels of involvement, so that when evaluating a potential marriage partner, they are nearly as choosy as women (10,12-14).

There is probably a range of females at the lower end of the attractiveness range (mostly older, non-fertile women, or those with phenotypic abnormalities) with zero mate value, for both short and long-term mating. But for short-term matings (like a single copulation) this range will be relatively small, and there will a low threshold value of attractiveness after which males start to derive mate value. Above this threshold value, the curve which maps female attractiveness to mate value will have a negative second derivative and be concave downward (Figure 1). The mate value will increase rapidly for lower values of female attractiveness and slower for higher values. In other words, from the vantage point of a male there will be a large difference between a moderately unattractive and an average-ly attractive female. Equal distances for larger values of female attractiveness will not yield as large mate value increments: intuitively, it does not seem likely that from the vantage point of the male there will be such a large difference in mate value between a very attractive and an extremely attractive short-term partner.

Figure 1: The relationship between female attractiveness and mate value for short and long-term relationships.



In contrast to the aforementioned curve, we would expect a long-term relationship context to produce a curve that is concave upward (Figure 1). The threshold attractiveness value that yields non-zero mate value will be set higher than before. For the values immediately after this threshold, men will still gain very little mate value, so that the difference between a very unattractive and a moderately unattractive female will be relatively small. For larger values of female attractiveness, we would expect mate value to rapidly increase, so that there will be a very large difference in mate value between a moderately attractive and a highly attractive female. For convenience I will refer to this curve as the long-term mate value curve (U_L) and the previously discussed curve as the short-term mate value curve (U_S).

Though I have just described the “typical” short-term and long-term mate value curves, it is easy to see that curves derived from individual male subjects will constitute more useful research instruments than these population-level curves. Let us assume - for illustrative purposes - that both mate value curves can be adequately approximated by a third degree polynomial of the general form ax^3+bx^2+cx+d . Estimating a male subject's values for a , b , c and d (separately for both curves) would allow us to integrate and calculate the area under the two curves, equivalent to the cumulative mate value a male enjoys in the two mating contexts across the entire range of female attractiveness. The result of this integration would afford a global estimate of male ‘choosiness’ that would be clearly superior, for most research purposes, to any particularistic measure. Each male subject could be assigned three scalar quantities: S , L and D . S is the area under U_S , L is the area under U_L , and D is the difference between the two ($D=S-L$). The higher S and L are, the larger the mate value gained by a given male across all levels of female attractiveness, and therefore the less choosy he is. On the other hand, D is a measure of the extent to which a male alters his mate value curve from short to long-term mating contexts. This can be interpreted as a gauge of how much a male lowers his mate criteria in the context of short-term matings or, equivalently, how much he raises them in long-term relationships. Having calculated these quantities for each individual in a set of male subjects, the experimenter has at his disposal global

variables whose practical use can be ascertained by finding, in the first place, how they correlate with such widely used variables as men's own attractiveness, dominance, resource acquisition potential, sociosexual orientation and so on (2,15-17).

The impossibility of theoretical derivation. A method of empirical derivation.

Ideally the curves discussed in the previous section would be derived theoretically, namely from an analysis of the various evolutionary pressures that have shaped male choice in relation to female attractiveness (18,19). This would presuppose a) knowledge of the precise fitness benefits female attractiveness conferred to ancestral males and b) the magnitude of these benefits as well as c) any relevant trade-offs, constraints etc. At the present time there is no consensus on the exact nature of these ancestral benefits. Though the role of female attractiveness as a cue to youthfulness and high reproductive potential is almost certain, its function as a cue for heritable genetic benefits or good health is less certain (7,20,21). Furthermore, even if we could be certain about the fitness benefits the preference for female attractiveness conferred on ancestral males, we would have no way of knowing the size of these benefits throughout evolution, or how they were traded off against each other. The theoretical derivation therefore, though undoubtedly the more aesthetically pleasing and elegant procedure, is an unattainable ideal.

But how could these curves be derived empirically? I suggest a possible method of derivation by trial and error. I will discuss the short-term mating context, though for a long-term context an analogous procedure could be used. Take a group of male subjects, where each subject is asked to make a series of forced choice decisions between pairs of female images as prospective short-term mates, or, in the language of today's western man, as hypothetical "one-night stands." Obviously presenting him with two photographs of women and asking him to choose one will reveal nothing we don't already know. He will invariably choose the most attractive of the two and merely confirm the obvious, namely that the curve is increasing. Pre-

senting him, however, with a choice of one attractive female on the one hand (one one-night stand) and two less attractive females on the other (two one-night stands, one with each) will be far more informative. For example, assume that the man has first rated the females for attractiveness on an attractiveness scale familiar to him, say 1 to 10. He is then presented with a series of n forced choices that would look something like the following.

Trial #	Choice A	Choice B
1	{9}	{7,6}
2	{6}	{4,1}
3	{4}	{3,2}
.	.	.
.	.	.
n	{7}	{4,2}

The numbers in brackets refer to the untransformed attractiveness ratings of the females. The experimenter has produced these pairings at random, following only the rule that the female on the left column is always more attractive than either female on the right. Let us assume our male subject selects A for trials 2 and 3, but B for trials 1 and n . Assuming no diminishing marginal mate value (in other words that the mate value of the second female on the right-hand column is not discounted), his choices reveal the following n bits of information:

1.	$U_s(9) < U_s(7) + U_s(6)$
2.	$U_s(6) > U_s(4) + U_s(1)$
3.	$U_s(4) > U_s(3) + U_s(2)$
.	.
.	.
n .	$U_s(7) < U_s(4) + U_s(2)$

It is then only a matter of trial and error to find the function U_s that best describes this set of inequalities, i.e. the function that correctly predicts the largest number of forced choices.

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Alternatively, if we assume a scenario of diminishing marginal mate value (for every additional sexual partner after the first), then the mate value of the least attractive female on the right-hand side can be discounted by a constant c_1 , where $0 < c_1 < 1$. This is the simplest scenario for diminishing marginal mate value; in principle the discounting functions could be far more complicated.

Having thus derived this "function of best fit" the next step would be to validate it by having every male subject make another set of choices and seeing how well the function fits the newly observed inequalities. We can explore the model's validity - and in particular the validity of the equal or diminishing marginal mate value assumption which we made in the previous step - by adding more complicated inequalities to the set, as in the following example:

t	Choice A	Choice B
1	{6}	{3,1}
2	{7,3}	{5, 5}
3	{9,4}	{5,4,2}
.	.	.
.	.	.
n	{8}	{6,5}

The scenario of equal marginal mate value involves a straightforward extension of the previous analysis. Alternatively, picking up from the least complicated scenario of diminishing marginal mate value discussed above, the simplest way to discount the third female on the right-hand side (or the second on the left) would be with a constant c_2 such that $1 < c_1 < c_2 < 0$. To explore this procedure's reliability and derive a baseline level of error, a separate set of male subjects could be asked, after a certain time interval, to choose again from the original set of stimuli.

Finally, it is worth asking if we will allow negative mate value to enter the analysis. I have up to this point assumed that the lowest possible mate value is zero, meaning that under a certain level of female attractiveness a male will refuse to mate. But this assumption can easily be modified, depending on the instructions given to male subjects. If the instructions stipu-

late that a male subject *must* mate with every single female on either side of the forced choice, then the mate value function should be modified to allow negative mate value associated with the least attractive females. Given the physiological costs associated with sexual activity such as time and energy expended, sexually transmitted diseases etc. (22), but most importantly the adverse social consequences arising from possible lowering of status and perceived mate value (23-25), it is likely that at least some males will shun mating opportunities with very unattractive females, so that "forcing" them to thus mate would confer negative mate value.

Conclusion

I have suggested that the mapping of female attractiveness onto mate value, if achieved, will allow a number of practical applications that won't otherwise be forthcoming. In addition to the forced choice method sketched here, other possible methods of derivation might involve allowing male subjects more freedom in manipulating the female stimuli (i.e. the setting of equalities in contrast to forced choices among inequalities), the use of monetary units etc. This line of research has the potential to provide insights unlikely to be reached through currently prevailing between-group and correlational designs.

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Case Report

CLOZAPINE RECHALLENGE WITH LITHIUM AFTER DOUBLE INDUCED NEUTROPENIA: A CASE REPORT

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Abstract

Clozapine is a second generation antipsychotic drug, which has been acknowledged as the gold standard for treating both positive and negative symptoms of treatment-resistant schizophrenic patients, despite its severe side effects, such as neutropenia. Evidence suggest rechallenging after clozapine-induced neutropenia. Nevertheless, no official guidelines exist in case that rechallenge fails. We present the case of a fifty-six year old man suffering from treatment resistant schizophrenia. The patient was diagnosed with chronic psychosis and was treated with clozapine, presenting good response. The patient developed clozapine induced neutropenia, only to be rechallenged after the neutrophil count returned at a normal range. However, another neutropenia incidence followed, and clozapine had to be ceased once more. Determining that the benefits outweighed risks, we attempted a second rechallenge with the adjustment of clozapine's dosage and the addition of Lithium carbonate. Since then, the patient did not develop any blood dyscrasia. What is more, the improvement in both psychopathology and functionality is ongoing. The mechanism of clozapine's action upon neutrophils remains unclear. The same goes for Lithium. Since literature suggests that both drugs have an effect on the bone marrow, resulting in opposite actions it only seems logical that Lithium could be used in preventing clozapine-induced neutropenia. Considering that the lack of guidelines leads to a restrain towards clozapine rechallenge after neutropenia incidence, more so after double induced neutropenia, more research is needed on the matter in the interest of a better quality of life for treatment resistant schizophrenia patients.

Key-words: Clozapine, Lithium, schizophrenia, resistant schizophrenia, neutropenia, clozapine-induced neutropenia,

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INTRODUCTION

Since the introduction of chlorpromazine in Psychiatry as an antipsychotic agent in 1952, many breakthroughs have been made in this field. Nevertheless, even after the second-generation antipsychotics' launch in the pharmaceutical industry, psychiatrists faced the problem of treatment resistant schizophrenia (TRS). It was not until the 90's that a long-discredited agent would shed some light in this domain. Reference is made to the molecule Clozapine.

Clozapine is an atypical neuroleptic agent identified in 1959 by the pharmaceutical company Walder Laboratories and introduced in the market at the early 70's **(1)**, only to be withdrawn a few years later in 1975, due to alarming reports of fatal agranulocytosis in Finland **(2)**. Around 1990, clozapine was approved by the FDA, after a pivotal study by Kane et al that proved its superior efficacy compared to chlorpromazine in TRS **(3)**. Since then it has been acknowledged as the gold standard for treating both positive and negative symptoms of treatment-resistant patients, which seems to be the case for up to one third of patients suffering from schizophrenia **(4)**.

Clozapine molecule has a complex structure which accounts for its multiple binding affinities and therefore its pharmacologic profile. Same as every atypical antipsychotic, this agent presents a combined antagonism to dopamine and serotonin receptors. Clozapine's effect on dopamine receptors situated in several neurological pathways throughout the brain reduces both positive and negative symptoms of schizophrenia and improves cognition as well as mood. Its antagonistic action upon D2 Dopaminergic receptors seems to be more fable and short-lived than the one upon D1-dopamine receptors, without being clear if the latest represents an antagonism or an agonism **(5,6)**. This second-generation antipsychotic is also known to have a high affinity for D4 dopamine receptors and a weaker one for D3 receptors **(6)**.

Apart from its preference to dopaminergic receptors, clozapine has a high affinity for serotonin receptors as well, and especially for the 5HT2B and the 5HT2A subtypes, with a robust antagonistic action on the latest. As a result, dopamine release

is enhanced in certain brain regions and thus cognitive and affective symptoms of schizophrenia are improved. What is more, the risk of extrapyramidal symptoms (EPS) is decreased **(7)**. Clozapine seems to bind strongly upon the 5HT2C, 5HT6, 5HT7 and other serotonin receptors, as well as the 5HT1A receptor which is activated thus causing dopamine release in the prefrontal cortex (PFC) **(8)**.

Another pharmaceutical property of clozapine is sedation, an action that is stimulated by blocking either M1-muscarinic cholinergic or H1-histaminic or α 1-adrenergic receptors or all of them at once. What is more, mood is improved. Antihistaminic and anticholinergic properties are also responsible for the anxiolytic effect of the drug **(9)**. In addition to this, Clozapine's partial and full agonistic activity on other subtypes of muscarinic receptors (M2, M3, M4) results in an improvement of cognitive functions. This is partially due to a metabolite, N-Desmethylclozapine (NDMC), and its nootropic attributes to the hippocampus and the PFC **(10)**. Finally, clozapine appears to have an antagonistic action for the NMDA receptor's glycine site, concluding in stabilizing DA neurons in both the PFC and the midbrain **(11)**.

Clozapine's affinity to the multiple forenamed receptors is not devoid of adverse effects. Although second generation antipsychotics are known to cause EPS at a lower scale due to a looser attachment to D2 dopamine receptors, as mentioned before, adverse reactions derived from its antidopaminergic, antimuscarinic, antihistaminic and adrenergic receptor blocking properties can be quite common and challenging. Weight gain, excessive sedation (20-40%), somnolence, dizziness, constipation (15-60%), metabolic syndrome, tachycardia (12-17%), orthostatic hypotension (8-13%) and excessive salivation (12-40%) are all products of clozapine's actions **(12,13)**. Not so frequent but potentially lethal side effects include myocarditis, seizures and pulmonary embolism, ileus and bowel ischemia, liver dysfunction, neuroleptic malignant syndrome and angioedema **(14)**.

The most disturbing side effect however, seems to be clozapine-induced blood dyscrasias and specifically neutropenia and agranulocytosis. Seen respectively in about 2-3% and 1% of the

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treated with clozapine patients these life-threatening adverse reactions limit the drugs' more widespread use **(15,16)**. Nearly 25 % of the patients cease clozapine on account of its side effects, with neutropenia being the main cause of discontinuation **(17)**. The process through which Clozapine causes those blood abnormalities is unclear, but it is speculated to be a heritable trait **(18)**.

Despite its side effects, as mentioned before, clozapine remains the gold standard for TRS, being the first line treatment after the failure of two antipsychotic trials according to treatment guidelines **(19)**. Even if a patient is not responding to other neuroleptics, the response-ratio to clozapine is as high as 30 to 60 % **(4, 20, 21, 22, 23)**. Apart from TRS, clozapine has shown efficacy as an anti-aggressive and anti-suicidal drug in patients with schizophrenia **(24)** and bipolar disorder as well **(25)**.

Due to the abovementioned adverse effects of clozapine, careful monitoring is applied in many countries before and after the initiation of the drug. More frequently it includes complete blood count with emphasis given on white blood cell (WBC) count and absolute neutrophil count (ANC), ECG, troponin levels, weight measurement, vital signs, lipidic profile and liver functioning tests, with different protocols implemented by each country **(25)**. The one guideline that seems to apply for the majority of them is mandatory WBC and ANC count.

For the initiation of clozapine, a WBC and ANC minimum count of 3000/mm³ and 1500/mm³ respectively must be obtained, according to the FDA **(26)**. Exception is made for Benign Ethnic Neutropenia (BEN), in which the limitation of clozapine's use is ANC count of at least 1000/mm³ **(27)**. If the patient's blood sample does not comply with the criteria above at any time during treatment clozapine should be discontinued **(28)**, especially if ANC falls below 1000/mm³ and if the benefits do not surpass the hazards **(26)**.

Rechallenging after a neutropenia incidence is a difficult decision. However, guidelines and evidence suggest it is a logical clinical option **(29)**. FDA is in favor of rechallenging if patients' WBC does not fall below 2000/mm³. Clozapine REMS program

suggests it might be the only solution in some cases, even after moderate and severe clozapine-related neutropenia **(26)**. A study carried out by Manu et al in 2012 concludes that 70 % of the patients who developed neutropenia because of clozapine, were rechallenged successfully without neutropenia re-appearing **(30)**. Nevertheless, no official guidelines exist for this 30% that rechallenge has failed.

CASE REPORT

G.K is a 56-year-old Caucasian man with a 25-year history of paranoid schizophrenia, appearing both positive and negative symptoms, as well as suicide attempts. For the last few years his mental health had deteriorated and his functionality had dropped off. As a result, he had been through many hospitalizations and received a wide range of neuroleptics, making him suitable to be characterized as a treatment resistant schizophrenia patient. As such he was referred to our psychiatric clinic. Upon his admission in the hospital he was under risperidone in the form of long-acting injection (50mg/15days), pipamperone (40 mg twice a day) levomepromazine (25mg daily) amisulpride (400mg three times a day) and biperiden (2mg twice a day) and he displayed the profile of a chronic psychotic patient with a GAF scale assessment of around 38.

In our unit, we performed cross tapering with clozapine on an outpatient basis. Before the patient was administered with clozapine a complete blood count was carried out, as well as an electrocardiogram, BMI measurement, reference biochemical blood analysis including lipidemic profile, blood sugar levels, liver and kidney functioning tests, electrolytes and troponin. Subsequently, blood count was monitored weekly in order to be in vigilance for changes of the WBC count. The initiation of clozapine and its gradual up-titration on a dosage of 350mg daily was followed by an amelioration of both negative and positive symptoms and an improvement on the GAF scale, with the patient's functionality ascending on the GAF scale from 38 up to 70.

One month after the completion of clozapine's titration, the first signs of WBC decline appeared, with an absolute count of

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WBC slightly over 4000/ μL . However, it was not until during the fourth month after clozapine's initiation that neutropenia developed. The patient's white blood cells and neutrophils (NEU) reached the point of 3380/ μL and 810/ μL respectively, which corresponds to a moderate blood dyscrasia. Hence, clozapine administration was ceased and a complete physical examination was performed. The absence of pathological findings, the failure of the patient to respond to other drugs suitable for schizophrenia, as well as the severity of the patient's mental condition, taking into account previous suicide attempts, led us to a first rechallenge.

After the restoration of WBC and NEU, about a week later, we re-administered clozapine. Nevertheless, the following month, neutropenia reappeared, with a WBC and NEU count of 3040/ μL and 630/ μL respectively which corresponds to a much more serious neutropenia with high risk for infection. That was the case for our patient, who presented a positive CRP and signs of GI tract infection. Thus, clozapine was withdrawn, the patient's infection was treated with antibiotics and daily blood tests were performed.

A rapid recovery of the WBC and NEU, was followed by a second rechallenge by our part, taking into account the impressive improvement of the patient's condition concerning both schizophrenia symptoms and functionality. This time, the addition of lithium carbonate in the treatment at a dosage of 300 mg per day (Li 0,33 mEq/L) and the adjustment of clozapine's dosage (200mg/day) in order to avoid neutropenia was crowned with success. No further leukopenia was observed, due to a Lithium induced true leukocytosis. What is more, for the last ten months the patient has not developed neutropenia and has managed to stabilize, even mitigate, his mental condition, while the improvement of his functionality is ongoing.

DISCUSSION

Lithium has been approved by the FDA since 1979 for the prophylaxis of manic episodes (31) and has been used both in the acute phase of mania and in preventing its re-occurrence. What is more, it is used as a stabilizer and as an amplifying agent in

affective disorders (32). Another important property is that it is linked with a reduction in suicidality in patients with mood disorders (33). It also has an off-label use in neutropenia (32). This last indication has been the thematic area for many mental health researchers. It has been observed that Lithium causes an increase in circulating neutrophils and accelerates their production from the bone marrow through an expansion of progenitor cells (34).

After many research on the topic, it seems that a plasma concentration of Lithium greater than 0.3mEq/L is efficient to produce and sustain leukocytosis especially neutrophils and eosinophils. To be more specific, it has been observed that an increase of neutrophils occurs for a week and followed by stabilization of their number (35). This action is thought to take place through stimulation of GM-CSF (granulocyte-macrophage colony stimulating factor) and CFU-GM (granulocyte-macrophage progenitors), as well as through an increase in life expectancy and number of CFU-S (multipotential stem cells) (35). So as long there is a sufficient in quantity group of precursor cells for it to act upon and a proper concentration of the drug in plasma, Lithium can cause leukocytosis. Except for the direct stem-cell stimulation, other theories have been proposed such as stimulation of cytokines, redistribution of demarginated leukocytes, and increased cortisol production (36).

The abovementioned action of Lithium has already been exploited in cases of faulty or inadequate neutrophil count caused by cytotoxic drugs (35) or even after carbamazepine-induced neutropenia, Felty syndrome and other types of WBC depression (37,38).

As mentioned before, clozapine can cause leukopenia. The risk of neutropenia or agranulocytosis induced by clozapine is not as high as other side effects caused by the medication. These adverse effects occur most commonly during the first six to eighteen weeks of therapy (16), then having the same relative risk of appearing as in any other atypical antipsychotic. However, this does not make them less life-threatening.

The mechanism through which clozapine induces neutropenia and agranulocytosis remains unclear even though many

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hypotheses have been expressed. It has been advocated that clozapine leads to a dose-dependent suppression of GM-CSF, followed by an inadequate increase of GM-CSF on the subsequent hematopoietic stress, also caused by the drug **(39)**. Another study, concludes that a nitrenium ion derived from clozapine could be the reason for neutropenia through direct action upon the bone marrow rather than a toxicity upon the peripheral neutrophils **(40)**. In 2018, Wiciński et al focus again on the nitrenium ion action, supporting the theory that neutropenia is more likely to be immune mediated rather than toxic **(41)**. Whatever the mechanism might be, clozapine-associated blood dyscrasias remain one of the main reasons for the medication's withdrawal.

Lithium has been suggested and used of in cases of clozapine-induced leukopenia and in preventing its recurrence or its development in the first place. Kanaan et al published a retrospective case analysis of patients rechallenged with clozapine co-administered with Lithium, after clozapine induced blood dyscrasias concerning a five year long period, resulting in supporting the theory that Lithium prevents recurrence of neutropenia. It also points out that the recurrence's possibility of happening was 4% while the patient is under co-administration of clozapine and Lithium **(42)**. The same year, another study was publicized, that included 53 patients rechallenged with clozapine in conjunction with lithium. The results were in agreement with the abovementioned, presenting a majority of patients not featuring neutropenia anew after co-prescription of lithium and clozapine **(43)**.

A few years later, Ghaznavi et al present a case of a late-onset neutropenia caused by clozapine, one that had been rechallenged successfully with lithium. In their work, is pointed out once again the fact that lithium causes true leukocytosis and great importance is attached to the fact that the co-administration of clozapine and lithium could, in some cases, result in synergy concerning the drugs' side effects, such as seizures, tremors and agranulocytosis, with that however being temporary (during initiation period) or rare **(44)**. In 2016, another report was published that presented the case of a clozapine rechallenge after neutropenia incidence with lithium's addition

to the treatment. The co-treatment was crowned with success (neutrophils remained at a normal range and the patient's psychopathology improved), until neurological side effects led to the discontinuation of lithium. As a result, blood dyscrasia occurred anew **(45)**.

The reference of international literature in long-term use of lithium to treat clozapine-induced neutropenia is sporadic. This lack of sufficient evidence concerning the co administration of lithium and clozapine after a neutropenia episode has made mental health practitioners skeptical towards using the combination. On the other hand, the failure of other antipsychotics on cases of TRS and the fact that precipitous cessation of clozapine, as in neutropenia for instance, is connected to relapse, sometimes unresponsive to typical antipsychotics **(46)**, poses a dilemma whether to rechallenge in a way that ensures the patient's well-being and neutrophil count or not to rechallenge at all. This dilemma remains and is aggravated where the gray zone of the guidelines concerning clozapine rechallenge lies. Namely, when two episodes of neutropenia have occurred because of clozapine.

Summarizing all the above, should we accept the beneficial effect of Lithium in preventing the recurrence of blood dyscrasias, it only seems logical that it should be used during clozapine rechallenge after neutropenia incidence. However, the fact that evidence concerning both Lithium's and clozapine's mechanism of action upon neutrophils and bone marrow are scarce, makes lithium's capability of preventing clozapine-induced neutropenia seem only a logical presumption. Adding to that, the lack of explicit guidelines leads to a restrain, for the mental health practitioners' part, towards clozapine rechallenge after neutropenia incidence, more so after double induced neutropenia. All the above, make the need for more research on the matter crucial, in order for patients with TRS to have a second or even a third chance of a dignified and more qualitative way of life.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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