

# XJENZA

VOLUME 5

ISSUE 2, 2017

ONLINE



www.xjenza.com

## Editorial Board

---

### Editor-in-Chief

---

Prof Giuseppe Di Giovanni  
Department of Physiology and Biochemistry,  
University of Malta,  
Msida, Malta.  
MSD 2080  
Tel.: +356 2340 2776  
Fax: +356 2131 0577  
giuseppe.digiovanni@um.edu.mt

---

### Associate Editors

---

#### *Cognitive and Social Sciences*

Ian Thornton  
ian.thornton@um.edu.mt

#### *Economics*

Ian Cassar  
ian.p.cassar@um.edu.mt

#### *Engineering Science*

Philip Farrugia  
philip.farrugia@um.edu.mt

#### *Geosciences*

Sebastiano D'Amico  
sebastiano.damico@um.edu.mt

#### *Information and Communication Technologies*

Nicholas Sammut  
nicholas.sammut@um.edu.mt

#### *Social Sciences*

Godfrey Baldacchino  
godfrey.baldacchino@um.edu.mt

#### *Medical Sciences*

Joseph Galea  
joseph.f.galea@um.edu.mt

#### *Biological Sciences*

David Mifsud  
david.a.mifsud@um.edu.mt

#### *Mathematical and Statistical Science*

Liberato Camilleri  
liberato.camilleri@um.edu.mt

#### *Physics and Chemical Sciences*

David Magri  
david.magri@um.edu.mt

#### *Psychological Science*

Carmel Cefai  
carmel.cefai@um.edu.mt

---

### Advisory Board Members

---

Prof. Angela A. Xuereb Anastasi, University of Malta  
Prof. David Eisner, Manchester University, UK  
Prof. Frank Vella, University of Saskatchewan, Canada  
Prof. Vincenzo Crunelli, Cardiff University, UK  
Prof. Giacomo Rizzolatti, Università degli Studi di Parma, Italy

angela.a.xuereb@um.edu.mt  
eisner@manchester.ac.uk  
f.vella@sasktel.net  
crunelli@cardiff.ac.uk  
giacomo.rizzolatti@unipr.it

---

### Editorial Board Members

---

Dr Katya De Giovanni, University of Malta, Malta  
Dr Sandro Lanfranco, University of Malta, Malta  
Prof. Mauro Pessia, University of Malta, Malta  
Prof. Maria Attard, University of Malta, Malta  
Dr Maurizio Casarrubea, Università degli Studi di Palermo, Italy  
Dr Roberto Frau, Università di Cagliari, Italy  
Dr Massimo Pierucci, University of Malta, Malta  
Dr Samantha Austen, Open University, UK  
Dr Tiziana Florio, University of L'Aquila, Italy

katya.degiovanni@um.edu.mt  
sandro.lanfranco@um.edu.mt  
mauro.pessia@um.edu.mt  
maria.attard@um.edu.mt  
maurizio.casarrubea@unipa.it  
roberto.frau@unica.it  
massimo.pierucci@um.edu.mt  
samantha.austen@open.ac.uk  
tizianamarilena.florio@univaq.it

---

### Project editor

Jackson Levi Said  
Department of Physics,  
University of Malta,  
Msida MSD 2080, Malta.  
jsaid01@um.edu.mt

### Copy Editor

Gabriel Farrugia  
Department of Physics,  
University of Malta,  
Msida MSD 2080, Malta.  
gfarr02@um.edu.mt

### Editorial Assistants

Katherine Todman  
TodmanK@cardiff.ac.uk  
Sunneth Lawrence  
Sunneth.Lawrence@wawrick.ac.uk

### Web Administrator

John Gabarretta  
Department of Chemistry,  
University of Malta,  
Msida MSD 2080, Malta.  
john.gabarretta.09@um.edu.mt



## Chronological List of Past and Present Editors of Xjenza The Journal of the Malta Chamber of Scientists

---

### 2013–2017

**Editor:** Giuseppe Di Giovanni

**Associate Editors:** *David Magri, Ian Thornton, Ian Cassar, Philip Farrugia, Sebastiano D'Amico, Nicholas Sammut, David Mifsud, Godfrey Baldacchino, Liberato Camilleri, Carmel Cefai*

Xjenza Online Vol. 5 Iss. 2 - 2017

Xjenza Online Vol. 5 SI MNS Proceedings - 2017

Xjenza Online Vol. 5 Iss. 1 - 2017

Xjenza Online Vol. 5 Virtual Issue COST - 2017

Xjenza Online Vol. 4 Iss. 2 - 2016

Xjenza Online Vol. 4 Iss. 1 - 2016

Xjenza Online Vol. 3 Iss. 2 - 2015

**Associate Editors:** *David Magri, Ian Thornton, Ian Cassar, Philip Farrugia, Sebastiano D'Amico, Nicholas Sammut, Joseph Galea, David Mifsud, Sandro Lanfranco, Mario Valentino, Godfrey Baldacchino, Liberato Camilleri*

Xjenza Online Vol. 3 Iss. 1 - 2015

Xjenza Online Vol. 2 Iss. 2 - 2014

Xjenza Online Vol. 2 Iss. 1 - 2014

Xjenza Online Vol. 1 Iss. 2 - 2013

Xjenza Online Vol. 1 Iss. 1 - 2013

---

### 2003–2007

**Editors:** Joseph N. Grima and Richard Muscat

Xjenza Vol. 12 - 2007

Xjenza Vol. 11 - 2006

Xjenza Vol. 10 - 2005

Xjenza Vol. 9 - 2004

Xjenza Vol. 8 - 2003

---

### 1996–2002

**Editor:** Angela Xuereb

**Associate Editor:** *Richard Muscat*

Xjenza Vol. 7 - 2002

Xjenza Vol. 6 - 2001

**Associate Editors:** *Martin Ebejer and Richard Muscat*

Xjenza Vol. 5 - 2000

Xjenza Vol. 4 Iss. 2 - 1999

Xjenza Vol. 4 Iss. 1 - 1999

**Associate Editors:** *Martin Ebejer, Richard Muscat, and Christian A. Scerri*

Xjenza Vol. 3 Iss. 2 - 1998

Xjenza Vol. 3 Iss. 1 - 1998

**Associate Editors:** *Martin Ebejer, Richard Muscat, Christian A. Scerri and Emmanuel Sinagra*

Xjenza Vol. 2 Iss. 2 - 1997

Xjenza Vol. 2 Iss. 1 - 1997

Xjenza Vol. 1 Iss. 2 - 1996

Xjenza Vol. 1 Iss. 1 - 1996

---

## Scope of Journal

Xjenza is the Journal of the Malta Chamber of Scientists and is published in an electronic format. Xjenza is a peer-reviewed, open access international journal. The scope of the journal encompasses research articles, original research reports, reviews, short communications and scientific commentaries in the fields of: mathematics, statistics, geology, engineering, computer science, social sciences, natural and earth sciences, technological sciences, linguistics, industrial, nanotechnology, biology, chemistry, physics, zoology, medical studies, electronics and all other applied and theoretical aspect of science.

The first issue of the journal was published in 1996 and the last (No. 12) in 2007. The new editorial board has been formed with internationally recognised scientists, we are planning to restart publication of Xjenza, with two issues being produced every year. One of the aims of Xjenza, besides highlighting the exciting research being performed nationally and internationally by Maltese scholars, is to provide insight to a wide scope of potential authors, including students and young researchers, into scientific publishing in a peer-reviewed environment.

## Instructions for Authors

Xjenza is the journal of the Malta Chamber of Scientists and is published by the Chamber in electronic format on the website: <http://www.mcs.org.mt/index.php/xjenza>. Xjenza will consider manuscripts for publication on a wide variety of scientific topics in the following categories

1. Communications
2. Research Articles
3. Research Reports
4. Reviews
5. Notes
6. News and Views
7. Autobiography

**Communications** are short peer-reviewed research articles (limited to three journal pages) that describe new important results meriting urgent publication. These are often followed by a full Research Article.

**Research Articles** form the main category of scientific papers submitted to Xjenza. The same standards of scientific content and quality that applies to Communications also apply to Research Articles.

**Research Reports** are extended reports describing research of interest to a wide scientific audience characteristic of Xjenza. Please contact the editor to discuss the suitability of topics for Research Reports.

**Review Articles** describe work of interest to the wide readership characteristic of Xjenza. They should provide an in-depth understanding of significant topics in the sciences and a critical discussion of the existing state of knowledge on a topic based on primary literature. Review Articles should not normally exceed 6000 words. Authors are strongly advised to contact the Editorial Board before writing a Review.

**Notes** are fully referenced, peer-reviewed short articles limited to three journal pages that describe new theories, concepts and developments made by the authors in any branch of science and technology. Notes need not contain results from experimental or simulation work.

**News and Views:** The News section provides a space for articles up to three journal pages in length describing leading developments in any field of science and technology or for reporting items such as conference reports. The Editor reserves the right to modify or reject articles for consideration as 'news items'.

**Commentaries:** Upon Editor's invitation, commentaries discuss a paper published in a specific issue and should set the problems addressed by the paper in the wider context of the field. Proposals for Commentaries may be submitted; however, in this case authors should only send an outline of the proposed paper for initial consideration. The contents of the commentaries should follow the following set of rules: 3000 words maximum, title 20 words maximum, references 10 maximum (including the article discussed) and figures/tables 2 maximum.

**Errata:** Xjenza also publishes errata, in which authors correct significant errors of substance in their published manuscripts. The title should read: Erratum: "Original title" by \*\*\*, Xjenza, vol. \*\*\* (year). Errata should be short and consistent for clarity.

**Invited Articles and Special Issues:** Xjenza regularly publishes Invited Articles and Special Issues that consist of articles written on invitation by the Editor or member of the editorial board.

## Submission of Manuscripts

Manuscripts should be sent according to the guidelines given hereafter to [submissionxjenzaonline@gmail.com](mailto:submissionxjenzaonline@gmail.com).

**Referees** All manuscripts submitted to Xjenza are peer reviewed. Authors are requested to submit with their manuscript the names and addresses of three referees, preferably from overseas. Every effort will be made to use the recommended reviewers; however the editor reserves the right to also consult other competent reviewers.

**Conflict of Interest** Authors are expected to disclose any commercial or other associations that could pose a conflict of interest in connection with the submitted manuscript. All funding sources supporting the work, and institutional or corporate affiliations of the authors, should be acknowledged on the title page or at the end of the article.

**Policy and Ethics** The work described in the submitted manuscript must have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans (<http://www.wma.net/en/30publications/10policies/b3/index.html>); EU Directive 2010/63/EU for animal experiments ([http://ec.europa.eu/environment/chemicals/lab\\_animals/legislation\\_en.htm](http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm)); Uniform Requirements for manuscripts submitted to Biomedical journals (<http://www.icmje.org>). This must be stated at an appropriate point in the article.

**Submission, Declaration and Verification** Submission of a manuscript implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis), that it is not under consideration for publication elsewhere, that it has been approved for publication by all authors, and tacitly or explicitly, by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright-holder.

**Permissions** It is the responsibility of the corresponding author of a manuscript to ensure that there is no infringement of copyright when submitting material to Xjenza. In particular, when material is copied from other sources, a written statement is required from both the author and/or publisher giving permission for reproduction. Manuscripts in press, unpublished data and personal communications are discouraged; however, corresponding authors are expected to obtain permission in writing from at least one author of such materials.

## Preparation of Manuscripts

Xjenza accepts submissions in MS Word, Libre Office Writer and L<sup>A</sup>T<sub>E</sub>X with the latter being the preferred option. Anyone submitting in L<sup>A</sup>T<sub>E</sub>X should use the journal template, the latest version of which can be found at <http://github.com/hicklin/Xjenza-Journal-Template>. All the necessary files to run the L<sup>A</sup>T<sub>E</sub>X document should be supplied together with the rendered PDF.

If a word processor is used the styling should be kept to a minimum, only introducing bold face, italics, subscript and superscript text where the context requires it. Text should be in single-column format and the word processor options should not be used in order to justify text or hyphenate words. Together with the native format of the word processor, a pdf, generated by the word processor, must be given. Furthermore, artwork should be in accordance with the artwork guidelines give below and must be submitted separately from the word processor file. Similarly, the bibliographic data of the cited material should be submitted separately as an Endnote (\*.xml), Research Information Systems (\*.ris), Zotero Library (zotero.split) or a B<sup>I</sup>B<sup>T</sup>E<sub>X</sub> (\*.bib) file.

## Article Structure

A manuscript for publication in Xjenza will ordinarily consist of the following: Title page with contact information, Abstract, Highlights, Keywords, Abbreviations, Introduction, Materials and Methods, Results, Discussion, Conclusion, Appendices and References.

The manuscript will be divided into clearly defined numbered sections. Each numbered subsection should be given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by the section number as opposed to simply 'the text'.

### Title page

- The title should be concise yet informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
- Author names and affiliations. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript number immediately after each author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address.
- Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, including post-publication. Ensure that telephone and fax numbers (with country and area code) are provided in addition to the e-mail address and complete postal address. Contact details must be kept up to date by the corresponding author.
- Present/permanent address. If an author has changed the address since the work described, this can be indicated as a footnote to the author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

**Abstract** A concise and factual abstract is required of up to about 250 words. The abstract should state briefly the background and purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, references and non-standard abbreviations should be avoided. If essential, these must be defined at first mention in the abstract itself.

**Abbreviations** Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention as well as in the footnote and should be used consistently throughout the text.

**Introduction** State the objectives of the work and provide an adequate background, avoid a detailed literature survey or a summary of the results.

**Materials and Methods** Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described.

**Results** Results should be clear and concise. Numbered/tabulated information and/or figures should also be included.

**Discussion** This should explore the significance of the results of the work, yet not repeat them. Avoid extensive citations and discussion of published literature. A combined section of Results and Discussion is often appropriate.

**Conclusion** The main conclusions based on results of the study may be presented in a short Conclusions section. This may stand alone or form a subsection of a Discussion or Results and Discussion section.

**Appendices** Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

**Acknowledgements** Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided assistance during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

**Units** Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI. Anyone using L<sup>A</sup>T<sub>E</sub>X should use the package `siunitx` in all cases.

**Footnotes** Footnotes should be used sparingly. Number them consecutively throughout the article, using superscript Arabic numbers. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes by a superscript number in the text and present the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

**Table Footnotes** Indicate each footnote in a table with a superscript lower case letter.

**Artwork** Electronic artwork General points:

- Make sure you use uniform lettering and sizing of your original artwork.
- Save text in illustrations as 'graphics' or enclose the font.
- Only use the following fonts in your illustrations: Arial, Courier, Times, Symbol or Computer Modern Roman, the latter is preferred.
- Number the illustrations according to their sequence in the text.
- Name your artwork files as 'fig $x$ ' or 'tab $z$ ' where  $x$  corresponds to the sequence number in your document.
- Provide captions to illustrations separately.
- Produce images near to the desired size of the printed version or grater.
- Make sure that the artwork has no margins and borders.
- Submit each figure as a separate file.



**Formats** Regardless of the application used, when your electronic artwork is finalised its file format should be one of the following (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

- PDF or SVG: Vector drawings. Embed the font or save the text as ‘graphics’.
- JPEG or PNG: Color or grayscale photographs (halftones): always use a minimum of 300 dpi.
- JPEG or PNG: Bitmapped line drawings: use a minimum of 1000 dpi.
- JPEG or PNG: Combinations bitmapped line/half-tone (color or grayscale): a minimum of 500 dpi is required.

Where possible use a vector format for your artwork (PDF or SVG). If this is not possible, supply files that have an adequate resolution.

**Colour Artwork** Make sure that color artwork files are in an acceptable format (JPEG, PNG, PDF or SVG) and have the correct resolution.

**Figure Captions** Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum, but explain all symbols and abbreviations used.

**Tables** Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article. Large tables should be submitted in CSV format.

**Citations and References** Reference and citation styles for manuscripts submitted to Xjenza should be in accordance to the APA v6 style.

**Citation in text** References to cited literature in the text should be given in the form of an author’s surname and the year of publication of the paper with the addition of a letter for references to several publications of the author in the same year. For further information regarding multiple authors consult the APA v6 guidelines. Citations may be made directly

Kramer et al. (2010) have recently shown ...

or parenthetically

as demonstrated (Allan, 2000a, 2000b, 1999; Allan and Jones, 1999).

Groups of references should be listed first alphabetically, then chronologically. When writing in L<sup>A</sup>T<sub>E</sub>X use `\textcite{}` and `\parencite{}` for the respective cases mentioned.

**The reference section** Every reference cited in the text should also be present in the reference list (and vice versa). The reference list should also be supplied as an Endnote (\*.xml), Research Information Systems (\*.ris), Zotero Library (zotero.splite) or a BiB<sub>T</sub>E<sub>X</sub> (\*.bib) file. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either ‘Unpublished results’ or ‘Personal communication’. Citation of a reference as ‘in press’ implies that the item has been accepted for publication.

References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters ‘a’, ‘b’, ‘c’, etc., placed after the year of publication. Consult the APA v6 guidelines for multiple authors. Below are some examples of referencing different bibliographic material.

### Reference to a Journal Publication:

- Agree, E. M. and Freedman, V. A. (2011). A Quality-of-Life Scale for Assistive Technology: Results of a Pilot Study of Aging and Technology. *Phys. Ther.*, 91(12):1780–1788.
- McCreadie, C. and Tinker, A. (2005). The acceptability of assistive technology to older people. *Ageing Soc.*, 25(1):91–110.

### Reference to a Book:

- Brownsell, B. (2003). *Assistive Technology and Telecare: Forging Solutions for Independent Living*. Policy Press, Bristol.
- Fisk, M. J. (2003). *Social Alarms to Telecare: Older People’s Services in Transition*. Policy Press, Bristol, 1st edition.

### Reference to a Chapter in an Edited Book:

- Brownsell, S. and Bradley, D. (2003). New Generations of Telecare Equipment. In *Assist. Technol. Telecare Forg. Solut. Indep. Living*, pages 39–50.

**Web references** The full URL should be given together with the date the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately or can be included in the reference list.

**References in a Special Issue** Please ensure that the words ‘this issue’ are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

**Journal Abbreviations** Journal names should be abbreviated according to:

- Index Medicus journal abbreviations: <http://www.nlm.nih.gov/tsd/serials/lji.html>;
- List of title word abbreviations: <http://www.issn.org/2-22661-LTWA-online.php>;
- CAS (Chemical Abstracts Service): <http://www.cas.org/sent.html>.

**Video data** Xjenza accepts video material and animation sequences to support and enhance the presentation of the scientific research. Authors who have video or animation files that they wish to submit with their article should send them as a separate file. Reference to the video material should be clearly made in text. This will be modified into a linked to the paper’s supplementary information page. All submitted files should be properly labelled so that they directly relate to the video files content. This should be within a maximum size of 50 MB.

## Submission check list

The following list will be useful during the final checking of a manuscript prior to sending it to the journal for review. Please consult this Guide for Authors for further details of any item.

- One author has been designated as the corresponding author with contact details:
  - E-mail address.
  - Full postal address.
  - Telephone and fax numbers.
- All necessary files have been sent, and contain:
  - All figures are given separately in PDF, SVG, JPEG or PNG format.
  - Caption for figures is included at the end of the text.
  - All tables (including title, description, footnotes) are included in the text and large tables have been given separately as CSV.
  - The reference list has been given in XML, RIS, zotero.splite or BIB file format.
- Further considerations
  - Abstract does not exceed about 250 words.
  - Manuscript has been ‘spell-checked’ and ‘grammar-checked’.

- References are in the required format.
- All references mentioned in the reference list are cited in the text, and vice versa.
- Bibliographic data for all cited material has been given.
- Permission has been obtained for use of copyrighted material from other sources (including the Web).
- A PDF document generated from the word processor used is given.

## After Acceptance

**Use of the Digital Object Identifier** The Digital Object Identifier (DOI) may be used to cite and link to electronic documents. The DOI consists of a unique alpha-numeric character string which is assigned to a document by the publisher

upon the initial electronic publication. The assigned DOI never changes. Therefore, it is an ideal medium for citing a document, particularly 'Articles in press' because they have not yet received their full bibliographic information. When you use a DOI to create links to documents on the web, the DOIs are guaranteed never to change.

**Proofs, Reprints and Copyright** Authors will normally be sent page proofs by e-mail or fax where available. A list of any necessary corrections should be sent by fax or email to the corresponding editor within a week of proof receipt to avoid unnecessary delays in the publication of the article. Alterations, other than essential corrections to the text of the article, should not be made at this stage. Manuscripts are accepted for publication on the understanding that exclusive copyright is assigned to Xjenza. However, this does not limit the freedom of the author(s) to use material in the articles in any other published works.



*Editorial*

## The Last Editorial

**Giuseppe Di Giovanni**\*<sup>1</sup>

<sup>1</sup>*Department of Physiology and Biochemistry, University of Malta, Msida, Malta*

As we get ready to welcome 2018, *Xjenza Online* will enter a new era under the leadership of the new editor Dr Cristiana Sebu, Associate Professor of Biomathematics at the University of Malta. It is incredible how fast time has gone by as I am now writing my last editorial as the Editor-in-Chief of *Xjenza Online*. It has been an honour and a privilege for me to have had the opportunity to lead this prestigious Journal, the official organ of the Malta Chamber of Scientists, for the past 5 years. My Editorship has been a rewarding and fulfilling experience. During this time, *Xjenza Online* has been reborn, grown in size and become the Maltese journal for authoritative reports in all the areas of science. We have published 10 issues, 2 per year, 1 virtual issue on Maltese COST Actions and 1 as Proceedings of the International Mediterranean Neuroscience Conference (MNS2017) held in Malta in 2017.

When I look back on my Editorship, I am very proud of what *Xjenza Online* has achieved and of what it has become. The tremendous growth in science and technology has resulted in a proliferation of high-quality research articles published in *Xjenza Online* from both Maltese and international Scholars.

This, my last issue of *Xjenza Online*, continues this trend, showcasing some local and international important research and offering several valuable insights into different fields. The issue opens with the contribution by Melanie Grima and colleagues who have reviewed the molecular mechanisms of the sleep wake cycle with the aim of finding some therapeutic applications for insomnia. Gabriella Gatt et al., show that the prevalence of an easily preventable tooth condition such as erosive tooth wear is high in school aged Maltese children. Brockdorff and Bernice Amaira produce an estimate for human capital stock for Malta over the period 2005 to 2013 and compare Malta's performance with that of other countries. Emanuele Colica et al., present a 3D digital model of Ramla Bay (Gozo) obtained by using photograms taken from drones useful for monitoring the dynamics of the beach-dune system and the characterization of the coast for the mitigation of coastal erosion. Jennifer Fiorentino present a revised appraisal of Lichens of the Maltese Islands described by S. Sommier and A. Caruana Gatto in 1915. Yanica Ellul and Katya De Giovanni report on the social impact of the American University of Malta's Cospicua site on the Cottonera and the surrounding localities. The selection contains three commentaries. Manuela Radic and colleagues' contri-

bution from Malta and Palermo, Italy focused on liver diseases induced by alcohol, cannabinoids and nicotine; Tiziana M. Florio from L'Aquila, Italy gives her view of Parkinson's Disease motor disorganization and temporal processing and finally Cristiana Sebu has revised the application of the Electrical Impedance Mammography for low-cost, portable and non-invasive breast cancer screening. The collection ends with 6<sup>th</sup> Annual Science in the House Exhibition by David C. Magri.

The success of this Journal would not have been possible without the involvement, commitment, and support from a large group of associates and colleagues. First, I would like to thank Professor Alex Felice for his trust and support. Then, there are the Associate Editors, without their important work, it would not be possible to maintain the Journal's high standards of publication. Additionally, I take this opportunity to thank my visiting students from Cardiff University who have served as Editorial Assistants during these years (Stephanie in 2013, Caitlin 2014, Magdalena 2015, Katie and Amber 2016, Katie and Sunneth 2017) and above all Dr Jackson Said the Managing Editor and the copy editors William Hicklin and Gabriel Farrugia.

Last but not least, the continued success of this Journal is only possible through the combined cooperation of authors and reviewers. Without their contributions, there would be no *Xjenza Online*! I am grateful to the authors for their high-standard of work and to the reviewers for their crucial help in the peer-review process.

In turning the reins over to the new Editor-in-Chief, with great hopes I look forward to the future of *Xjenza Online* and I wish all the best to the new editorial team.

The new *Xjenza Online* will continue to make every effort to improve content and wide fields, for the benefit of our readers and all others interested in the recent development in the different branches of science in Malta and abroad.

It is now time to pass the baton to the new Editor and to conclude my last Editorial, but this is not my final farewell to *Xjenza*. Indeed, I have been asked to act as Publication Manager for the Chamber of Scientists to continue supporting the new Editors behind the scenes in furthering the success of *Xjenza Online*.

*Giuseppe Di Giovanni*  
*Editor-in-Chief of Xjenza Online*  
*December 2017*

\*Correspondence to: Giuseppe Di Giovanni (giuseppe.digiovanni@um.edu.mt)





## Molecular Mechanisms of the Sleep Wake Cycle: Therapeutic Applications to Insomnia

Melanie Grima<sup>1</sup>, Thérèse Hunter<sup>1</sup> and Yimeng Zhang<sup>\*1</sup>

<sup>1</sup>Department of Physiology and Biochemistry, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

**Abstract.** The aim of this review is to explore the molecular mechanism and genetic components of the sleep-wake cycle and insomnia. Moreover, we wanted to review the correlation between primary insomnia and its comorbidities. With this aim, a systematic review of recent evidence of the molecular and genetic mechanisms involved in the causation of primary insomnia, along with associations between primary insomnia and other diseases were conducted. Primary insomnia is a complex disorder which accounts for 25% of total chronic insomnia and has several effects other than on sleep. It is manifested by a variety of genetic, cultural, social, psychological and environmental factors. Chronic insomnia has been shown to be 24-hour hyperarousal with reduced relative metabolism in the prefrontal cortex while awake. Insomnia can cause various physiological effects and memory capacity alterations; with chronic activation of the hypothalamic–pituitary–adrenal axis also leading to the development of depression and anxiety. Orexins and melatonin are important regulators of sleep and wakefulness. Detailed mechanisms of alterations to the neuroendocrine components highlight the therapeutic potential of orexin antagonists, as well as exogenous melatonin and melatonin receptor agonists. Genetics plays an important role in the development of insomnia, with several single nucleotide polymorphisms implicated in sleep regulation. Further research is crucial to aid understanding of this common disorder and enhance treatment options.

**Keywords:** Primary Insomnia, Genetics, Orexins, Melatonin, Insomnia-Related Morbidity

### Abbreviations

β-TrCP1: Beta-transducin repeat containing protein 1; 5-HT: serotonin; 5-HTT: serotonin trans-

porter; 5-HTTLPR: serotonin-transporter-linked polymorphic region; ABCC9: ATP-binding cassette, subfamily C member 9; ATP: adenosine triphosphate; CACNA1C: Calcium Voltage-Gated Channel Subunit Alpha1 C; CSF: cerebrospinal fluid; Cry: Cryptochrome; CSNK1D: Casein Kinase 1 Delta; CSNK1E: Casein Kinase 1 Epsilon; DEC2: Differentiated embryo chondrocyte 2; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EEG: Electroencephalography; Elp3: Elongator complex protein 3; FDA: Food and Drug Administration; GABA: Gamma-Aminobutyric Acid; HPA: hypothalamic–pituitary–adrenal; LD: light/dark; LH: lateral hypothalamus; nAChR: nicotinic acetylcholine receptor; NE: norepinephrine; NPS: Neuropeptide S; NPSR1: neuropeptide S receptor 1; NREM: non-rapid eye movement; OX<sub>1</sub>R: Hypocretin (orexin) receptor type 2; OX<sub>2</sub>R: Hypocretin (orexin) receptor type 2; Per: Period; PLCB1: phospholipase C beta 1; REM: rapid eye movement; ROR: RAR-related orphan receptors; RORE: retinoic acid related orphan receptor response element; SCN: suprachiasmatic nucleus; SIRT1: Sirtuin 1; SSS: Sleepless; SUR2: Sulfonylurea receptor 2; SWS: short wave sleep; VNTR: variable-number tandem repeat.

### 1 Background

Sleep is essential for all humans, contributing to approximately a third of our lives. Hence, the inability to sustain good quality and refreshing sleep can have detrimental effects on individuals. Approximately one-third of the American population report symptoms of insomnia (Ancoli-Israel & Roth, 1999), with 10–15% of the general population meeting the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) criteria, thereby making it the most common sleep complaint. DSM-5 defines insomnia as a syndrome char-

\*Correspondence to: Yimeng Zhang (yimeng.zhang900@gmail.com)

acterised by problems in one or more of four sleep domains: difficulty initiating sleep, difficulty maintaining sleep, early morning awakening and non-restorative sleep, which may be associated with impairment in daytime functioning. The severity of insomnia is dependent on its frequency, duration and impairment in functioning (Ohayon, 1996). As well as the effects on wellbeing, the direct cost of insomnia alone is estimated to be around 14 billion dollars annually in the United States (Walsh & Engelhardt, 1999), with its burden and prevalence on the increase (Ford, Cunningham, Giles & Croft, 2015, 3).

Sleep is modulated by a combination of two internal influences that work partly independent of each other: the sleep homeostatic mechanism and the circadian mechanism. The homeostatic drive for sleep is regulated mainly by adenosine and melatonin, which accumulates throughout the waking day. The 24-hour rhythms of the sleep/wake cycle are synchronised to the external environment, mostly influenced by light (Moore, 2007).

The suprachiasmatic nucleus (SCN) is the main circadian pacemaker of the body, which regulates the circadian oscillators via neural and endocrine control (Moore, 2007) and controls the pineal gland through a neuronal pathway (Hardeland, 2013). Light signals activate the SCN which then inhibit the release of melatonin from the pineal gland. The light-dark cycle is therefore important in controlling the circadian rhythm of sleep (Pandi-Perumal et al., 2007). A decrease in SCN neuron firing rate, due to less light, allows for an increase in sympathetic action potential, more norepinephrine (NE) release on the pineal gland and an increase in melatonin production. Melatonin, in turn, decreases the activity of SCN neurons, thus lowering the circadian drive for arousal in a positive feedback manner (Moore, 2007). Lesions of the hypothalamus affecting and restricted to the SCN can result in disruption of the sleep-wake cycle (Moore, 2007; Pandi-Perumal et al., 2007). The synchronization of the circadian clock is not a completely hierarchical SCN-driven system. Peripheral clocks may be regulated independently of the SCN both by light and other external factors thereby increasing the plasticity of the circadian system, at even down to the level of cell to cell communication and paracrine regulation (Duffy & Czeisler, 2009; Gibbs et al., 2014; Husse, Eichele & Oster, 2015; Scheer, Wright K. P., Kronauer & Czeisler, 2007).

The aetiology of insomnia is a complex interaction of genetic, environmental, physiological and behavioural factors. Chronic insomnia leads impaired occupational performance along with a large variety of serious health complaints (Chevalier et al., 1999). Rather than solely sleep deprivation, investigations now suggest that insomnia is actually a state of 24-hour hy-

perarousal that causes changes in electroencephalogram (EEG) recordings, increased night sympathetic activity, higher adenosine triphosphate (ATP) utilisation in the grey matter and increased activation of hypothalamic-pituitary-adrenal (HPA) axis, with reduced relative metabolism in the prefrontal cortex while awake (Nofzinger et al., 2004). These are consistent with an alternating daytime cytokine secretion pattern and hypersecretion in patients with primary insomnia, further supported by the alterations to the endocrine and immune system (Riemann et al., 2007). Long-term sympathetic hyperactivity is associated with elevated plasma insulin, a decrease in high density lipoproteins, an increase in triglyceride, total cholesterol, plasma angiotensin, haematocrit, as well as an increase in cardiac arrhythmias and hypertension. Chronic activation of the HPA axis can lead to depression, chronic anxiety, hypertension, visceral obesity, along with various other pathologies (Vgontzas, Liao, Bixler, Chrousos & Vela-Bueno, 2009). This highlights the detrimental effect insomnia has on the overall health of its sufferers.

## 2 Insomnia Related Morbidity

Insomnia is an independent factor for increased hospitalisation in the general population (Parthasarathy et al., 2015). An inappropriate amount of habitual sleep may impact many physiological processes, affecting performance and both mental and physical health (Sivertsen et al., 2014).

Insomnia and reduced sleep duration correlate with an increase in body weight (Gupta, Mueller, Chan & Meininger, 2002; Kripke, Garfinkel, Wingard, Klauber & Marley, 2002), with individuals who sleep less than five hours at a greater risk of obesity (Patel et al., 2008). A high body mass index, in turn, increases the risk of various cancers, metabolic diseases such as ischemic stroke, coronary heart disease and type 2 diabetes mellitus (WHO, 2014). A decrease in leptin, increase in ghrelin and body mass index have been associated with habitual sleep duration of below 7.7 hours a day (Taheri, Lin, Austin, Young & Mignot, 2004).

Both chronic insomniacs and people who regularly sleep less than 5 hours a day have been associated with a three-fold increase in the likelihood of having type 2 diabetes mellitus. Insomnia and short sleep duration have synergistic effects to increase the incidence of diabetes further (Vgontzas et al., 2009). Impaired glycaemia control has also been observed in individuals with acute or short-term modest sleep loss (Mallon, Broman & Hetta, 2005).

Cardiovascular disease is the leading cause of death in both men and women (Heron, 2012). Various hypotheses explain how insomnia and short sleep duration affect the cardiovascular system, ranging from alterations

in hormone secretion to creating an inflammatory state (Bansil, Kuklina, Merritt & Yoon, 2011; Vgontzas et al., 2009). A meta-analysis by Sofi et al. (2014) of thirteen prospective studies, concluded that subjects who reported to have difficulty initiating sleep or maintaining sleep have a 45% increased risk of morbidity and/or mortality from cardiovascular diseases, compared with normal sleepers. Hypotheses for this relate to the correlation of insomnia with metabolic and endocrine changes along with sympathetic activation and increased cytokine production and inflammatory response (Parthasarathy et al., 2015).

Sleep is vital in the functioning and development of the brain, including gene expression as well as the processes of memory formation and learning. This allows the cortical plasticity to form long-term memory as well as synaptic modifications and may explain the strengthening of memory traces during sleep (Niethard, Buralossi & Born, 2017). This occurs in the hippocampal-neocortical networks. In fact, the hippocampus has shown to be smaller in those suffering from primary insomnia (Riemann et al., 2007). Long-term potentiation is central for memory and learning and it is known to be dependent on a prolonged period of sleep with no interruptions (Kirkpatrick et al., 2017; Niethard et al., 2017; Rasch & Born, 2013). Five to six hours of sleep deprivation impairs long-term potentiation maintenance, as shown in rat models (Campbell, Guinan & Horowitz, 2002). The different stages of sleep have been shown to aid in the processing of different aspects of memory consolidation and cognitive performance (Nissen et al., 2011). In insomniacs there is reduced improvement in procedural memory across a 12-hour period, which includes sleep. Declarative memory in particular is hindered in the individuals suffering from primary insomnia, compared to normal sleepers (Griessenberger et al., 2013). The reprocessing of newly acquired information in the hippocampal and neocortical networks occurs during slow wave sleep (SWS) or deep sleep and could be the basis for long-term memory consolidation (Gais & Born, 2004). During SWS, the acetylcholine in the hippocampus drops to very low levels, aiding consolidation further. Rats that experience limited sleep have a small hippocampus. Sleep deprivation is related to lowered cell proliferation and elevated levels of glucocorticoids in the bloodstream, which inhibit adult neurogenesis (Mirescu, Peters, Noiman & Gould, 2006).

### 3 The Neuroendocrine Component

#### 3.1 Orexins

Orexin-A and Orexin-B are hypothalamic neuropeptides involved in wakefulness (de Lecea et al., 1998; Sakurai et al., 1998). Orexinergic neurons stabilise wakefulness by innervating several nuclei in the brain contain-

ing monoaminergic and cholinergic neurons. The dorso-medial nucleus of the hypothalamus sends information about the circadian rhythms and timing of wakefulness to influence orexin neurons. Orexinergic neurons are highly active during wakefulness and cease during sleep (Adamantidis, Zhang, Aravanis, Deisseroth & de Lecea, 2007; Brisbare-Roch et al., 2007; de Lecea & Huerta, 2014; Gotter et al., 2016; Herring et al., 2012). Inappropriately activated orexin neurons at night may contribute to insomnia and cause signs of hyperarousal, such as increased metabolic rate and sympathetic tone (Bonnet & Arand, 1998, 2003). When orexin is injected into rodents, rapid eye movement (REM) and non-rapid eye movement (NREM) sleep decrease and wakefulness increases. In humans, orexin deficiency is associated with narcolepsy, while mice develop a phenotype of narcolepsy or cataplexy when orexin receptors, OX<sub>1</sub>R and OX<sub>2</sub>R, are knocked out (Chemelli et al., 1999). Thus, orexin is a master regulator of the sleep-wake cycle, with high activity of the lateral hypothalamus (LH), cells during wake, and a trivial amount in sleep. Locus coeruleus noradrenergic, tuberomammillary nucleus histaminergic, raphe serotonergic, basal forebrain cholinergic neurons and pedunculopontine/laterodorsal tegmental nuclei are all activated to increase wakefulness (Hara et al., 2001; Hoyer & Jacobson, 2013; Mieda & Sakurai, 2013; Sakurai, 2007).

Orexin-A and orexin-B suppress REM sleep through G protein-coupled receptors, OX<sub>1</sub>R and OX<sub>2</sub>R, by increasing the duration of long waking bouts (Bettica et al., 2012; Sakurai et al., 1998). OX-A has similar affinity to OX<sub>1</sub>R and OX<sub>2</sub>R, while OX-B has a ten-fold preferential towards OX<sub>2</sub>R (Brown, Basheer, McKenna, Strecker & McCarley, 2012). During NREM and REM sleep, orexin neurons are inhibited by GABAergic neurons acting on GABA<sub>A</sub> and GABA<sub>B</sub> receptors. GABA<sub>A</sub> receptor antagonism increases orexin neurons during NREM sleep (Alam et al., 2010; Brown et al., 2012; Li, Gao, Sakurai & van den Pol, 2002; Sergeeva, Eriksson, Sharonova, Vorobjev & Haas, 2002).

Orexin antagonists block OX<sub>2</sub>R, or both OX<sub>1</sub> and OX<sub>2</sub> receptors, to promote sleep in animals. They specifically target arousal and thus have fewer side effects than benzodiazepine receptor agonists, which affect several other brain functions (Scammell & Winrow, 2011). Administration of such antagonists has been found to be more effective during the wake phase, and is less effective when administered during the normal sleep period when orexin activity is low. NREM and REM sleep are increased in humans whilst wakefulness is decreased (Brown et al., 2012). Orexin receptor antagonists improve onset and maintenance of sleep without significant tolerability issues or withdrawal effects in patients with chronic insomnia (Winrow & Renger, 2014). Narcolepsy



is, however, a possible side effect of orexin antagonists, with symptoms including hallucinations, cataplexy, sleep onset REM episodes and sleep paralysis (Mieda & Sakurai, 2013).

In clinical trials, dual orexin receptor antagonists have improved sleep latency, increased sleep duration and decreased wake after sleep onset (Winrow & Renger, 2014). Suvorexant is a dual orexin receptor antagonist which has been found to decrease active wake, time to sleep onset and wake after sleep onset, and increase total sleep time (Hoyer & Jacobson, 2013). Suvorexant is a small molecular, diazepam-based antagonist which binds to human OX<sub>1</sub>R and OX<sub>2</sub>R with similar potency and inhibits by dose-dependent receptor occupancy. It promotes the transition to REM and SWS in animals and humans (Yin, Mobarec, Kolb & Rosenbaum, 2015), and increases sleep in rats. Suvorexant reduces sleep onset latency for primary insomnia patients, and increases persistent sleep time. After three months of trials, patients on daily suvorexant exhibited improved latency to persistent sleep and wake after sleep onset. Unlike benzodiazepines, these do not suppress REM sleep, nor affect memory, and have no claimed following day effects, unlike GABA<sub>A</sub> modulators (Hoyer & Jacobson, 2013). There were no serious side effects or next-day residual effects, and no rebound insomnia on stopping the drug. No narcolepsy-like symptoms were observed. This is preferred over benzodiazepine receptor agonists in chronic primary insomnia since it induces natural sleep without serious side effects (Mieda & Sakurai, 2013).

SB-649868 is a dual orexin receptor antagonist currently in development by GlaxoSmithKline, it has been shown to improve the sleep of healthy individuals disrupted by noise when given in 10 mg or 30 mg doses. Wake after sleep onset was shown to be reduced with the 30 mg dose. Thus, it helps both sleep initiation and maintenance. Number of awakenings is not affected. In humans, it has hypnotic activity without noticeable changes in the power density of NREM sleep, unlike benzodiazepine receptor agonists which alter NREM sleep EEG. Thus sleep induction by dual antagonists is similar to spontaneous sleep in this manner (Bettica et al., 2012; Scammell & Winrow, 2011). SB-649868 enhances REM sleep propensity by increasing REM sleep duration and reducing REM latency.

MK-6096, a potent, reversible, orally bioavailable dual orexin receptor antagonist, similar to its close analogue dual orexin receptor antagonist-22, is a highly selective reversible antagonist for both orexin receptors. MK-6096 causes reductions in wakefulness and increases in REM and NREM sleep in various species (Winrow & Renger, 2014).

### 3.2 Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a lipid and water soluble hormone released mainly from the pineal gland of the brain directly into capillary beds and cerebrospinal fluid (CSF), to reach various tissues around the body (Berra & Rizzo, 2009). Melatonin has several functions in the body, such as regulating immunity, hormone secretion, reproductive and circadian rhythms, and sleep regulation (Dubocovich, 2007). Foetuses and new-borns obtain melatonin from placental blood and breast milk respectively. Cyclic melatonin secretion increases in 9–12 week old infants, with nocturnal levels peaking in children of less than five years, and a gradual decrease of melatonin synthesis then occurs with further aging (Zhdanova, Lynch & Wurtman, 1997). Although the melatonin profile changes amongst individuals, in a healthy person the timing, amplitude and profile remain constant over several weeks with no recognizable difference between genders, when weight is accounted for (Klerman, Gershengorn, Duffy & Kronauer, 2002).

The process by which melatonin induces sleep is unclear. Melatonin can improve sleep quality by decreasing sleep onset latency and sleep fragmentation while increasing sleep efficiency. Melatonin may increase total sleep duration by 12.8 minutes (Brzezinski et al., 2005; Koch et al., 2009). It also appears to involve a phase-shift of the circadian rhythm, a reduced core body temperature and/or a direct action on somnogenic structures with the central nervous system (CNS) (Buscemi et al., 2005; Rajaratnam, Dijk, Middleton, Stone & Arendt, 2003). Reports have shown that day-time secretion of melatonin correlates with the onset of nocturnal sleepiness. This is re-enforced by the fact that the sleep-wake cycle in infants stabilizes at three months of age, which is the same time when the melatonin nocturnal peak becomes highest and there is consolidation of nocturnal sleep. Furthermore, sleep efficacy decreases with age as does melatonin secretion (Zhdanova et al., 1997).

Exogenous melatonin can be given to patients suffering from primary insomnia to prolong sleep, improve sleep efficiency, improve functional performance, and provide patients with better sleep quality. Normal sleep onset latency is 15–20 minutes, with 30 minutes being characteristic of insomnia. Exogenous melatonin can shorten sleep onset latency by four minutes and improves sleep efficiency by 2.2%. Although these are not clinically significant, patients on treatment with exogenous melatonin reported better sleep quality. Exogenous melatonin also increased endogenous melatonin levels during the evening and night, which coincides with increased sleepiness leading to improved daytime function and alertness (Koch et al., 2009). Exogenous melatonin appears to be relatively safe, with headache, nausea,

dizziness and drowsiness as the only reported side-effects during three months of use (Buscemi et al., 2005). However, the safety of longer use has not been assessed.

Melatonin acts on melatonin receptors MT1 and MT2 (Moore, 2007) that are high-affinity G-protein coupled receptors which can be expressed by the SCN (Dubocovich, 2007). By acting on MT1 and MT2 receptors, melatonin regulates the amplitude and phase of circadian oscillations. Melatonin is a chronobiotic as it adjusts the phase of the circadian clock and helps to entrain the light-dark cycle with the external light-day cycle (Hardeland, 2013).

In response to melatonin, the MT1 receptor is associated with the acute suppression of SCN (Liu et al., 1997), causing the inhibition of the pituitary adenylate cyclase activating polypeptide (PACAP)-mediated-CREB-phosphorylation, which in turn inhibits neuronal firing within the SCN, thus promoting sleep. When melatonin binds to MT2, there is phase-shifting of the neuronal firing rate of the SCN, with a resultant phase shift of sleep onset (Dubocovich, 2007).

Activation leading to desensitization can occur during low day-time levels of melatonin due to prolonged exposure to the hormone. Oral doses of melatonin larger than 1 mg will result in supra-physiological plasma melatonin levels that can cause an increase in the expression of MT1 receptors whilst decreasing the affinity and function. However, there is no internalization of MT1 receptors despite significant desensitization. MT2 receptors, when exposed to supra-physiological or prolonged physiological levels of melatonin, are desensitized and internalised, affecting the phase-shift effect of MT2. The potency of exogenous melatonin plateaus after 1 mg. MT2 recovers through protein synthesis after physiological desensitization within eight hours. Recovery after supra-physiological levels takes longer. Desensitisation after supra-physiological concentrations is counterproductive when treating circadian rhythm sleep disorders (Dubocovich, 2007; Wassmer, Ross & Whitehouse, 2000).

MT1 and MT2 receptor agonists such as ramelteon and agomelatine are high-affinity but non-selective. Ramelteon, a tricyclic synthetic melatonin analogue is FDA-approved for insomnia with sleep onset difficulty. It has a much stronger affinity to MT1 receptor than melatonin and is highly selective for the melatonin receptors. It is a chronobiotic and hypnotic and promotes both sleep initiation and maintenance, with few next-day effects, withdrawal symptoms or rebound insomnia (Dubocovich, 2007; Pandi-Perumal et al., 2007). Agomelatine, an acetamide naphthalene analogue of melatonin, has high affinity receptor agonist for MT1 and MT2 receptors, causing circadian rhythm regulation. Agomelatine is also a 5-HT<sub>2C</sub> receptor antag-

onist resulting in an anti-depressant effect. Thus, MT1 and MT2 receptor agonists can be used to mimic the effects of endogenous melatonin (Priyadarshini, Rai & Shewede, 2015).

### 3.3 The Genetic Component

As with many diseases, insomnia has a significant genetic predisposition. A good understanding of the aetiology of insomnia contributes greatly to the understanding of the disease, as well as aiding future advances in research.

Monozygotic twins have a higher concordance rate than dizygotic twins for sleep duration, sleep onset, and EEG spectrum (Ambrosius et al., 2008; Sehgal & Mignot, 2011). There are a 0.47 and 0.15 correlations between monozygotic and dizygotic twins respectively, with an estimated heritability of 57% for insomnia, and 38% for sleepiness. There is a correlation between insomnia and sleepiness, as well as insomnia with obesity within twins, indicating a common genetic influence in those phenotypes.

### 3.4 Single Nucleotide Polymorphisms

Only a few rare sleep disorders, such as fatal familial insomnia, narcolepsy with cataplexy, and restless legs syndrome have been directly linked to single gene defects. In general, sleep disorders are caused by several mutations and single nucleotide polymorphisms which have small but accumulative effects (Seugnet et al., 2009).

Although genome wide association studies have not identified single nucleotide polymorphisms (SNPs) that reach the genome-wide significance threshold, plausible association has been observed with several candidate genes. A link has been identified between short sleep duration and SNPs in the neuropeptide S receptor 1 (*NPSR1*), *CACNA1C* and the *ABCC9* gene. The neuropeptide S receptor and its ligand NPS together with histamine and orexin are implicated in the regulation of the wake/sleep cycle. The identified SNP rs324981 in the *NPSR1* gene that is related to bedtime and presents a short sleep duration phenotype, is the homozygous T/T genotype (Asn<sup>107</sup> to Ile<sup>107</sup> substitution) (Spada et al., 2014). Groups of SNPs in the third intron of the *CACNA1C* gene are associated with sleep latency and sleep quality (Byrne et al., 2013). Notably, this gene encodes a voltage-gated calcium channel subunit that is also down-regulated in bipolar disorder and diabetes. Individuals homozygous for an intronic variant of the *ABCC9* gene also exhibit short sleep duration. SUR2, the protein product of the *ABCC9* gene has been identified as the regulatory subunit of plasma membrane potassium channel implicated in the regulation of energy metabolism (Allebrandt et al., 2013).

A study comparing 1,439 Korean insomniacs with 7,280 controls identified two significant SNPs found in

intronic regions within the *ROR* genes and the *PLCB1* gene (phospholipase C beta). *ROR* genes participate in neurite growth and synapse formation, with 16 and 14 SNPs in *ROR1* and *ROR2* respectively. The *PLCB1* gene functions via calcium signalling. However, the *ROR1* SNPs were more strongly associated with female insomniacs while the *PLCB1* SNPs were associated more with males. *PLCB1* and *ROR1* maintain open chromatin structure in the human pancreas via the binding sites PAX6 and CTCF, therefore it was concluded that SNPs in these genes may play a role in both circadian and metabolic phenotypes in insomniacs (Ban, Kim, Seo, Kang & Choi, 2011).

### 3.5 CLOCK Genes

Polymorphisms of the ubiquitous circadian clock genes involved in sleep correlate with insomnia, disease chronicity, psychiatric conditions, and age of onset of bipolar disorder (Takahashi, Hong, Ko & McDearmon, 2008). The C allele of *clock ck*, caused by a T3111C/rs1801260 SNP at the 3' non-translated region of chromosome 4q12, is associated with evening preference in North-American populations, delayed sleep onset and decreased sleep duration. It is correlated with initial insomnia in individuals with major depressive disorder, as well as night-long insomnia in those suffering from bipolar disorder. These groups show a decreased need of sleep throughout their lifetime and experience more sleep disturbance with a higher recurrence of initial, middle and early insomnia in homozygotes for the C variants. The *clock* gene polymorphism may be responsible for sleep dysregulation in patients with psychiatric disorders; however, the 3111C *clock* polymorphism is not correlated with a psychiatric disorder (Katzenberg et al., 1998; Serretti et al., 2010; Voinescu, Thome & Orasan, 2009). The incidence rate for the genotype has been shown to be similar to that found in normal people and a similar phenotype shown has also been demonstrated in a normal sample of adults (Katzenberg et al., 1998).

The circadian clock mechanism in the suprachiasmatic nucleus (SCN) and peripheral tissues involves transcriptional-translational feedback control of core clock components (Ko & Takahashi, 2006). Neuronal PAS domain protein 2 (NPAS2) is a paralogue of CLOCK and a circadian rhythm regulator (DeBruyne, Weaver & Reppert, 2007; Takahashi et al., 2008). CLOCK-BMAL1, a transcription-activator complex, increases the transcription of *Per* (Period) and *Cry* (Cryptochrome). When PER:CRY heterodimers enter the nucleus, they inhibit their own transcription by suppressing BMAL1 and CLOCK/NPAS2 transcription systems. PER:CRY heterodimers are degraded during the night, allowing CLOCK/NPAS2 and BMAL1 to activate another cycle of transcription. This forms

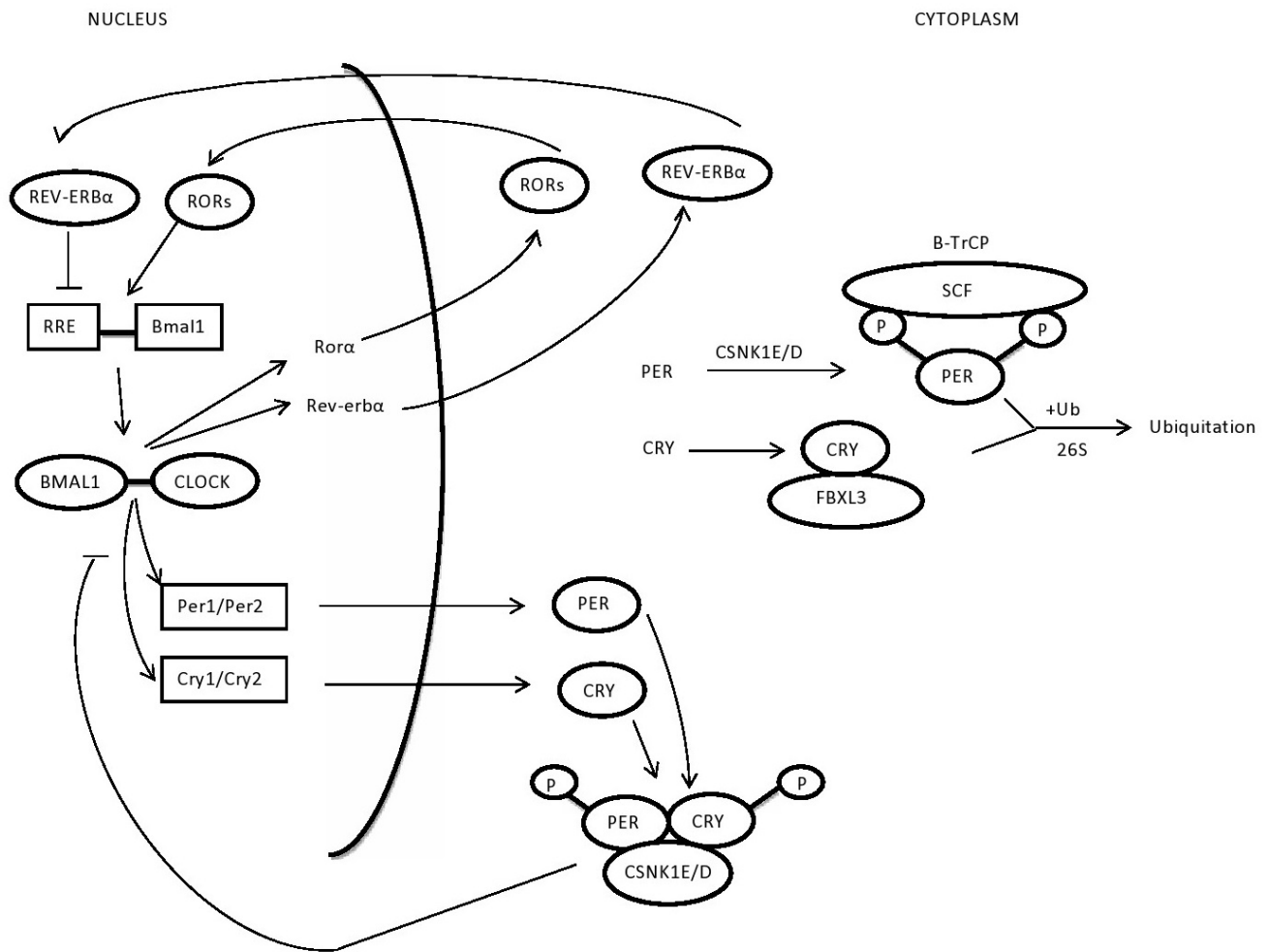
a primary negative-feedback loop that lasts approximately 24 h (Ko & Takahashi, 2006; Takahashi et al., 2008). The ubiquitination-directed degradation of CRY is controlled by the opposing effects of the two ubiquitin E3 ligase complexes FBXL3 and FBXL21, the balance of which determines the length of the circadian period in mice. FBXL3 degrades CRY in the nucleus, however, FBXL21 forms an SCF ubiquitin ligase complex which antagonises the E3 ligase activity of FBXL3 to protect CRY from degradation in the nucleus. Furthermore, FBXL21 forms an SCF E3 ligase complex to promote CRY degradation within the cytoplasm. The balance of these competing E3 ligases which cause CRY degradation will then determine the length of the circadian clock (Yoo et al., 2013).

In *Drosophila*, Casein kinase 1 delta and epsilon phosphorylate PER1/2 and CRY1/2 in the late afternoon and night as they accumulate, targeting them for degradation by the ubiquitin-proteasome pathway. Mutations in *Csnk1e* and *Csnk1d* cause shorter circadian rhythms in mammals. The 178C missense mutation in *Csnk1e* causes a *tau* mutant in hamster, with a 20 hour (h) circadian period. *Tau* mutation does this by hyperphosphorylating PER, thus destabilizing by making it a target for ubiquitination by  $\beta$ -TrCP and proteasomes. *Past-time* (*Psttm*) mutation has also been shown to shorten the circadian period by destabilizing CRY proteins.  $\beta$ -TrCP1 and FBXL3E3 ubiquitin ligase complexes respectively target PER and CRY for degradation. Mutations in *Fbxl3* lead to long circadian rhythms by stabilizing CRY, and thus reducing its ubiquitination (Ko & Takahashi, 2006; Takahashi et al., 2008; Yoo et al., 2013).

In a secondary feedback loop, CLOCK-BMAL1 targets directly Rev-erb $\alpha$ , a nuclear hormone receptor, which suppresses the transcription of *Bmal1*. CLOCK-BMAL1 increases the level of ROR that in turn activates *Bmal1* (Takahashi et al., 2008). ROR $\alpha$  and Rev-erb $\alpha$  compete to bind to the *Bmal1* promoter via retinoic acid related orphan receptor response elements (ROREs) (Ko & Takahashi, 2006).

CLOCK has histone acetyltransferase activity and acetylates BMAL1 on lysine 537. This, and lysine 9 and 14 of Histone H3, can be deacetylated by histone deacetylase sirtuin 1 (SIRT1), which is expressed cyclically. It controls gene expression by its interaction with CLOCK-BMAL1 and deacetylation and degradation of Per2 (Takahashi et al., 2008). The T2434C polymorphism in the C allele of Per1 correlates with morning preference and disruptions in sleep timing (Carpen, von Schantz, Smits, Skene & Archer, 2006). Variable-number tandem repeats (VNTRs) cause a shorter allele, Per34, which correlates to evening preference and a longer allele, Per35, which correlates to morning pref-





**Figure 1:** Transcriptional-Translational Feedback Loops Regulating the Circadian Clock Genes.

erence (Voinescu et al., 2009).

Circadian oscillations continue when one gene is mutated in either the PER or CRY families. However, if two or more mutations occur within these protein families, arrhythmicity results. The roles of mutated clock genes cannot be fully compensated by the other normal family. In mice, *Per1*<sup>-/-</sup> and *Per2*<sup>-/-</sup> cause a reduction of circadian rhythm by 0.5–1.0 h and 1.5 h respectively. *Cry1*<sup>-/-</sup> and *Cry2*<sup>-/-</sup> cause a reduction and addition of 1 h to the circadian rhythm respectively. Deficiency of CRY1 and CRY2 increases NREM sleep episodes and a lack of compensatory mechanisms of sleep deprivation. *Bmal*<sup>-/-</sup> causes loss of circadian rhythms, weight loss, infertility and shortened life expectancy. It is associated with increased sleep duration and fragmentation. *Clock*<sup>-/-</sup> has different effects depending on which tissues are affected. *Clock*<sup>-/-</sup> increases the overall levels of *Per1* in the liver and decreases it in the SCN (Ko & Takahashi, 2006). CLOCK deficiency in mice results in

a 2 h loss of sleep. BMAL deficiency and *Cry1/Cry2* double knockout both result in increased sleep duration (Carpen et al., 2006; Laposky et al., 2005; Wisor et al., 2002).

A homozygous dominant-negative antimorphic *Clock* allele mutation (*Clock* $\Delta 19/\Delta 19$ ) causes a long circadian rhythm, with loss of rhythm on prolonged constant darkness. *Per2* is produced rhythmically in liver and muscle with this mutation, however, it is decreased in kidney and heart. This results in a reduction of sleep duration in mice. CLOCK-deficient mice however, still produce normal molecular rhythms, implying that CLOCK-BMAL1 is not necessarily essential in initiating rhythms (Ko & Takahashi, 2006).

DEC2 is a transcription factor associated with reduced sleep (Ban et al., 2011). It represses CLOCK-BMAL1 activity and mutations in mice causing increased wakefulness (Sehgal & Mignot, 2011). In fact, a point mutation in *Dec2* causes reduced sleep duration

in human. Sleep onset occurs at a usual time, however, waking occurs earlier (He et al., 2009).

## 4 Conclusion

Despite considerable research to determine the importance of sleep quality and duration, it has been difficult to draw clear conclusions regarding the aetiology of insomnia as many studies focus on sleep disturbance as a secondary consequence to other disorders such as cardiovascular disease or respiratory disease. It is uncertain whether studies which focus on participants with reduced sleep duration are relevant in the insomniac population as pathological or lifestyle factors could influence sleep. Furthermore, studies are dependent on the patient feedback whose subjectivity may cause inaccuracies. Undiagnosed conditions, especially mood disorders, are difficult to rule out when recruiting participants for primary insomnia. In fact, it was noted by the National Institute of Health (2005) that “insomnia usually appears in the presence of at least one disorder. Particularly common co-morbidities are major depression, generalized anxiety, substance abuse, attention deficit/hyperactivity in children, dementia, and a variety of physical problems” (p. 11).

There were some contradictory results regarding the effect of insomnia and cardiovascular disease as the cause or effect relationship is not yet clear. Researchers noted a change in the secretion patterns of the pro-inflammatory cytokines in participants with insomnia, expressing different peak times and secretion patterns. These patterns of secretions, however, have not yet been linked with the development of cardiovascular disease itself.

Although many chemicals have been implanted in the pathophysiology of primary insomnia, it remains unclear as to its exact aetiology. Several alleles and single nucleotide polymorphisms have been identified as contributors of insomnia, however, these are likely to be only predisposing factors to insomnia, rather than causative agents.

Numerous pharmacological agents are available or currently being investigated such as exogenous melatonin, melatonin receptor agonists and orexin antagonists. Despite this, no specific therapy has yet been successfully shown to control insomnia effectively whilst having minimal side-effects and next-day effects.

There are limited studies that focus on the biochemical mechanism of which insomnia affects the physiological systems mentioned as well as the aetiology itself of insomnia. If more research is conducted in this area, it may be easier to interpret the data collected from current trials. Many of the studies relied on either self-reported insomnia severity or polysomnography recordings of one to four nights. A longer term study, with

adequate follow-up may provide some more insight into the more chronic physiological effects.

## Acknowledgements

The authors would like to acknowledge Prof. Gary Hunter for his advice.

## References

- Adamantidis, A. R., Zhang, F., Aravanis, A. M., Deisseroth, K. & de Lecea, L. (2007). Neural substrates of awakening probed with optogenetic control of hypocretin neurons. *Nature*, *450*(7168), 420–424.
- Alam, M. N., Kumar, S., Suntsova, N., Bashir, T., Szymusiak, R. & McGinty, D. (2010). GABAergic regulation of the perifornical-lateral hypothalamic neurons during non-rapid eye movement sleep in rats. *Neuroscience*, *167*, 920–928.
- Allebrandt, K. V., Amin, N., Muller-Myhsok, B., Esko, T., Teder-Laving, M., Azevedo, R. V., ... Roenneberg, T. (2013). A K(ATP) channel gene effect on sleep duration: from genome-wide association studies to function in *Drosophila*. *Mol Psychiatry*, *18*, 122–132.
- Ambrosius, U., Lietzenmaier, S., Wehrle, R., Wichniak, A., Kalus, S., Winkelmann, J., ... Friess, E. (2008). Heritability of sleep electroencephalogram. *Biol Psychiatry*, *64*, 344–348.
- Ancoli-Israel, S. & Roth, T. (1999). Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. I. *Sleep*, *22*, S347–53.
- Ban, H. J., Kim, S. C., Seo, J., Kang, H. B. & Choi, J. K. (2011). Genetic and metabolic characterization of insomnia. *PLoS One*, *6*(4), e18455.
- Bansil, P., Kuklina, E. V., Merritt, R. K. & Yoon, P. W. (2011). Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: results from the National Health and Nutrition Examination Survey, 2005 to 2008. *J. Clin. Hypertens.* *13*, 739–743.
- Berra, B. & Rizzo, A. M. (2009). Melatonin: circadian rhythm regulator, chronobiotic, antioxidant and beyond. *Clin Dermatol*, *27*, 202–209.
- Bettica, P., Squassante, L., Groeger, J. A., Gennery, B., Winsky-Sommerer, R. & Dijk, D. J. (2012). Differential effects of a dual orexin receptor antagonist (SB-649868) and zolpidem on sleep initiation and consolidation, SWS, REM sleep, and EEG power spectra in a model of situational insomnia. *Neuropsychopharmacology*, *37*, 1224–1233.
- Bonnet, M. H. & Arand, D. L. (1998). Heart rate variability in insomniacs and matched normal sleepers. *Psychosom Med*, *60*, 610–615.

- Bonnet, M. H. & Arand, D. L. (2003). Insomnia, metabolic rate and sleep restoration. *J Intern Med*, *254*, 23–31.
- Brisbare-Roch, C., Dingemans, J., Koberstein, R., Hoever, P., Aissaoui, H., Flores, S., ... Jenck, F. (2007). Promotion of sleep by targeting the orexin system in rats, dogs and humans. *Nat Med*, *13*(2), 150–155.
- Brown, R. E., Basheer, R., McKenna, J. T., Strecker, R. E. & McCarley, R. W. (2012). Control of sleep and wakefulness. *Physiol Rev*, *92*, 1087–1187.
- Brzezinski, A., Vangel, M. G., Wurtman, R. J., Norrie, G., Zhdanova, I., Ben-Shushan, A. & Ford, I. (2005). Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev*, *9*, 41–50.
- Buscemi, N., Vandermeer, B., Hooton, N., Pandya, R., Tjosvold, L., Hartling, L., ... Vohra, S. (2005). The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. *J Gen Intern Med*, *20*, 1151–1158.
- Byrne, E. M., Gehrman, P. R., Medland, S. E., Nyholt, D. R., Heath, A. C., Madden, P. A., ... Wray, N. R. (2013). A genome-wide association study of sleep habits and insomnia. *Am J Med Genet B Neuro-psychiatr Genet*, *162B*, 439–451.
- Campbell, I., Guinan, M. J. & Horowitz, J. M. (2002). Sleep deprivation impairs long-term potentiation in rat hippocampal slices. *J Neurophysiol*, *88*, 1073–1076.
- Carpen, J. D., von Schantz, M., Smits, M., Skene, D. J. & Archer, S. N. (2006). A silent polymorphism in the PER1 gene associates with extreme diurnal preference in humans. *J Hum Genet*, *51*, 1122–1125.
- Chemelli, R. M., Willie, J. T., Sinton, C. M., Elmquist, J. K., Scammell, T., Lee, C., ... Yanagisawa, M. (1999). Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell*, *98*(4), 437–451.
- Chevalier, H., Los, F., Boichut, D., Bianchi, M., Nutt, D. J., Hajak, G., ... Crowe, C. (1999). Evaluation of severe insomnia in the general population: results of a European multinational survey. *J Psychopharmacol*, *13*(4 Suppl 1), S21–4.
- de Lecea, L. & Huerta, R. (2014). Hypocretin (orexin) regulation of sleep-to-wake transitions. *Front Pharmacol*, *5*, 16.
- de Lecea, L., Kilduff, T. S., Peyron, C., Gao, X., Foye, P. E., Danielson, P. E., ... Sutcliffe, J. G. (1998). The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci U S A*, *95*, 322–327.
- DeBruyne, J. P., Weaver, D. R. & Reppert, S. M. (2007). CLOCK and NPAS2 have overlapping roles in the suprachiasmatic circadian clock. *Nat Neurosci*, *10*, 543–545.
- Dubocovich, M. L. (2007). Melatonin receptors: role on sleep and circadian rhythm regulation. *Sleep Med*, *8*, 34–42.
- Duffy, J. F. & Czeisler, C. A. (2009). Effect of Light on Human Circadian Physiology. *Sleep Med Clin*, *4*(2), 165–177.
- Ford, E. S., Cunningham, T. J., Giles, W. H. & Croft, J. B. (2015). Trends in insomnia and excessive daytime sleepiness among U.S. adults from 2002 to 2012. *Sleep Med*, *16*, 372–378.
- Gais, S. & Born, J. (2004). Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proc Natl Acad Sci U S A*, *101*, 2140–2144.
- Gibbs, J., Ince, L., Matthews, L., Mei, J., Bell, T., Yang, N., ... Loudon, A. (2014). An epithelial circadian clock controls pulmonary inflammation and glucocorticoid action. *Nat Med*, *20*(8), 919–926.
- Gotter, A. L., Forman, M. S., Harrell, C. M., Stevens, J., Svetnik, V., Yee, K. L., ... Winrow, C. J. (2016). Orexin 2 Receptor Antagonism is Sufficient to Promote NREM and REM Sleep from Mouse to Man. *Sci Rep*, *6*, 27147.
- Griessenberger, H., Heib, D. P., Lechinger, J., Luketina, N., Petzka, M., Moeckel, T., ... Schabus, M. (2013). Susceptibility to declarative memory interference is pronounced in primary insomnia. *PLoS One*, *8*, e57394.
- Gupta, N., Mueller, W. H., Chan, W. & Meisinger, J. C. (2002). Is obesity associated with poor sleep quality in adolescents? *Am. J. Hum. Biol.* *14*, 762–768.
- Hara, J., Beuckmann, C. T., Nambu, T., Willie, J. T., Chemelli, R. M., Sinton, C. M., ... Sakurai, T. (2001). Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. *Neuron*, *30*, 345–354.
- Hardeland, R. (2013). Chronobiology of Melatonin beyond the Feedback to the Suprachiasmatic Nucleus—Consequences to Melatonin Dysfunction. *Int J Mol Sci*, *14*(3), 5817–5841.
- He, Y., Jones, C. R., Fujiki, N., Xu, Y., Guo, B., Holder, J. L., J., ... Fu, Y. H. (2009). The transcriptional repressor DEC2 regulates sleep length in mammals. *Science* (80-. ). *325*(5942), 866–870.
- Heron, M. (2012). Deaths: leading causes for 2009. *Natl Vital Stat Rep*, *61*, 1–94.
- Herring, W. J., Snyder, E., Budd, K., Hutzelmann, J., Snavely, D., Liu, K., ... Michelson, D. (2012). Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology*, *79*(23), 2265–2274.
- Hoyer, D. & Jacobson, L. H. (2013). Orexin in sleep, addiction and more: is the perfect insomnia drug at hand? *Neuropeptides*, *47*, 477–488.

- Husse, J., Eichele, G. & Oster, H. (2015). Synchronization of the mammalian circadian timing system: Light can control peripheral clocks independently of the SCN clock: alternate routes of entrainment optimize the alignment of the body's circadian clock network with external time. *Bioessays*, *37*(10), 1119–1128.
- Katzenberg, D., Young, T., Finn, L., Lin, L., King, D. P., Takahashi, J. S. & Mignot, E. (1998). A CLOCK polymorphism associated with human diurnal preference. *Sleep*, *21*, 569–576.
- Kirkpatrick, J., Pascanu, R., Rabinowitz, N., Veness, J., Desjardins, G., Rusu, A. A., ... Hadsell, R. (2017). Overcoming catastrophic forgetting in neural networks. *Proc Natl Acad Sci U S A*, *114*(13), 3521–3526.
- Klerman, E. B., Gershengorn, H. B., Duffy, J. F. & Kronauer, R. E. (2002). Comparisons of the variability of three markers of the human circadian pacemaker. *J Biol Rhythm*, *17*, 181–193.
- Ko, C. H. & Takahashi, J. S. (2006). Molecular components of the mammalian circadian clock. *Hum Mol Genet*, 271–277.
- Koch, B. C., Nagtegaal, J. E., Hagen, E. C., van der Westerlaken, M. M., Boringa, J. B., Kerkhof, G. A. & Ter Wee, P. M. (2009). The effects of melatonin on sleep-wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, cross-over study (EMSCAP study). *Br J Clin Pharmacol*, *67*, 68–75.
- Kripke, D., Garfinkel, L., Wingard, D. L., Klauber, M. R. & Marley, M. R. (2002). Mortality associated with sleep duration and insomnia. *Arch. Gen. Psychiatry*, *59*, 131–136.
- Laposky, A., Easton, A., Dugovic, C., Walisser, J., Bradfield, C. & Turek, F. (2005). Deletion of the mammalian circadian clock gene BMAL1/Mop3 alters baseline sleep architecture and the response to sleep deprivation. *Sleep*, *28*, 395–409.
- Li, Y., Gao, X. B., Sakurai, T. & van den Pol, A. N. (2002). Hypocretin/Orexin excites hypocretin neurons via a local glutamate neuron-A potential mechanism for orchestrating the hypothalamic arousal system. *Neuron*, *36*, 1169–1181.
- Liu, C., Weaver, D. R., Jin, X., Shearman, L. P., Pieschl, R. L., Gribkoff, V. K. & Reppert, S. M. (1997). Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron*, *19*, 91–102.
- Mallon, L., Broman, J. E. & Hetta, J. (2005). High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care*, *28*, 2762–2767.
- Mieda, M. & Sakurai, T. (2013). Orexin (hypocretin) receptor agonists and antagonists for treatment of sleep disorders. Rationale for development and current status. *CNS Drugs*, *27*, 83–90.
- Mirescu, C., Peters, J. D., Noiman, L. & Gould, E. (2006). Sleep deprivation inhibits adult neurogenesis in the hippocampus by elevating glucocorticoids. *Proc Natl Acad Sci U S A*, *103*, 19170–19175.
- Moore, R. Y. (2007). Suprachiasmatic nucleus in sleep-wake regulation. *Sleep Med*, *8*, 27–33.
- National Institute of Health. (2005). NIH Consensus State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. *NIH Consensus and State-of-the-Science Statements*, *22*(2), 11.
- Niethard, N., Burgalossi, A. & Born, J. (2017). Plasticity during Sleep Is Linked to Specific Regulation of Cortical Circuit Activity. *Front Neural Circuits*, *11*, 65.
- Nissen, C., Kloepfer, C., Feige, B., Piosczyk, H., Spiegelhalder, K., Voderholzer, U. & Riemann, D. (2011). Sleep-related memory consolidation in primary insomnia. *J Sleep Res*, *20*, 129–136.
- Nofzinger, E. A., Buysse, D. J., Germain, A., Price, J. C., Miewald, J. M. & Kupfer, D. J. (2004). Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry*, *161*, 2126–2128.
- Ohayon, M. (1996). Epidemiological study on insomnia in the general population. *Sleep*, *19*, S7–15.
- Pandi-Perumal, S. R., Smits, M., Spence, W., Srinivasan, V., Cardinali, D. P., Lowe, A. D. & Kayumov, L. (2007). Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. *Prog Neuropsychopharmacol Biol Psychiatry*, *31*(1), 1–11.
- Parthasarathy, S., Vasquez, M. M., Halonen, M., Bootzin, R., Quan, S. F., Martinez, F. D. & Guerra, S. (2015). Persistent insomnia is associated with mortality risk. *Am J Med*, *128*, 268–275.
- Patel, S., Blackwell, T., Redline, S., Ancoli-Israel, S., Cauley, J. A., Hillier, T. A., ... Stone, K. L. (2008). The association between sleep duration and obesity in older adults. *Int. J. Obesity*, *32*, 1825–1834.
- Priyadarshini, R., Rai, G. M. & Shewede, D. G. (2015). Pathophysiological and pharmacological modulation of melatonergic system. *Int. J. Basic Clin. Pharmacol.* *4*, 632–639.
- Rajaratnam, S. M., Dijk, D. J., Middleton, B., Stone, B. M. & Arendt, J. (2003). Melatonin phase-shifts human circadian rhythms with no evidence of changes in the duration of endogenous melatonin secretion or the 24-hour production of reproductive hormones. *J Clin Endocrinol Metab*, *88*, 4303–4309.

- Rasch, B. & Born, J. (2013). About sleep's role in memory. *Physiol Rev*, *93*(2), 681–766.
- Riemann, D., Voderholzer, U., Spiegelhalder, K., Hornyak, M., Buysse, D. J., Nissen, C., ... Feige, B. (2007). Chronic insomnia and MRI-measured hippocampal volumes: a pilot study. *Sleep*, *30*, 955–958.
- Sakurai, T. (2007). The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nat Rev Neurosci*, *8*, 171–181.
- Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R. M., Tanaka, H., ... Yanagisawa, M. (1998). Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*, *92*(5), 573–585.
- Scammell, T. E. & Winrow, C. J. (2011). Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol*, *51*, 243–266.
- Scheer, F. A., Wright K. P., J., Kronauer, R. E. & Czeisler, C. A. (2007). Plasticity of the intrinsic period of the human circadian timing system. *PLoS One*, *2*(8), e721.
- Sehgal, A. & Mignot, E. (2011). Genetics of sleep and sleep disorders. *Cell*, *146*, 194–207.
- Sergeeva, O. A., Eriksson, K. S., Sharonova, I. N., Vorobjev, V. S. & Haas, H. L. (2002). GABA(A) receptor heterogeneity in histaminergic neurons. *Eur J Neurosci*, *16*, 1472–1482.
- Serretti, A., Gaspar-Barba, E., Calati, R., Cruz-Fuentes, C. S., Gomez-Sanchez, A., Perez-Molina, A. & De Ronchi, D. (2010). 3111T/C clock gene polymorphism is not associated with sleep disturbances in untreated depressed patients. *Chronobiol Int*, *27*, 265–277.
- Seugnet, L., Suzuki, Y., Thimman, M., Donlea, J., Gimbel, S. I., Gottschalk, L., ... Shaw, P. J. (2009). Identifying sleep regulatory genes using a Drosophila model of insomnia. *J Neurosci*, *29*, 7148–7157.
- Sivertsen, B., Lallukka, T., Salo, P., Pallesen, S., Hysing, M., Krokstad, S. & Simon, O. (2014). Insomnia as a risk factor for ill health: results from the large population-based prospective HUNT Study in Norway. *J Sleep Res*, *23*, 124–132.
- Sofi, F., Cesari, F., Casini, A., Macchi, C., Abbate, R. & Gensini, G. (2014). Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur. J. Prev. Cardiol.* *21*(1), 57–64.
- Spada, J., Sander, C., Burkhardt, R., Hantzsch, M., Mergl, R., Scholz, M., ... Hensch, T. (2014). Genetic association of objective sleep phenotypes with a functional polymorphism in the neuropeptide S receptor gene. *PLoS One*, *9*, e98789.
- Taheri, S., Lin, L., Austin, D., Young, T. & Mignot, E. (2004). Short sleep duration is associated with reduced leptin, elevated ghrelin and increased body mass index. *PLOS Med.* *1*, 210–217.
- Takahashi, J. S., Hong, H. K., Ko, C. H. & McDearmon, E. L. (2008). The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet*, *9*, 764–775.
- Vgontzas, A. N., Liao, D., Bixler, E. O., Chrousos, G. P. & Vela-Bueno, A. (2009). Insomnia with objective short sleep duration is associated with a high risk of hypertension. *Sleep*, *32*, 491–497.
- Voinescu, B., Thome, J. & Orasan, R. (2009). The rs1801260 CLOCK polymorphism, links to depression, insomnia and diurnal preference—preliminary findings from a Romanian sample. *Hum. Vveterinary Med.* *1*, 67–70.
- Walsh, J. K. & Engelhardt, C. L. (1999). The direct economic costs of insomnia in the United States for 1995. *Sleep*, *22*, 386–393.
- Wassmer, E., Ross, C. & Whitehouse, W. (2000). Therapeutic options for melatonin use in children. *Paediatr. Perinat. Drug Ther.* *4*, 45–51.
- WHO. (2014). Obesity. Retrieved June 2016, from [http://www.who.int/gho/ncd/risk%7B%5C\\_%7Dfactors%7B%5C\\_%7Dtext/en/](http://www.who.int/gho/ncd/risk%7B%5C_%7Dfactors%7B%5C_%7Dtext/en/).
- Winrow, C. J. & Renger, J. J. (2014). Discovery and development of orexin receptor antagonists as therapeutics for insomnia. *Br J Pharmacol*, *171*, 283–293.
- Wisor, J. P., O'Hara, B. F., Terao, A., Selby, C. P., Kilduff, T. S., Sancar, A., ... Franken, P. (2002). A role for cryptochromes in sleep regulation. *BMC Neurosci*, *3*, 1–14.
- Yin, J., Mobarec, J. C., Kolb, P. & Rosenbaum, D. M. (2015). Crystal structure of the human OX2 orexin receptor bound to the insomnia drug suvorexant. *Nature*, *519*, 247–250.
- Yoo, S. H., Mohawk, J. A., Sieppka, S. M., Shan, Y., Huh, S. K., Hong, H. K., ... Takahashi, J. S. (2013). Competing E3 ubiquitin ligases govern circadian periodicity by degradation of CRY in nucleus and cytoplasm. *Cell*, *152*, 1091–1105.
- Zhdanova, I. V., Lynch, H. J. & Wurtman, R. J. (1997). Melatonin: a sleep-promoting hormone. *Sleep*, *20*, 899–907.



## Erosive Tooth Wear in Children and Adolescents

Gabriella Gatt<sup>\*1</sup>, Miriam Schembri<sup>2</sup>, Paula Vassallo<sup>2</sup>, Maria Luisa Gainza-Cirauqui<sup>3</sup>, Ethel Vento Zahra<sup>2</sup> and Nikolai Attard<sup>2</sup>

<sup>1</sup>Department of Child Dental Health and Orthodontics, Faculty of Dental Surgery, University of Malta, Mater Dei Hospital, Msida, Malta

<sup>2</sup>Department of Oral Rehabilitation and Community Care, Faculty of Dental Surgery, University of Malta, Mater Dei Hospital, Msida, Malta

<sup>3</sup>Department of Dental Surgery, Faculty of Dental Surgery, University of Malta, Mater Dei Hospital, Msida, Malta

**Abstract.** To determine the local prevalence of erosive tooth wear in the child population and to identify the degree to which local demographic and socio-economic factors influence prevalence, a multi-stage cluster sample of three, five, eight, twelve and fifteen-year old Maltese school children were identified. The children were clinically examined under standardised conditions and provided a questionnaire to be filled directly (twelve and fifteen-year-olds) or by the parents/legal guardians (three, five and eight-year-olds). A total of 2508 children were examined. Of these, 232 three-year-old, 338 five-year-old children, 337 eight-year-old children, 642 twelve-year-old children and 560 fifteen-year-old children returned a questionnaire and were analysed. The prevalence of erosive tooth wear was > 70% in all age cohorts. Erosion experience also increased in both extent and severity with age in each dentition. Significant higher incidences were observed in eight-year old males, eight-year old overweight children, eight and fifteen-year-olds attending public schools, locality (Gozo > Malta), history of vomiting in fifteen-year olds, and children from lower socioeconomic parental status in five, eight and fifteen-year-olds.

The prevalence of erosive tooth wear is high in school aged Maltese children. This easily preventable tooth condition deserves targeted public health programmes to improve the oral health of future generations.

**Keywords:** Dental erosion, children, prevalence, demographic factors

## 1 Introduction

Wear of the dentition is a normal physiological process that may be observed in both the primary and permanent dentition. When the rate of wear, however, exceeds the reparative efforts of the tooth complex, wear becomes pathological. Wear due to repetitive contact with exogenous items such as incorrect toothbrush use, an excessively fibrous diet or the habitual holding of items by the teeth is termed abrasion. Attrition produces opposing highly polished wear facets arising due to the tooth to tooth contact. Erosive wear, on the other hand, is the chemical dissolution of tooth tissue due to successive episodes of exposure to intrinsically or extrinsically derived acids over a long enough span of time (Ganss, 2014). Erosive dental wear presents as a flattening of convex tooth surfaces, rounded cusps, occlusal concavities and in severe cases the loss of all tooth morphology (Fig. 1). Al-Dlaigan, Shaw and Smith (2001) describe how in younger populations, erosive tooth wear is the main contributory factor towards all tooth wear observed, rather than attrition or abrasion. Unlike dental caries, erosive tooth wear is not related to the longstanding presence of bacteria and the consumption of sugar.

Despite the concept that wear is a chronic condition requiring a long period of time between the exposure to the risk factors and subsequent clinical signs, erosive dental wear is, however, being increasingly diagnosed globally in the primary dentition in pre-school aged children (Al-Malik, Holt & Bedi, 2002; Harding, Whelton, O'Mullane & Cronin, 2003; Huang, Leishman, Newman & Seow, 2015; Mantonanaki, Koletsi-Kounari, Mamai-Homata & Papaioannou, 2013; Murakami et al., 2016) affecting dentitions that therefore have been present in

\*Correspondence to: Gabriella Gatt (gabriella.gatt@um.edu.mt)



**Figure 1:** Erosive tooth wear in a nine-year-old child.

the oral environment for a mere two to four years.

Erosive tooth surface loss has been largely associated with the high consumption of acidic soft drinks, fruit juices and carbonated drinks (Holbrook, Arnadottir & Kay, 2003). Erosive tooth wear is also linked to socioeconomic status, as exemplified by parental education, notably the mother's education is significantly influential (Kumar, Kroon & Laloo, 2014). Various studies though, present conflicting results concerning gender differences due to regional- and age-related differences (El Aidi, Bronkhorst & Truin, 2008; Milosevic, Young & Lennon, 1994; Nayak, Ashokkumar, Ankola & Hebbal, 2010). Moreover erosive lesions in primary molars are strongly and positively correlated to gastroesophageal reflux disease (GERD) (Campisi et al., 2008), eating disorders, such as anorexia and bulimia nervosa (Clearfield & Roth, 1985; Jarvinen, Rytomaa & Meurman, 1992), and asthma (Al-Dlaigan, Shaw & Smith, 2002).

Results of published erosion prevalence studies range from 7% in three-year-old children (Huang et al., 2015), to 77% in two to four-year-old children (Taji & Seow, 2010). The percentage of teeth with exposed dentine in fourteen-year-olds rose from 30% in 1994 (Milosevic et al., 1994) to 53% in 2004 (Bardsley, Taylor & Milosevic, 2004). The UK National Child Dental Health Surveys showed an increase of 3% of exposed dentine excluding incisal edges in fifteen-year olds in 2003 as compared to 1993 (Chadwick, White, Morris, Evans & Pitts, 2006). In a study carried out on twelve-year-old Indian school children, a prevalence of erosion was found to be 34.12% (Sinha, Abdullah, Saha & Verma, 2016).

Diagnosing erosive wear in the child is important for various reasons. The presence of erosive lesions in the primary dentition, particularly those with exposed dentine (Harding, Whelton, Shirodaria, O'Mullane & Cronin, 2010), carry with them a risk for the person presenting later with lesions in the permanent dentition

(Ganss, Klimek & Giese, 2001). Uncontrolled wear of the dentition leads to exposure of underlying dentine with associated sensitivity, whilst severe wear may also result in the deterioration of the dentition. The erosive process also produces a decrease in micro hardness of dental tissues rendering the tooth surfaces more susceptible to alternative wear processes: abrasion and attrition. This ongoing process can lead to irreversible, invasive and costly treatment (Ganss, 2014) and deterioration in the quality of life (Li & Bernabe, 2016).

The aim of the study was to determine the local prevalence of erosive tooth wear in the child population and to identify the degree to which local demographic and socio-economic factors influence prevalence. This will help policy makers plan appropriate interventions and target resources accordingly.

## 2 Materials and Methods

### 2.1 Sample

**Sample size:** A review of the pertinent literature was carried out to analyse prevalence data figures for dental erosion in children. Due to the wide ranging published prevalence figures ranging from 0.6% (Moimaz, Araujo, Chiba, Garbin & Saliba, 2013) to 100% (Jaeggi & Lussi, 2014) an expected frequency of 50% was set. The statistical package Epi-Info<sup>TM</sup> (CDC, 2007) set sample sizes. This was in accordance with total national population numbers (NSO, 2014), a degree of accuracy of  $p = 0.05$  and a confidence level of 95%. Deliberate over-sampling was carried out in anticipation of study cohort attrition due to factors including non-compliance from pre-cooperative participants, absentees, refusals of consent and failure of returned questionnaires. Data from final sample numbers of 232 three-year-old children, 338 five-year-old children, 337 eight-year-old children, 642 twelve-year-old children and 560 fifteen-year-old children was analysed.

**Sampling Procedure:** The cross-sectional study was designed using a multi-stage cluster sampling technique. Representations of both localities of residence and school type were considered in order to incorporate all socio-economic bands. A planned sampling ratio was embodied into the school selection process reflecting the proportional distribution of children found within the three schooling systems. Within each individual school, the classes to screen were then cluster-selected in a simple random method.

**Inclusion Criteria:** Children who were included in the study were those resident on the Islands all their lives and who turned three, five, eight, twelve or fifteen years old in that calendar year.

**Exclusion Criteria:** Children who did not return a signed consent form were also excluded.



## 2.2 Ethical Approval

A detailed research protocol was prepared to abide to all the requirements as stated in the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (General Assembly of the World Medical Association, 2014). The protocol was submitted for consideration, guidance and approval to the Faculty of Dental Surgery Research Ethics Committee and subsequently to the University of Malta Research Ethics Committee (UREC MD 31/2013). The study was also registered with the Local Data Protection Officer.

Approval was also sought from the relevant authorities in the three school streams. (State schools, Church schools and Independent schools). Additional signed parental consent was also sought after having distributed information sheets to all parents/legal guardians at least three weeks prior to the school visit.

## 2.3 Calibration of examiners

Training and calibration of examiners and scribes in the use of the Basic Erosive Wear Examination Index (BEWE) were carried out by an internationally renowned researcher in the field. The examiners included four dental surgeons; the scribes were two dental hygienists. Training and calibration programs organised by the Faculty of Dental Surgery included seminars, discussions, simulation laboratory sessions and clinical sessions over several days. Further calibration sessions were carried out involving duplication of examination of clinical cases in order to assess intra- and inter-examiner reliability.

An inter-rater reliability analysis using the Kappa statistic was performed to determine consistency among examiners. Additional intra-examiner reliability was determined by carrying out repeat examinations of random participants during the study.

## 2.4 Clinical Examination

Examinations were held on school premises during school hours. A portable dental unit (Jiangsu Dynamic DU892, Zhengzhou Smile Dental Equipment Co., Ltd. Henan, China) provided compressed air. A Daray X200LED mobile examination light provided a standardised source of light delivering 8,000 lux at 1 m and 32,000 lux at 0.5 m (Daray Lighting Ltd., Leighton Buzzard, Luton, UK). Sterile wrapped packs containing a front surface reflecting mirror and a ball-ended WHO CPITN-E probe was available for each participant. Data were recorded by trained scribes onto number coded data input sheets. Examiners wore individual protection equipment while the children were examined in a supine position. Repeat examinations of two randomly selected children were carried out at each school

visit to assess intra-examiner reproducibility. Participants were screened for erosive tooth wear, dental caries and dental fluorosis. They were also charted for the presence of plaque, calculus, dental traumatic injuries and soft tissue lesions. Each child needing treatment was given a referral note. Repeated observations at two separate visits were carried out for the three-year-old cohort and the five-year-old cohort two and three years apart respectively.

## 2.5 Indices

Erosive tooth wear – The Basic Erosive Wear Examination (BEWE) Index was used to score an index value per participant. The BEWE Index examines all surfaces of all teeth (excluding third molars) and records the highest score (0–3) for each sextant (55–54, 53–63, 64–65, 75–74, 73–83, 84–85). The sum of all six scores (max 18) is the participant’s cumulative score. Cut-off values of the cumulative scores then guide the clinical management for that level of erosive tooth wear (Bartlett, Ganss & Lussi, 2008). For the purpose of this study, participants were assigned to an erosion experience category according to their individual cumulative score. Table 1 depicts the distribution of categories.

**Table 1:** BEWE Erosion Experience Categories according to cumulative score

Cumulative Score of all Sextants	Experience Level	BEWE Erosion Experience Categories for this study
0–2	None	BEWE 1
3–8	Low	BEWE 2
9–13	Medium	BEWE 3
14–18	High	

The Erosion Experience Level Groups ‘Medium’ and ‘High’ (cumulative scores 9–18) were grouped together as they form a homogeneous group in terms of the clinical management recommended by the BEWE Index (Bartlett et al., 2008).

## 2.6 Height and Weight Measurements – Body Mass Index (BMI)

Anthropometric measurements were recorded in a consistent and systematic manner by examiners and scribes using a portable stadiometer (SECA 214 Portable Stadiometer) and portable digital scales (SECA 875 flat scales). Children were asked to remove their school shoes and were measured wearing their uniforms. Participants were instructed to hold the Frankfort plane parallel to the ground whilst measuring their height. The calculated BMI values were then divided into four cat-

egories (Thinness, Normal, Overweight and Obesity) according to the International Obesity Task Force (IOTF) cut-off values (Cole & Lobstein, 2012). Cut-off points at the mid-year value (3.5 years and 5.5 years, 8.5 years, 12.5 years and 15.5 years) were utilised. This is the recommended procedure when carrying out epidemiological studies including age groups of one-year width (Cole & Lobstein, 2012).

## 2.7 Questionnaire

A piloted and sequentially refined questionnaire in both English and Maltese was set-up and was distributed to parents/legal guardians of all three, five and eight-year-old children screened. The twelve and fifteen-year-old age cohorts were given a self-administered questionnaire to complete.

The questionnaire was designed to enquire about sociodemographic factors, parental/self-perceptions of oral health, oral health habits, dietary habits and general health factors. Sociodemographic variables included gender, age, locality and duration of residence, parental educational level (divided into 4 levels: Primary School level, Secondary School level, Post-Secondary School level and Tertiary level), and parental job type (4 subdivisions: Professional, Clerical/Business, Manual labourer and Unemployed). A question regarding the self/parents' level of satisfaction with dental appearance asked participants to list whether they were 'satisfied', 'not satisfied' or 'don't know'. Participants were asked whether they perceived their own or their child's oral health to be 'good', 'average', 'poor' or 'don't know'. The frequency of visits to the dentist in the past 12 months was also questioned and divided into the following categories: 'Never at all', 'Never in the last year', 'Once', 'Twice', 'Three times' and 'Don't remember'. Six questions from the 13 item Early Childhood Oral Health Impact Scale (ECO-HIS) (Pahel, Rozier & Slade, 2007) instrument were also asked. These included questioning about reports of pain, difficulty eating, sensitivity to hot and cold foods, avoidance of smiling, missed days of school and parental days of work. General health-related questions enquired about the use of medications, asthma and its treatment, hospitalisation, gastro-oesophageal reflux disease, history and duration of vomiting and symptoms of dry mouth. The distributed questionnaires were number coded per participant to match the data input forms.

## 2.8 Data Analysis

The primary outcome of this study was the prevalence of erosive tooth wear in the relative age cohorts. The secondary outcomes were the effect of independent variables upon the BEWE Erosion Experience Category scores. The independent variables included aspects of

socio-demographic status and were analysed as categorical variables. Descriptive statistics, tests for normality of data, frequencies and cross tabulations were performed. The Pearson Chi-squared test was used to analyse the differences in proportions in the categories of the various socio-demographic factors presenting in the three BEWE erosion experience categories. Similarly, the Pearson Chi-squared test was also used to explore the relationship between the categories of Parental perception of oral health and further categorical independent variables. When a cell presented with a value  $\leq 5$  the Fischer's Exact Probability Test was employed instead. The Kruskal-Wallis H Test allowed comparison of the mean ranks scored when carrying out a 'between groups' analysis of BEWE scores, Parental Perception of oral health and parental level of education.

Statistical significance for all tests was set at  $p < 0.05$ . Statistical tests were carried out using SPSS 20.0 software (IBM Company, Chicago, IL, USA).

## 3 Results

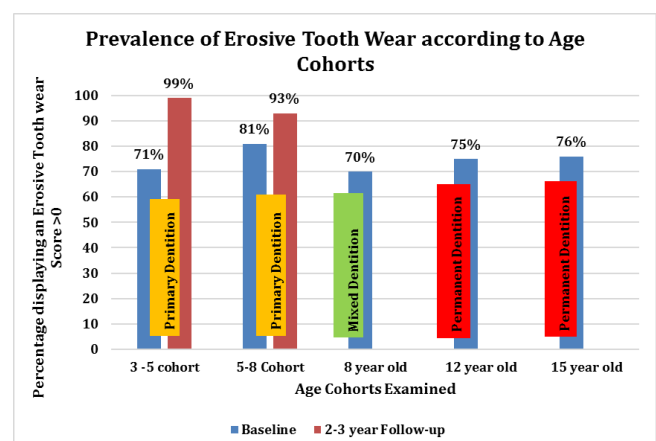
Kappa values for intra- and inter-examiner reproducibility for the BEWE Index were 0.86 and 0.79 respectively.

### 3.1 Sample Descriptors

Table 2 depicts the relevant characteristics of the three and five, eight, twelve and fifteen-year-old child samples that participated.

### 3.2 Prevalence of Erosive Wear according to Age Cohort

Fig. 2 shows how signs of erosive wear on at least one tooth surface (BEWE cumulative score  $> 0$ ) increased both with increasing age in each dentition type (primary, mixed and permanent dentitions) and also with time between baseline and follow-up examinations, in the three and five-year-old cohorts two to three years apart.



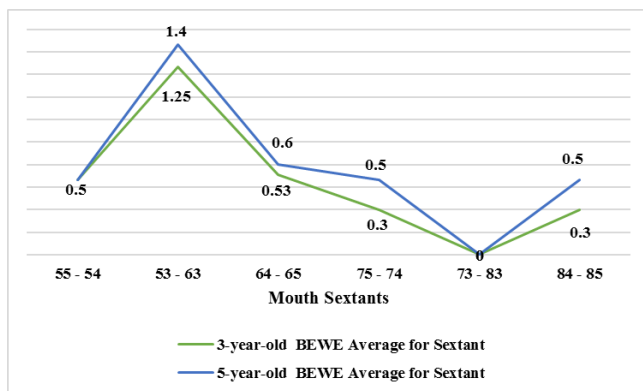
**Figure 2:** Prevalence of erosive tooth wear according to age cohorts.

Table 2: Sample characteristics.

AGE THREE. TOTAL POPULATION – 4026					
52% males, 48% females					
SCHOOL TYPE	TARGET	REMAINING AFTER DROPOUTS*	MATCHED WITH QUESTIONNAIRE	QUESTIONNAIRE RESPONSE RATE	
INDEPENDENT	80	70	43	61%	
CHURCH	40	53	38	72%	
STATE	280	213	151	71%	
<b>TOTAL</b>	<b>400</b>	<b>336</b>	<b>232</b>		
AGE FIVE. TOTAL POPULATION – 3788					
54% males, 46% females					
SCHOOL TYPE	TARGET	REMAINING AFTER DROPOUTS*	MATCHED WITH QUESTIONNAIRE	QUESTIONNAIRE RESPONSE RATE	
INDEPENDENT	60	61	36	59%	
CHURCH	120	128	118	92%	
STATE	240	251	184	73%	
<b>TOTAL</b>	<b>420</b>	<b>441</b>	<b>338</b>		
AGE EIGHT. TOTAL POPULATION – 4,393					
51% males, 49% females					
SCHOOL TYPE	TARGET	REMAINING AFTER DROPOUTS*	MATCHED WITH QUESTIONNAIRE	QUESTIONNAIRE RESPONSE RATE	
INDEPENDENT	40	55	40	72.7%	
CHURCH	120	164	87	53%	
STATE	240	276	210	76%	
<b>TOTAL</b>	<b>400</b>	<b>495</b>	<b>337</b>		
AGE TWELVE. TOTAL POPULATION – 4255					
54% males, 46% females					
SCHOOL TYPE	TARGET	REMAINING AFTER DROPOUTS*	MATCHED WITH QUESTIONNAIRE	QUESTIONNAIRE RESPONSE RATE	
INDEPENDENT	40	38	38	100%	
CHURCH	180	273	273	100%	
STATE	280	331	331	100%	
<b>TOTAL</b>	<b>500</b>	<b>642</b>	<b>642</b>		
AGE FIFTEEN. TOTAL POPULATION – 5,031					
53% males, 47% females					
SCHOOL TYPE	TARGET	REMAINING AFTER DROPOUTS*	MATCHED WITH QUESTIONNAIRE	QUESTIONNAIRE RESPONSE RATE	
INDEPENDENT	40	6	6	100%	
CHURCH	180	173	172	99%	
STATE	360	416	382	92%	
<b>TOTAL</b>	<b>580</b>	<b>594</b>	<b>560</b>		
<b>DROPOUTS*</b> : Absent or uncooperative participants					

### 3.3 BEWE Erosion Experience, Severity and Distribution according to sextants

Erosion experience also increased in both extent and severity with age in each dentition – primary and permanent. Participants with a BEWE Erosion Experience Category 3 (medium–high) increased from 8% to 13% from age three to five respectively in the primary dentition. While in the Mixed dentition stage 17% of 8-year-old children scored a BEWE 3 category. When into the permanent dentition, 1.5% of twelve year olds scored a BEWE 3 Erosion Experience Category moving up to 5.7% by age fifteen. In all age cohorts, the upper anterior sextant (53–63) (13–23) was the sextant most affected by erosive tooth wear. However, Fig. 3 depicts how erosive wear has a near whole mouth affect with BEWE scores increasing mostly in the upper labial sextant and the lower buccal sextants. The lower labial sextant remained generally unaffected.



**Figure 3:** Trends in average BEWE scores per mouth sextant in 3- and 5-year-old children.

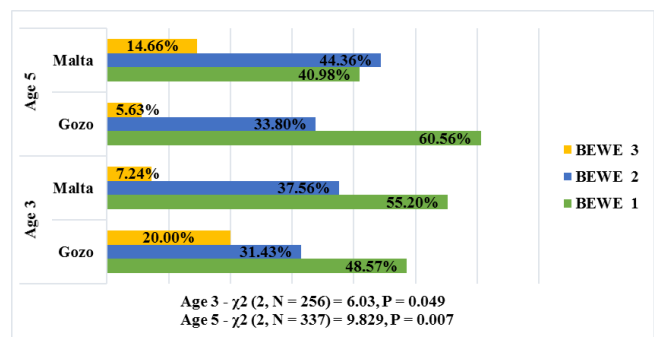
### 3.4 BEWE Erosion Experience and Gender, School Type and Locality of Residence

In the 8-year old group, there was a statistically significant difference between genders; the incidence of erosion being higher in males compared to females (Unpaired *t*-test:  $p = 0.0147$ ). In all the other cohorts, there was no statistical significant difference between BEWE Erosion Experience Category distribution between males and females.

The type of school attended by the subjects was found to be statistically significant for both 8 and 15-year-old age groups in relation to the incidence of erosion observed, the latter being highest for students attending public schools and lowest reported in students attending independent schools (Fisher's Exact test:  $p = 0.0001$ ). BEWE Erosion Experience Categories within the three different schooling types frequented showed no statistically significant differences in the three, five and twelve-year-old age cohorts (1-way ANOVA *F* test,  $p = 0.071$ ),

( $p = 0.371$ ) and ( $p = 0.305$ ) respectively.

Statistical tests revealed no significant differences in BEWE Erosion Experience Category between the various districts within the mainland. When, however, all the districts within the island of Malta were compared collectively to the sister island, statistically significant differences were observed. Twenty percent of Gozitan three-year-old child fell into BEWE Erosion Experience Category 3. This was found to be a statistically significant difference to the 7% of Maltese children falling into BEWE Erosion Experience Category 3 ( $\chi^2(2, N = 256) = 6.03, p = 0.04$ ). Fig. 4 illustrates how the trend reverses in the five year-old Gozitan cohort who exhibited a significantly lower percentage of children (5.6%,) in BEWE Erosion Experience Category 3 compared to those in Malta (15%,) ( $\chi^2(2, N = 337) = 9.829, p = 0.007$ ).



**Figure 4:** BEWE distribution according to district in 3 and 5-year-old children.

### 3.5 BEWE Erosion Experience Category and General Health Conditions

Fourteen percent of the preschool aged cohort, 15% of the eight-year-old cohort, 10% of the twelve-year-old adolescents and 8% of the fifteen-year-old teenagers in this study were reported to be asthmatic. In three, five and twelve-year-old children, all factors relating to current ( $p = 0.67$ ), ( $p = 0.574$ ), ( $p = 0.585$ ) or a past history ( $p = 0.155$ ), ( $p = 0.224$ ), ( $p = 0.730$ ) of asthma, and the use of inhalers and any other medications, were found to be unrelated to erosion experience ( $p > 0.05$ ). Additionally, all factors related to hospitalisation ( $p = 0.783$ ), ( $p = 0.606$ ), ( $p = 0.260$ ) vomiting ( $p = 0.528$ ), ( $p = 0.164$ ), ( $p = 0.880$ ) and any symptoms related to gastroesophageal reflux disorder (GERD) did not reach significance in these three age cohorts. These included regurgitation, dry mouth, thirst, heartburn and reports of a bad taste upon awakening ( $p > 0.05$ ). The only medical condition that was statistically related to the incidence of erosion was a history of vomiting in the 15-year old subjects (Fisher's Exact test:  $p = 0.01$ ).

### 3.6 BEWE Erosion Experience Category and BMI

BMI figures indicated a shift whereby there is a reduced number of children in the Thinness weight range and increased numbers in the Normal, Overweight and Obesity weight ranges in the younger three-year old cohort when compared to the five-year-old group. Statistical tests did not result in significant relationships between BMI category allocation and BEWE Erosion Experience Category allocation for these age cohorts ( $p > 0.05$ ). In both the three and five-year-old age groups a trend was observed whereby a higher representation of children in the overweight/obese group was present in the BEWE Erosion Experience Category 1 (53% ( $N = 50$ ) and 47% ( $N = 54$ )). In the eight-year-old cohort, however, both males and females in the overweight range were at a higher risk of tooth erosion compared to children identified in the other predefined categories since they represent the lowest percentage of participants in the BEWE Erosion Experience Category 1 (Chi-square test:  $p = 0.003$ ).

### 3.7 BEWE Erosion Experience Category and Socioeconomic Indicators

In the five (Fig. 5) and fifteen-year-old cohorts alone, children of parents with a tertiary level of education had the lowest representation within the BEWE Erosion Experience Category 3 (10%). Results reached statistical significance ( $\chi^2(6, N = 319) = 16.836, p = 0.012$ ), (Fischer’s Exact test at  $p = 0.035$ ) respectively. There is a gradual increase in the percentage of subjects at no risk of tooth erosion as the highest level of the mothers’ education attained progress from primary school level education to a post-graduate level. A statistically significant relationship between the level of tooth erosion and the occupation of the main breadwinner was observed for the 8-year-old cohort (Fig. 6).

The frequency of visits to the dentist was seen to be unrelated to the parental level of education in the three and five-year-old cohorts ( $\chi^2(15, N = 234) = 17.879, p = 0.269$ ).

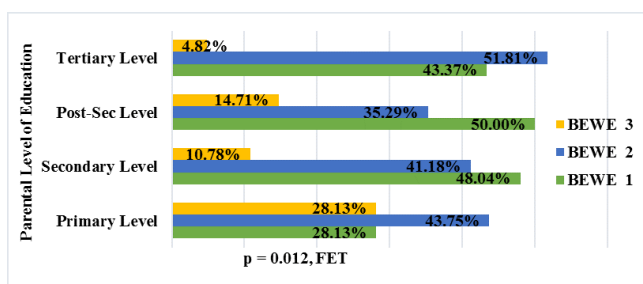


Figure 5: BEWE distribution in 5-year-old children according to the parental level of education.

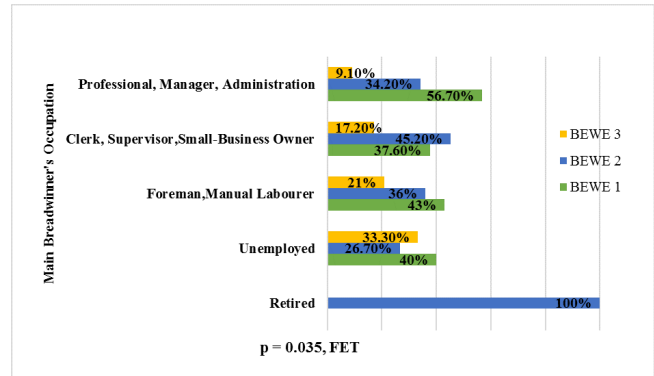


Figure 6: BEWE distribution in 8-year-old children according to occupation of family’s main breadwinner.

### 3.8 Parental Perception of the Oral Health status of their child in relation to BEWE Erosion Experience Category and Parental Level of Education

The higher the level of education of the parents of three and five-year-old children, the more positive were the comments, irrespective of BEWE Erosion Experience Category. A Kruskal-Wallis H test revealed a statistically significant difference in parental perception of the oral health of their children across the different parental levels of education  $\chi^2(3, N = 310) = 17.43, p = 0.001$ . The group with a tertiary level of education recorded a more positive oral health status score for their children ( $Md = 2$ ) as compared to the other groups ( $Md = 3, 5$ ). The parental perception of oral health was seen to be statistically related to appearance, experience of pain and the presence of dental decay but not to erosive wear experience (Table 3).

Eight, twelve and fifteen-year-old participants were asked to describe their own state of health of their teeth. Of note, the highest percentage of respondents in the three age groups perceive their oral health as ‘Good’ followed by respondents deeming their personal oral health as ‘Very good’ or ‘Average’. Very few respondents classify their oral health as poor or very poor. In eight and fifteen-year-old age groups, no significant correlation was found between the subjects’ perception of dental health and the incidence of tooth erosion, possibly indicating that patients are suffering from tooth erosion might be unaware of, or do not appreciate the problem. In the twelve-year-old age group, however, BEWE scores were significantly different ( $p = 0.010$ ) according to the perception of the status of health of their own teeth.

On the other hand, the relation between the self-reported perceptions of dental appearance and the incidence of tooth erosion was significant in the 8-year-old (FET,  $p = 0.002$ ), 12-year-old (ANOVA F test,

**Table 3:** Parental perception of the child's level of oral health in relation to erosion experience, pain, dental caries and appearance.

	AGE THREE	AGE FIVE
Parental perception of oral health in relation to BEWE score	$\chi^2(6, n = 243) = 4.6, p = \mathbf{0.0564}$	$\chi^2(6, n = 334) = 3.371, p = \mathbf{0.739}$
Parental perception of oral health in relation to reporting of pain	$\chi^2(12, n = 243) = 27.58, p = \mathbf{0.027}$	$\chi^2(12, n = 336) = 64.228, p < \mathbf{0.001}$
Parental perception of oral health in relation to presence of caries	$\chi^2(9, n = 245) = 44.313, p < \mathbf{0.001}$	$\chi^2(9, n = 336) = 56.655, p < \mathbf{0.001}$
Parental perception of oral health in relation to appearance	$\chi^2(9, n = 212) = 51.171, p < \mathbf{0.001}$	$\chi^2(4, n = 304) = 21.4, p < \mathbf{0.001}$

$p = 0.022$ ) and 15-year-old (FET,  $p = 0.025$ ) groups. This is an indication that tooth erosion might have some psychological effects on the affected subjects.

#### 4 Discussion

This cross-sectional study is the first of its kind to assess the prevalence of erosive tooth wear in three and five-year-old pre-school aged children, in eight-year-old children and in twelve and fifteen-year-old adolescents in the Maltese islands. A parent administered questionnaire was distributed to the parents of the three, five and eight-year-old participants while the twelve and fifteen-year-old cohorts completed a self-administered questionnaire. The questionnaire data were used to study the possible influence of socio-demographic factors upon oral health.

Although the final sample size was reduced due to exclusion criteria and non-response of the questionnaire, together with a potential bias from those parents/guardians who were interested in health issues, the study still presents a representative sample of the population studied. Interpretation of the results of this study, therefore, takes into account all these factors associated with the use of questionnaires and the need for parental consent when collecting data.

In this study the prevalence of erosive tooth wear (BEWE Cumulative Score  $\geq 1$ ) was recorded at 71% ( $n = 238$ ) in the three-year-old cohort, at 81% ( $n = 356$ ) in the five-year-old cohort, 70% ( $n = 320$ ) in the eight-year-old cohort, 75% ( $n = 477$ ) in the twelve-year-old cohort and 76.3% ( $n = 441$ ) in the fifteen-year-old cohort. Age-specific significant socio-demographic factors that influenced erosion scores were gender, the location of residence, school type, BMI, a history of vomiting and parental level of education.

Comparison of prevalence results with those from other studies is difficult due to the use of different erosion indices. However, results obtained by this study

for the preschool aged cohorts are most similar to those reported by Taji and Seow (2010) at 77% in two to four-year old children (Modified Smith and Knight clinical index) and Mantonanaki et al. (2013) at 78.8% in five-year-old children where the BEWE Index was utilised. That by Tschammler, Muller-Pflanz, Attin, Muller and Wiegand (2016) is the one other study that utilised the BEWE index together with the O'Sullivan Index on both three and five-year-old children reporting agreement between the two indices. This latter study reported the prevalence of 14.2% in three-year-old children and 58.8% in five-year-old children. Similarly, a national study carried out in Iceland in 2010 on fifteen-year-olds concluded that 30% of examined subjects suffered tooth erosion to some degree (Arnadottir et al., 2010) whilst in a study carried out in the Netherlands in 2009, 44.2% of fifteen-year old students suffered erosion (El Aidi, Bronkhorst, Huysmans & Truin, 2010). This study also follows the pattern seen in results of a study carried out by Kreulen et al. (2010) where higher percentages of wear into dentine of deciduous teeth were observed when compared to permanent teeth. The difference is partially attributable to the examination of the deciduous teeth for the younger age groups which would have been exposed to acidic threats for a longer period of time compared to the permanent dentition, including the buccal segments, examined in the twelve and fifteen-year olds subjects, which, besides having a higher micro hardness level, would have only just recently erupted into the mouth.

Similar to the findings by Moimaz et al. (2013), Tong, Rudolf, Muyombwe, Duggal and Balmer (2014) who reported no gender difference in erosion prevalence in four to six-year-old children, this study also found no statistically significant association between gender and prevalence of erosion in the preschool aged cohorts. These age groups did, however, show an 8% increment in the count of males in the BEWE Erosion Experience Categories 2

and 3 proceeding from the three to the five-year-old cohort while a 5% difference was observed in the female groups. Consistent with findings from epidemiological surveys carried out in other countries (Arnadottir et al., 2010; Milosevic et al., 1994), gender was found to be a predisposing factor for erosion for the eight and fifteen-year-old age groups. As suggested by Bardsley et al. (2004) the lower incidence of tooth wear in females could be attributed to better oral hygiene and lower consumption of carbonated beverages or alcoholic drinks when compared to their male counterparts. These attributes were also observed in this study.

The socioeconomic standing of a child is most often measured in terms of the type of school attended, locality of residence and the main caregiver/breadwinner's occupation and/or level of education. As stated previously, studies assessing the association between socioeconomic standing and erosion experience have given widely opposing results (Dugmore & Rock, 2004; Harding et al., 2003, 2010; Kumar et al., 2014; O'Brien, 1994; Vazquez-Nava et al., 2010). This study found an association between the parental occupation and erosion experience. Erosion experience was however found to be related to the parental level of education in most age groups but to a statistically significant level in the 5 and 15-year-old age cohorts alone. In accordance with some studies (Kumar et al., 2014) but contrary to other studies (O'Brien, 1994), this study showed that a higher level of parental education and occupation appeared to protect against erosive wear in select age cohorts.

The schooling system on the island may only be loosely associated with demographic properties and socioeconomic status. A stratified cluster-sampling technique was however employed when selecting the participating schools in order to ensure proportionate representations for each functioning school type. Results reached statistical significance in the eight and fifteen-year-old cohorts alone. This highlights that oral health educational programs are to target all children irrespective of socioeconomic standing.

This study also sought to investigate any association between general health parameters and chronic illnesses that may be related to erosive tooth wear, including asthma and reflux disorders. The Body Mass Index (BMI), which is a reflection of lifestyle/dietary habits and used to assess risk for chronic diseases, was calculated for each child. Attempts have been made to study the link between BMI and oral health findings. While D'Mello, Chia, Hamilton, Thomson and Drummon (2011) found no association between obesity and dental caries in children less than 8 years of age, a systematic review carried out found a significant association (Hayden et al., 2013). Though there is an established link between obesity and poor periodontal

health in adults (Saito, Shimazaki, Koga, Tsuzuki & Ohshima, 2001), there is little published data referring to the child patient, and further studies are needed to confirm the hypothesis of this link (Katz & Bimstein, 2011). Dental erosion, obesity and dietary habits are an interconnected triad sharing common risk factors. Similar to other studies which found an association between BMI and erosion risk in 7 to 15 year old children (Tong et al., 2014), this study found a significant relationship between these two factors in just the eight-year-old cohort. These results are indicative that the components contributing towards overweight/obesity are not constantly in common with those predisposing to erosive tooth wear. Use of the common risk factor approach in preventive management for these two conditions would, therefore, have to be applied cautiously.

The associations between erosive tooth wear, asthma and gastroesophageal reflux disorder (GERD) (O'Sullivan, Curzon, Roberts, Milla & Stringer, 1998; Tootla, Toumba & Duggal, 2004) have been researched extensively. Dental erosion has been described as an extra oesophageal manifestation of GERD while GERD itself is extremely common in child patients and is often overlooked (Yuksel, Yilmaz, Kirmaz, Aydogdu & Kasirga, 2006). Asthma has been directly linked to erosive dental wear due to the low pH values of relief bronchodilators, and the low oral pH conditions they cause. A study measured the inherent pH and titratable acidity of commercially available paediatric asthma inhalers and reported the inherent pH of dry powder inhalers to have a mean value of 5.06. When used regularly, beta-2 adrenoceptor agonists reduce the salivary flow rate and therefore indirectly, cause erosion (Thomas, Parolia, Kundabala & Vikram, 2010). The resulting oral dehydration may also lead to an increase in consumption of acid drinks further contributing to a higher risk for erosive tooth wear. This study found no statistically significant association between dental erosion and both GERD and asthma possibly due to the young age of the participants and therefore an insufficient exposure time for a visible effect to be observed clinically.

Similar to the findings observed in our study, vomiting over a period of time has also been identified as being crucial in approximately one quarter of all cases of dental erosion (Jarvinen et al., 1992). While medical assistance should be sought to treat disorders with vomiting, regurgitation or reflux of gastric contents over a prolonged period, it is important to minimize the tooth wear whilst the condition is being treated. A neutralisation procedure is useful for the prevention of erosion, given it is employed immediately following the acid challenge (Imfeld, 1996b). Acid neutralization may be attempted by holding some milk in the mouth for a short



time after vomiting (Imfeld, 1996a). Consuming milk or cheese (Gedalia et al., 1991) was reported to rehardened pre-softened enamel specimens.

The educational level of the parent was significantly linked to the parent's perception of oral health in the five-year-old age group ( $p = 0.035$ ) and was not associated with the number of dental visits. Aesthetics and erosive wear were significantly linked in the eight, twelve and fifteen-year-old participants; the perception of the level of dental health and erosive wear was not.

## 5 Conclusion

This study has provided evidence that erosive tooth wear is significantly present in the young child and adolescent irrespective of most socio-demographic factors. These findings reinforce the need for more public health programs which target the whole spectrum of society including childcare personnel, social workers and general healthcare providers in an effort to increase levels of oral health literacy and thereby help young children access better dietary habits and the dental care they require. Additionally, more preventive interventions are to be targeted at teenagers in order to promote healthier lifestyle choices.

## Acknowledgements

The authors thank Joseph Galea, Sandra Milton and Veronica Montebello for their assistance with scribing during the screening procedures. In addition, we also thank Joseph Galea for his help with the input of the data. The project was funded by the University of Malta Research Grants.

## References

- Al-Dlaigan, Y. H., Shaw, L. & Smith, A. (2001). Dental erosion in a group of British 14-year-old, school children. Part I: Prevalence and influence of differing socioeconomic backgrounds. *Br Dent J*, *190*(3), 145–149.
- Al-Dlaigan, Y. H., Shaw, L. & Smith, A. J. (2002). Is there a relationship between asthma and dental erosion? A case control study. *Int J Paediatr Dent*, *12*(3), 189–200.
- Al-Malik, M. I., Holt, R. D. & Bedi, R. (2002). Erosion, caries and rampant caries in preschool children in Jeddah, Saudi Arabia. *Community Dent Oral Epidemiol*, *30*(1), 16–23.
- Arnadottir, I. B., Holbrook, W. P., Eggertsson, H., Gudmundsdottir, H., Jonsson, S. H., Gudlaugsson, J. O., ... Agustsdottir, H. (2010). Prevalence of dental erosion in children: a national survey. *Community Dent Oral Epidemiol*, *38*(6), 521–526.
- Bardsley, P. F., Taylor, S. & Milosevic, A. (2004). Epidemiological studies of tooth wear and dental erosion in 14-year-old children in North West England. Part 1: The relationship with water fluoridation and social deprivation. *Br Dent J*, *197*(7), 413–6, discussion 399.
- Bartlett, D., Ganss, C. & Lussi, A. (2008). Basic Erosive Wear Examination (BEWE): a new scoring system for scientific and clinical needs. *Clin Oral Investig*, *12 Suppl 1*, S65–8.
- Campisi, G., Lo Russo, L., Di Liberto, C., Di Nicola, F., Butera, D., Vigneri, S., ... Di Fede, O. (2008). Saliva variations in gastro-oesophageal reflux disease. *J Dent*, *36*(4), 268–271.
- CDC. (2007). Epi Info™. Retrieved May 2014, from <https://www.cdc.gov/epiinfo/index.html>
- Chadwick, B. L., White, D. A., Morris, A. J., Evans, D. & Pitts, N. B. (2006). Non-carious tooth conditions in children in the UK, 2003. *Br Dent J*, *200*(7), 379–384.
- Clearfield, H. R. & Roth, J. L. A. (1985). *Anorexia, Nausea and vomiting in Blockus gastroenterology*. Philadelphia: Saunders.
- Cole, T. J. & Lobstein, T. (2012). Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes*, *7*(4), 284–294.
- D'Mello, G., Chia, L., Hamilton, S. D., Thomson, W. M. & Drummon, B. K. (2011). Childhood obesity and dental caries among paediatric dental clinic attenders. *Int J Paediatr Dent*, *21*(3), 217–222.
- Dugmore, C. R. & Rock, W. P. (2004). A multifactorial analysis of factors associated with dental erosion. *Br Dent J*, *196*(5), 283–6, discussion 273.
- El Aidi, H., Bronkhorst, E. M., Huysmans, M. C. & Truin, G. J. (2010). Dynamics of tooth erosion in adolescents: a 3-year longitudinal study. *J Dent*, *38*(2), 131–137.
- El Aidi, H., Bronkhorst, E. M. & Truin, G. J. (2008). A longitudinal study of tooth erosion in adolescents. *J Dent Res*, *87*(8), 731–735.
- Ganss, C. (2014). Is erosive tooth wear an oral disease? *Monogr Oral Sci*, *25*, 16–21.
- Ganss, C., Klimek, J. & Giese, K. (2001). Dental erosion in children and adolescents—a cross-sectional and longitudinal investigation using study models. *Community Dent Oral Epidemiol*, *29*(4), 264–271.
- Gedalia, I., Dakuar, A., Shapira, L., Lewinstein, I., Goultshin, J. & Rahamim, E. (1991). Enamel softening with Coca-Cola and rehardening with milk or saliva. *Am J Dent*, *4*(3), 120–122.
- General Assembly of the World Medical Association. (2014). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent*, *81*(3), 14–18.

- Harding, M. A., Whelton, H. P., Shirodaria, S. C., O'Mullane, D. M. & Cronin, M. S. (2010). Is tooth wear in the primary dentition predictive of tooth wear in the permanent dentition? Report from a longitudinal study. *Community Dent Heal.* 27(1), 41–45.
- Harding, M. A., Whelton, H., O'Mullane, D. M. & Cronin, M. (2003). Dental erosion in 5-year-old Irish school children and associated factors: a pilot study. *Community Dent Heal.* 20(3), 165–170.
- Hayden, C., Bowler, J. O., Chambers, S., Freeman, R., Humphris, G., Richards, D. & Cecil, J. E. (2013). Obesity and dental caries in children: a systematic review and meta-analysis. *Community Dent Oral Epidemiol.* 41(4), 289–308.
- Holbrook, W. P., Arnadottir, I. B. & Kay, E. J. (2003). Prevention. Part 3: prevention of tooth wear. *Br Dent J.* 195(2), 75–81.
- Huang, L. L., Leishman, S., Newman, B. & Seow, W. K. (2015). Association of erosion with timing of detection and selected risk factors in primary dentition: a longitudinal study. *Int J Paediatr Dent.* 25(3), 165–173.
- Imfeld, T. (1996a). Dental erosion. Definition, classification and links. *Eur J Oral Sci.* 104(2 (Pt 2)), 151–155.
- Imfeld, T. (1996b). Prevention of progression of dental erosion by professional and individual prophylactic measures. *Eur J Oral Sci.* 104(2 (Pt 2)), 215–220.
- Jaeggi, T. & Lussi, A. (2014). Prevalence, incidence and distribution of erosion. *Monogr Oral Sci.* 25, 55–73.
- Jarvinen, V., Rytomaa, I. & Meurman, J. H. (1992). Location of dental erosion in a referred population. *Caries Res.* 26(5), 391–396.
- Katz, J. & Bimstein, E. (2011). Pediatric obesity and periodontal disease: a systematic review of the literature. *Quintessence Int.* 42(7), 595–599.
- Kreulen, C. M., Van 't Spijker, A., Rodriguez, J. M., Bronkhorst, E. M., Creugers, N. H. & Bartlett, D. W. (2010). Systematic review of the prevalence of tooth wear in children and adolescents. *Caries Res.* 44(2), 151–159.
- Kumar, S., Kroon, J. & Lalloo, R. (2014). A systematic review of the impact of parental socio-economic status and home environment characteristics on children's oral health related quality of life. *Heal. Qual Life Outcomes.* 12(1), 41.
- Li, M. H. & Bernabe, E. (2016). Tooth wear and quality of life among adults in the United Kingdom. *J. Dent.* 55, 48–53.
- Mantonanaki, M., Koletsi-Kounari, H., Mamai-Homata, E. & Papaioannou, W. (2013). Dental erosion prevalence and associated risk indicators among preschool children in Athens, Greece. *Clin Oral Investig.* 17(2), 585–593.
- Milosevic, A., Young, P. J. & Lennon, M. A. (1994). The prevalence of tooth wear in 14-year-old school children in Liverpool. *Community Dent Heal.* 11(2), 83–86.
- Moimaz, S. A., Araujo, P. C., Chiba, F. Y., Garbin, C. A. & Saliba, N. A. (2013). Prevalence of deciduous tooth erosion in childhood. *Int J Dent Hyg.* 11(3), 226–230.
- Murakami, C., Tello, G., Abanto, J., Oliveira, L. B., Bonini, G. C. & Bonecker, M. (2016). Trends in the prevalence of erosive tooth wear in Brazilian preschool children. *Int J Paediatr Dent.* 26(1), 60–65.
- Nayak, S. S., Ashokkumar, B. R., Ankola, A. V. & Hebbal, M. I. (2010). Distribution and severity of erosion among 5-year-old children in a city in India. *J Dent Child.* 77(3), 152–157.
- NSO. (2014). *Demographic Review 2013*. National Statistics Office. Valletta, Malta.
- O'Brien, M. (1994). *Children's dental health in the United Kingdom 1993: a survey carried out by the Social Survey Division of OPCS, on behalf of the United Kingdom Health departments, in collaboration with the Dental Schools of the Universities of Birmingham and Newcastle*. London: H.M.S.O., 1994: Office of Population Censuses and Surveys. Social Survey Division; University of Birmingham. Dental School; University of Newcastle upon Tyne. Dental School.
- O'Sullivan, E. A., Curzon, M. E., Roberts, G. J., Milla, P. J. & Stringer, M. D. (1998). Gastroesophageal reflux in children and its relationship to erosion of primary and permanent teeth. *Eur J Oral Sci.* 106(3), 765–769.
- Pahel, B. T., Rozier, R. G. & Slade, G. D. (2007). Parental perceptions of children's oral health: the Early Childhood Oral Health Impact Scale (ECOHIS). *Heal. Qual Life Outcomes.* 5, 6.
- Saito, T., Shimazaki, Y., Koga, T., Tsuzuki, M. & Ohshima, A. (2001). Relationship between upper body obesity and periodontitis. *J Dent Res.* 80(7), 1631–1636.
- Sinha, P., Abdullah, S., Saha, S. & Verma, A. (2016). Prevalence of dental erosion in 12-year old school children of Lucknow City. *J. Indian Assoc. Public Heal. Dent.* 14, 409–412.
- Taji, S. & Seow, W. K. (2010). A literature review of dental erosion in children. *Aust Dent J.* 55(4), 358–67, quiz 475.
- Thomas, M. S., Parolia, A., Kundabala, M. & Vikram, M. (2010). Asthma and oral health: a review. *Aust Dent J.* 55(2), 128–133.

- Tong, H. J., Rudolf, M. C., Muyombwe, T., Duggal, M. S. & Balmer, R. (2014). An investigation into the dental health of children with obesity: an analysis of dental erosion and caries status. *Eur Arch Paediatr Dent*, *15*(3), 203–210.
- Tootla, R., Toumba, K. J. & Duggal, M. S. (2004). An evaluation of the acidogenic potential of asthma inhalers. *Arch Oral Biol*, *49*(4), 275–283.
- Tschammler, C., Muller-Pflanz, C., Attin, T., Muller, J. & Wiegand, A. (2016). Prevalence and risk factors of erosive tooth wear in 3-6 year old German kindergarten children-A comparison between 2004/05 and 2014/15. *J Dent*, *52*, 45–49.
- Vazquez-Nava, F., Morales Romero, J., Crodova Fernandez, J. A., Saldivar-Gonzales, A. H., Vazquez-Rodriguez, C. F., Barrientos Gomez Mdel, C., ... Vazquez Rodriguez, E. M. (2010). Association between obesity and asthma in preschool Mexican children. *Scientific World Journal*, *10*, 1339–1346.
- Yuksel, H., Yilmaz, O., Kirmaz, C., Aydogdu, S. & Kasirga, E. (2006). Frequency of gastroesophageal reflux disease in nonatopic children with asthma-like airway disease. *Respir Med*, *100*(3), 393–398.



*Research Article*

## Measuring Human Capital: A Comparative Study with Emphasis on Malta

Philip von Brockdorff\*<sup>1</sup> and Bernice Amaira<sup>1</sup>

<sup>1</sup>*Faculty of Economics, Management and Accountancy, Department of Economics, University of Malta, Msida, Malta*

**Abstract.** The main aim of this paper was to produce an estimate for human capital stock for Malta over the period 2005 to 2013 and to compare Malta's performance with that of other countries, wherever possible. The paper attempts to answer two main questions, the first, is how can one give a value to the amount of capital embodied in humans, and the second is what was the human capital dynamics in Malta over the years, particularly when compared with other countries. This research is primarily motivated by the fact that human resources are Malta's only resource, in the absence of any natural endowments. The conclusions of this paper are as follows: First, the lifetime income approach was found to be a more reliable monetary metric. Second, the human capital stock of Malta grew by 70% in nominal terms from 2005 to 2013 whereas the nominal average annual growth rate was approximately equal to 7%. The real human capital stock grew by 32% over the same period. The real change in human capital was attributed to a 2% increase in the labour force population and a 1% increase in real lifetime income per capita. Third, human capital stock were estimated to be on average twice the value of physical capital stock and four times the value of Malta's GDP. Fourth, the level of human capital stock estimates was found to be sensitive to the choice of the expected future income growth and the rate used to discount the future income.

**Keywords:** Human capital stock; lifetime income approach; physical capital stock; growth rate; education

### 1 Introduction

For over three centuries economists have been interested in valuing the productive capacity of the workers in an economy. A country's human capital endowment or the

knowledge and skills embodied in individuals can reflect the economy's potential for economic growth, fuller employment and social cohesion. Growth economics literature suggests that other things being equal, countries with higher levels of human capital have greater potential output and income in the future. Optimising the use of a country's human capital endowment requires not only a focus on unemployment rates alone but a metric which takes stock of the skills and education of the labour market population.

The rapidly expanding literature has revealed the utility of the human capital concept in both the micro and macro spheres of economics. At the microeconomic level, the skills and level of education of individuals determine the risk of unemployment and social exclusion. The differences in human capital are generally believed to translate into inequality in earnings. Furthermore, a human capital measure can be used in the assessment of the impact of an ageing population, changes in retirement ages and in the evaluation of the economic benefits of different levels of education. In the macroeconomic theory, human capital is among the four factors of economic development together with natural resources, capital formation and technology. Human capital has become the most important among the factors, as the capital goods can be bought, but can be effectively used in the economic process only by well-educated and skilled workers.

This paper considers the lifetime income approach to measuring Malta's human capital stock. This approach was developed by Jorgenson and Fraumeni (1989, 1992b, 1992a). Lifetime income is measured as the discounted future labour income flows of a representative individual. An empirical variant of Jorgenson and Fraumeni's approach is used, resulting in a monetary measure which can be directly linked to Gross Domestic

\*Correspondence to: Philip von Brockdorff (philip.von-brockdorff@um.edu.mt)

Product (GDP). This estimate is based on detailed data on labour remuneration across different groups of workers. The methodology behind the estimate is intended to track the progress Malta has made over the period under study. The paper first presents the lifetime income per capita for different age and education cohorts. It then deduces a figure for the aggregate human capital for Malta by summing the lifetime incomes for all cohorts. Further analysis is conducted to determine the human capital in real terms. The methodology adopted and the results derived for Malta are contrasted with measures of human capital for other countries. This will serve to highlight the need for a more harmonious approach to measuring human capital by laying out the differences, benefits and shortcomings of the measures of human capital across countries.

## 2 Measuring Human Capital

Before measuring human capital, it is essential to define the term on which research has been built. Becker (1964) views human capital to include “embodied knowledge and skills”. Becker, Mincer and Schultz, the founding fathers of human capital theory, regard human capital as the result of investment activities. This paper will examine human capital within the framework of growth theory. The knowledge and skills that will be considered will be those entering the production process and yielding an income to the individual. Human capital will be viewed as the “productive capacity of individuals” (Nerdrum, 1998).

As stated by Kiker (1966), throughout the history of economic thought, many economists have considered the skills and capacities embodied in human beings as a component of capital. In his “Wealth of Nations”, Smith (1937) treated the acquisition of a skill as an investment which had a cost and returns a profit. Therefore, the basic idea of the human capital theory is that the variety of talents is mainly acquired through different activities, such as education or working experience. These activities have a cost, but produce benefits in future.

Schultz (1961) noted that the increases in national output could not be solely explained by the increases in the conventional factor inputs of land, man-hours and physical capital. He attributed this discrepancy to the quality of the labour input. Mincer (1958) provides an extensive study which establishes the term “human capital” and lays the foundation for human capital theory, with his major contribution being the “human capital earnings function”. Becker complemented Mincer’s work in the theoretical and empirical work on human capital. Becker (1964) initiates the book “Human Capital” with a lengthy discussion on on-the-job training, explaining that training is unlikely to be profitable for the firm in the current time period but may be profit-

able for the firm if future receipts are sufficiently raised or future payments sufficiently lowered.

Given that human capital is not directly observable, its measurement can be quite complex. It can be captured in different ways giving way to subjectivity in the assumptions imposed. It is generally acknowledged that there are three main approaches to measuring the human capital stock: the education approach, the cost-based approach and the income-based approach.

The education approach involves quantifying one of the key elements to human capital formation, that is, education. In the literature, several education measures are used such as literacy rates and school enrolment rates. Psacharopoulos and Arriagada (1986, 1992) and Barro and Lee (1996) used years of schooling as a proxy for human capital. Other measures include test scores (J.-W. Lee & Barro, 2001) and educational attainment, as measured by the International Standard Classification of Education (ISCED). However, educational attainment measures ignore learning that does not lead to a recognised qualification. Although it is a relevant indicator of the quality of human capital, this approach focuses solely on one input to human capital formation.

The cost of production approach estimates the human capital stock by taking the depreciated value of the monetary amount spent on the resources invested in the education and other human capital related sectors. Kendrick (1976) and Eisner (1985, 1989) are among those that have made use of this approach in measuring human capital. In “The Formation and Stocks of Total Capital” (1976), Kendrick divided human capital investments into tangible, being the durable goods owned by government and consumers, and intangible investment, including research and development, education and training, health and mobility. This approach focuses on the supply when in reality the value of human capital is also determined by its demand. Another limitation of this approach is that not all costs may be classified as an investment in human capital. Some costs may provide some consumption benefits. Therefore, some difficulty lies in distinguishing between investment and consumption costs (Schultz, 1961). Furthermore, determining the depreciation rate is crucial when using this approach since skills wear out due to ageing, illness or insufficient use or may become obsolete due to technological change or shifts in employment.

The income-based approach measures human capital by taking the sum of all discounted future income streams that all individuals in the population expect to earn over their lifetime. This approach focuses on the expected returns on investment and can therefore be described as ‘forward-looking’, as opposed to ‘backward-looking’ approaches taking into account the historical costs of production. Fender (2013) explains that the

depreciation rate is implicitly captured when using this approach, avoiding the need to determine an arbitrary rate. This approach is however based on some limiting assumptions. It assumes that labour is paid according to the marginal productivity, thus ignoring non-market impacts on wages such as unions and government intervention. It also assumes a discount rate and a retirement age and relies upon accurate data of earnings, employment and life expectancy tables.

Becker (1964) adopted this approach to estimate the rate of return on the human capital investment. He derives the rate of return on the investment by calculating the differences in the present value of the net earnings between an activity that requires investment and an activity requiring no investment beyond the initial period. Mincer (1974) also contributed further to the development of this approach through his “human capital earnings function”. He points out that investment after schooling is likely to decline as earnings and experience increase, due to the higher opportunity cost of investment as more skill is acquired.

This paper applies the income-based approach to measuring the human capital of Malta and uses a variant of the Jorgenson and Fraumeni method (1989, 1992b, 1992a). Through their method, they estimated the human capital of the whole US population using 2,196 cohorts of sex, age and education. Their major contribution was in simplifying the discounting of future income streams to the present value. They estimated the lifetime labour income of a particular cohort by adding that cohort’s current annual income and the present value of that cohort’s lifetime income in the next period weighted by survival probabilities. It is given as

$$V_{s,a,e} = Y_{s,a,e} + S_{s,a+1} V_{s,a+1,e} \frac{1+g}{1+i}, \quad (1)$$

where  $V$  is the lifetime income,  $Y$  is the annual earnings,  $S_{a+1}$  is the probability of surviving for another year and the subscripts  $s$ ,  $a$  and  $e$  represent the sex, age and education of the individual.

An estimate of Malta’s human capital is given by the Human Capital Index published by the World Economic Forum (WEF). This index takes a life-course approach to human capital, evaluating the levels of education, skills and employment available to people on a scale from 0 (worst) to 100 (best) across different age groups. Malta’s human capital index in 2016 was estimated to stand at 75.66, ranking Malta at the 35th place from the 130 countries studied. The highest score of 85.86 was attained by Finland. To the best of our knowledge, there is no other study which derives an estimate of the human capital in Malta and studies its dynamics over time. This highlights the need to engage in further research within this domain so as to address gaps in the literature.

The income method of measuring human capital is preferred to the cost-based approach or the education-based approach for several reasons. It allows the output from investment in human capital to be measured independently of the inputs. Both the cost and education-based approach focus on what is invested whereas the income-based approach looks at the productivity of the education sector, on-the-job training and other inputs. Quantifying the elements of inputs to human capital which yield higher output is quite difficult. The income-based approach immediately seeks to evaluate the labour market to determine the worth of an individual. Higher investment in an individual (for instance, due to slow learning difficulties) may not always result in higher productivity. Finally, the Organisation for Economic Co-operation and Development (OECD) adopts the Jorgenson-Fraumeni lifetime income approach to compute the monetary value of the stock of human capital for each country. The Atkinson Report (2005, para. 9.33–9.34) also recommends exploring a lifetime income approach to measuring human capital.

### 3 Data and Methodology

The starting point for the measurement of lifetime labour incomes using a variant of Jorgenson and Fraumeni’s approach was the construction of a data set including data on the employment rate, annual labour compensation of employees and survival rates classified by age and education. The Jorgenson-Fraumeni income-based approach applies the neoclassical theory of investment to human capital. According to this theory, the price of capital goods depends upon the discounted value of all future capital services derived from the investments. Similar approaches have been used by a number of countries, such as Australia (Wei, 2004, 2007, 2008), New Zealand (Le, Gibson & Oxley, 2002), the United Kingdom (O’Mahony & Stevens, 2009; Fender, 2013), Norway (Greaker & Liu, 2008, November) and Canada (Gu & Wong, 2010). This method is also used by the OECD human capital consortium (Liu, 2011). The method adopted by this paper differs in a number of aspects from the approach taken by Jorgenson and Fraumeni:

- Jorgenson and Fraumeni considered the whole U.S population whereas this paper focuses on the Maltese labour force population, thus trying to estimate the “effective” human capital.
- Jorgenson and Fraumeni also took account of non-market activities which increased labour income, with full labour income being defined as the sum of market and non-market labour compensation after taxes. The main criticism to this approach is that it assumes that human capital raises the productivity of time spent at work and leisure equally. In

this paper, only labour market activities were considered. Several other studies, such as Wei (2004, 2007), Greaker and Liu (2008, November) also focus on the labour market activities when estimating this variable.

- The cohorts within Jorgenson and Fraumeni's study were classified according to their age, sex and education level. This paper does not distinguish between the sex of the individuals due to severe data limitations. This may impact on the human capital estimate for Malta and its dynamics since labour market prospects and survival probabilities tend to differ between males and females.
- The age cohort within Jorgenson and Fraumeni's study initiates from the age of 14 and continues up to 74 years old. This paper takes those individuals aged between 15 and 65 years old, allowing comparison to cross-country estimates of human capital produced by the OECD.
- In estimating lifetime incomes, Jorgenson and Fraumeni distinguish among three stages in the life cycle. In the first stage, individuals may participate in formal schooling but not in the labour market. In the second stage, individuals may enrol in school and also work. In the third stage, individuals may participate in the labour market but not in formal schooling. This paper does not consider the school enrolment rates in the estimation of human capital since such data was not available for the period studied<sup>1</sup>.

To construct a measure of aggregate human capital in Malta, the population is cross-classified by 4 age groups (15–24 years old, 25–49 years old, 50–64 years old and 65+ years) and 3 education levels (ISCED 0–2, ISCED 3–4 and ISCED 5–6). Therefore, the lowest level of education considered coincides with early childhood education or education received before entering primary school.

Variables used in the estimation of human capital such as age, educational attainment, labour force count, employment rates, mean annual basic salary and survival rates were obtained from the Labour Force Survey (LFS) issued by the National Statistics Office (NSO) or directly from the Eurostat database. The sample period chosen was the period from 2005 till 2013. The choice of this sample period was based on data availability and consistency in the methodology adopted by the NSO when compiling the LFS.

The mean annual basic salary used in this study is calculated before any social contributions or tax deductions. It also excludes payments on overtime, allowances

and bonuses. This paper uses survey data obtained by a private Human Resources consulting firm<sup>2</sup> to top up the mean annual basic salary by a percentage amount so as to take account of any performance bonuses, allowances and commissions earned. For those having an education level of ISCED 0–2, the mean annual basic salary is topped up by 4%, for those having an education level of ISCED 3–4 by 7% and finally, for those having an educational level of ISCED 5–6, it has been topped up by 12%.

For the variable of educational level, the ISCED was employed to facilitate international comparison. This paper defines educational attainment levels as per ISCED 1997, the second version of ISCED. The new version of ISCED was adopted by NSO in 2014. The 65+ age group refers to the working-age population aged 65 years and over, thus there is no limit on this age cohort. However, given that the data is related to employment, it is assumed that the majority of this age group is 74 years or less. The data on survival rates were obtained from the 'Life Table' published by Eurostat. While education tends to increase survival rates, no such data exists for Malta. The survival rates were assumed not to vary across education levels but to depend on age only.

To derive a measure of the effective human capital of Malta, this paper focuses on labour market activities with earnings potential for the working-age population. This paper truncates the age from the upper bound at an age limit that is defined as 65, by assuming that the mean annual basic salary of those aged over 65 years old amounts to zero. In doing so, two main assumptions were made:

- the official retirement age of 65 years old applicable to those born after 1st January 1962 was assumed for all the labour force population and;
- those aged over 65 years old do not pursue employment after retirement.

These assumptions, although necessary, inevitably lead to an under-estimation of the human capital value.

The constructed cross-sectional data set forms the basis of the estimation of market lifetime labour income for all individuals aged 15 years and over. For individuals having the same level of educational attainment, the expected future income of an individual is assumed to be equal to the income of those having an age which the individual will have in the future time period. This income is then adjusted for increases in real income. The lifetime incomes are therefore computed by a backward recursion, starting from the last age cohort of 65+.

Alternatively, this means that the expected lifetime income of a particular individual of age  $a$  is their current labour income plus their expected lifetime income at age  $a + 1$  multiplied by survival rates and adjusted

<sup>1</sup>School Enrolment rates for different cohorts of age, sex and educational level have been made available on Eurostat for the years starting from 2013.

<sup>2</sup>The Misco Salaries and Benefits Report 2014–2015.



for increases in real income. The following equation is used for estimating average human capital per capita for a cohort of individuals with age  $a$  and educational attainment  $e$ ,

$$h_{e,a} = w_a^e y_a^e + sr_{a,a+1} h_{e,a+1} \frac{(1+r)}{(1+\delta)}, \quad (2)$$

where  $e$  is the educational attainment levels,  $a$  is the age,  $h_{e,a}$  represents the average human capital for individuals with age  $a$  and educational level  $e$ ,  $w_{e,a}$  is the probability of engaging in paid employment for individuals with age  $a$  and educational level  $e$ , defined as the employment rate for that cohort,  $y_{e,a}$  is the annual labour compensation of paid workers with age  $a$  and education level  $e$ ,  $sr_{a,a+1}$  is the probability of surviving one more year from age  $a$ ,  $r$  is the growth rate of real income (labour productivity growth rate) and  $\delta$  is the social discount rate.

Eq. (2) is applied to each cohort of individuals for each period analysed – assuming that each individual progresses through time using the relative incomes of the succeeding cohorts. The relevant survival rates and employment rate for the period concerned are assumed. Future incomes are augmented with a projected labour income growth rate and discounted to the present with a constant discount rate. The real income growth rate  $r$  is assumed to be equal to labour productivity growth in the Maltese business sector, standing at 0.5% per annum. The discount rate employed in the economic analysis of investment projects to discount economic costs and benefits is the Social Discount Rate (SDR). Here it is assumed to be equal to 5% in line with the European Commission's Guidance for Cost-Benefit Analysis for investment projects (2014).

In this approach, the lifetime labour income of any individual is equal to his/her current income plus his/her expected lifetime income. Therefore, for an individual who is aged 64 years old (i.e. one year before the assumed retirement age), this is simply his/her current labour income because their expected lifetime income at 65 is assumed to be zero. Similarly, the lifetime labour income of a person aged 63 years old is equal to his/her labour income plus the present value of the lifetime labour income of a person aged 64. This is worked out for each age by backward recursion.

The annual basic salary was assumed to be constant for all ages pertaining to a particular cohort. Since the analysis is conducted in age groups, the proportion of each single age from the total age cohorts presented in this study was found by using data from Census 2005 and Census 2011.

The total stock of human capital is the sum of lifetime labour incomes across all classified categories of age and

education and is given by

$$HC = \sum_a \sum_e LLI_a^e N_a^e, \quad (3)$$

where  $HC$  is the monetary value of the stock of aggregate human capital,  $LLI_a^e$  is the average lifetime labour income per capita for individuals with age  $a$  and education level  $e$  and  $N_a^e$  is the number of individuals in the labour force with age  $a$  and education level  $e$ .

After establishing the level of aggregate human capital, this study sought to determine the value of the real human capital. This facilitates comparison across countries and provides a better view of the improvement in skills and talents embodied in individuals. One common approach to deducing the human capital in real terms found in the human capital literature is the Divisia quantity indices. The Divisia Index is a continuous time index which is widely used in productivity analysis. The index is used to retrieve the real changes in human capital, using the number of individuals in the labour force. These were constructed to measure the growth rate of the volume index of aggregate human capital stock. This is essentially a weighted sum of the growth rates of the number of individuals across different educational and age categories, using their share of the nominal value of human capital as weights,

$$d \ln H = \sum_a \sum_e \bar{v}_{a,e} d \ln L_{a,e}, \quad (4)$$

where  $H$  represents the volume indices of aggregate human capital stock,  $L_{a,e}$  is the number of individuals in the labour force with age  $a$  and education level  $e$  and  $d$  is the first difference, or the change between two consecutive periods, for instance,

$$d \ln H = \ln H(t) - \ln H(t-1). \quad (5)$$

The weights  $v$  are given by the average share of nominal human capital of the cohort concerned as a proportion of the aggregate human capital stock

$$\begin{aligned} \bar{v}_{a,e} &= \frac{1}{2} [v_{a,e}(t) + v_{a,e}(t-1)], \\ v_{a,e} &= \frac{h_{a,e} L_{a,e}}{\sum_a \sum_e h_{a,e} L_{a,e}}, \end{aligned} \quad (6)$$

where  $h_{a,e}$  represents the lifetime labour income of the individuals with age  $a$  and education level  $e$ .

'Ceteris paribus', the Divisia index increases if there is either an increase in the population or an increase in the proportion of those having higher remaining lifetime earnings. The difference between the growth of weighted population counts as estimated by the Divisia index and the growth of unweighted population counts, that is, the

growth in the labour force measures the real growth of human capital per capita. Changes in human capital per capita may be mainly attributed to demographic changes in the population such as ageing compositional effects and higher education levels. ‘Ceteris paribus’, the higher the proportion of younger and more educated individuals, the higher the expected lifetime income and thus human capital. Aggregate human capital per capita can be defined as

$$h = H/L, \quad (7)$$

where  $L$  is the number of individuals in the labour force.

The rates by which the volume of human capital stock increases represents the real increase in human capital. When subtracting these rates from the annual growth rates of nominal aggregate human capital stock, the human capital deflator is determined. In turn, this is used to establish the real aggregate human capital stock.

## 4 Results and Comparative Analysis

### 4.1 Nominal Human Capital in Malta

The nominal value of the aggregate human capital stock in Malta represents a measure of the capital contributed by the Maltese labour force population through their education, skills and experience. Table 1 presents the resulting values of nominal human capital stock for the period 2005 to 2013.

The nominal aggregate human capital stock amounted to approximately €20 billion in 2005, increasing to roughly €33 billion in 2013. This implies that over the 8-year period 2005 to 2013, Malta’s aggregate human capital increased by approximately 70% or an average compound growth rate of 7% per annum. This annual growth rate is quite significant. However, one must note that the dynamics of human capital stock are being analysed in the short-run. Nevertheless, this indicates that the level of nominal human capital in Malta has been improving over the past few years. In theory, this may be attributed to two main reasons:

- increase in labour force as more people join the labour market and;
- increase in earnings.

The earnings which are assumed to reflect the marginal productivity of the individual can increase either because the marginal productivity has increased (real increase in human capital) or else because the wages have increased (nominal increase in human capital).

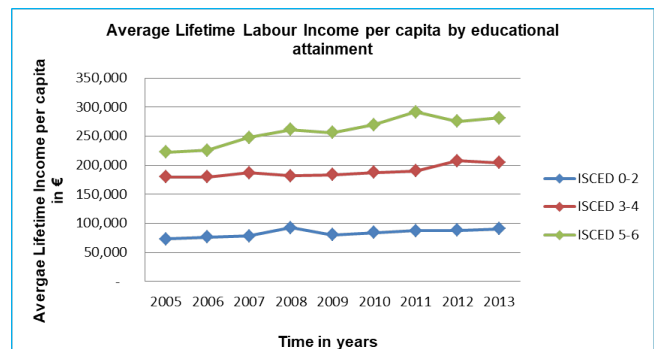
Table 2 displays the results for average lifetime labour income or human capital per capita<sup>3</sup> by types of individuals in the labour force population.

The results for the selected years 2005, 2009 and 2013

<sup>3</sup>The terms ‘average lifetime labour income per capita’ and ‘average human capital per capita’ are used interchangeably.

are presented<sup>4</sup>. The first row of Table 2 reports the average lifetime income for all individuals in the labour force, irrespective of their characteristics. The results reveal that human capital per capita increased from €122,366 in 2005 to €177,888 in 2013, that is, an average increase of 5% per annum.

Fig. 1 illustrates the average lifetime labour income per capita for different educational attainment categories. ‘A priori’, one would expect that the human capital per capita would be larger for those having a higher educational attainment. In fact, as is apparent in Fig. 1, those having an educational attainment level of ISCED 5–6 have a higher average human capital per capita than those possessing an educational level of ISCED 3–4. Similarly, the latter has a higher average human capital per capita than individuals with an ISCED 0–2 educational level. This is attributed to differences in lifetime incomes.



**Figure 1:** Average Lifetime Labour Income per capita by educational attainment. *Source: Authors’ estimates.*

### 4.2 Cross-Country Comparison of Educational Attainment and Human Capital Stock

A cross-country analysis of the relationship between the educational level and lifetime labour incomes further confirms this positive relationship. One of the most ambitious recent projects in this field of research is the Human Capital Project of the OECD (Liu, 2011). This project covers sixteen countries: Australia, Canada, Denmark, France, Israel, Italy, Japan, the Republic of Korea, Netherlands, New Zealand, Norway, Poland, Romania, Spain, the United Kingdom, and the United States. It measures the stock of human capital over time between 1997 and 2007, with the years covered differing from country to country depending on data availability.

The OECD uses the lifetime income approach of Jorgenson and Fraumeni (1989, 1992b, 1992a), thus making comparison to the estimates of human capital in Malta derived by this paper easier. While the original

<sup>4</sup>Refer to Appendix A for the human capital per capita results for each year in the period 2005 to 2013.

**Table 1:** Human Capital Stock, Growth rate and Index.

Years	Nominal Aggregate Human Capital Stock €	Growth Rate of Human Capital Stock	Index of Human Capital
2005	19,628,684,007	-	100.00
2006	20,410,997,016	4%	103.99
2007	22,304,727,892	9%	113.63
2008	23,367,067,182	5%	119.05
2009	24,230,749,722	4%	123.45
2010	26,247,338,866	8%	133.72
2011	28,613,341,867	9%	145.77
2012	31,239,711,317	9%	159.15
2013	33,427,757,739	7%	170.30

Source: Authors' estimates

**Table 2:** Average Lifetime Labour Income per capita.

	2005	2009	2013
	€	€	€
<b>All individuals</b>	122,366	141,523	177,888
<b>Educational Attainment</b>			
ISCED 0–2	73,500	80,572	90,861
ISCED 3–4	179,633	184,048	204,596
ISCED 5–6	222,728	256,459	281,677
<b>Age Group</b>			
15–24	166,180	194,680	237,314
25–49	136,633	162,409	211,614
50–64	42,127	43,831	57,177

Source: Authors' estimates.

Jorgenson-Fraumeni papers measured a version of the human capital stock that included all persons, including children, both this paper and the OECD project focus specifically on human capital embodied in persons of working age, defined as persons aged 15 to 64. This represents the “effective” or “active” human capital. Table 3 shows the similarities and differences between this paper and the OECD project.

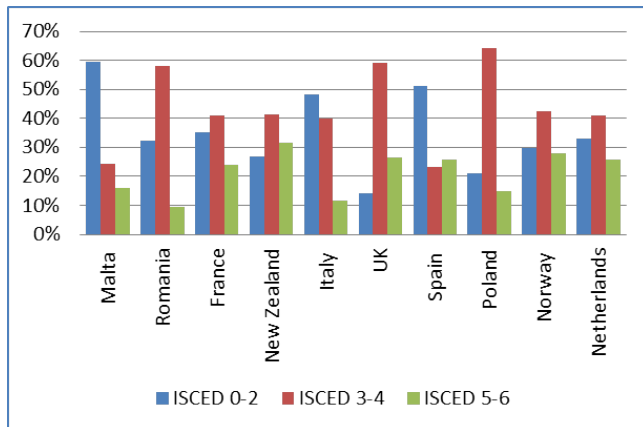
An analysis of the educational distribution across a number of countries is presented in Fig. 2. The data for Malta was derived from the NSO whereas that for other countries was taken from the OECD study.

In 2006, Malta had one of the lowest shares of labour force population having an educational attainment level of ISCED 5–6 (16%). The share of the labour force having an educational attainment level of ISCED 5–6 was even lower in Romania, Italy and Poland. This situation improved so that in 2013, Malta had approximately 24%

**Table 3:** Comparing approaches adopted by this paper and the OECD Project.

Estimates for Malta's Human Capital	OECD Project
<b>Similarities</b>	
Both studies use the lifetime income approach of Jorgenson and Fraumeni (1989, 1992b, 1992a).	
Both studies focus on the effective human capital and take the population aged from 15 to 64 years old.	
The treatment of education in both studies follows the 1997 International Standard Classification of Education (ISCED 97).	
<b>Differences</b>	
Period studied: 2005 to 2013	Period studied: 1997 to 2007
Does not consider the possibility for an individual to pursue studies at a higher educational level due to data limitations. This possibly leads to an underestimation of human capital.	Considers the possibility for an individual to pursue studies at a higher educational level. The human capital estimate for the age cohort 15–40 years old includes the school enrolment rates in its computation.
Annual social discount rate of 5%	Discount rate of 4.58% for all countries
Real income growth rate of 0.5%	Real income growth rate of 1.30%

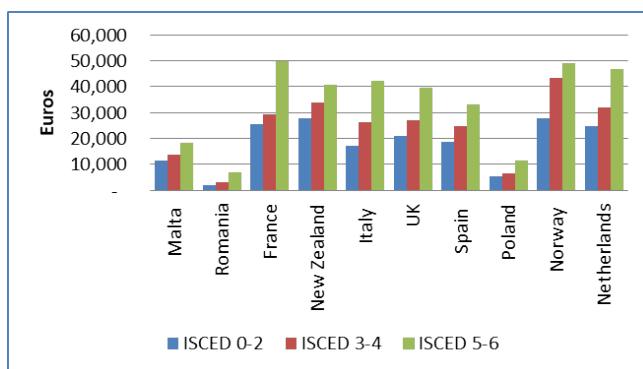
of the labour force population with an ISCED level of 5 to 6 and around 30% with an ISCED level of 3 to 4. This was principally attained through the implementation of measures targeting the early school leavers which dropped from around 32.2% in 2006 to 20.5% in 2013.



**Figure 2:** Distribution of educational qualifications in the labour force population in 2006. *Source: Authors' estimates based on OECD Data.*

Such measures included the significant investment in vocational training institutions.

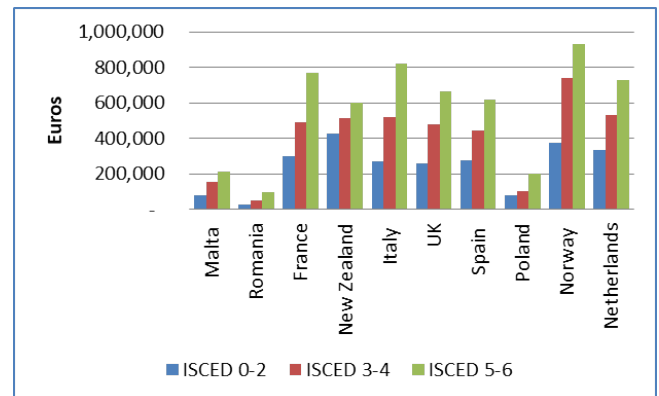
Given that the education level of an individual represents or signals higher productivity, a positive relationship exists between the level of education and annual income. Alternatively, those possessing a higher educational level, generally have higher annual incomes than their counterparts with a lower educational level. Fig. 3 shows the annual incomes of a number of countries, including Malta, in 2006. Romania, Poland and Malta feature as the countries with the lowest annual earnings across all ISCED levels studied whereas New Zealand, Norway and France were the countries with the highest annual earnings for ISCED 0–2, ISCED 3–4 and ISCED 5–6 respectively, relative to the countries presented in Fig. 3.



**Figure 3:** Annual income by the educational attainment level in 2006. *Source: OECD Data.*

This is also reflected when looking at the lifetime labour incomes of individuals having different educational attainment levels. As shown in Fig. 4, the lifetime incomes increase with higher educational attain-

ment levels. Romania, Poland and Malta had the lowest lifetime income in 2006 for each educational attainment level considered in Fig. 4.

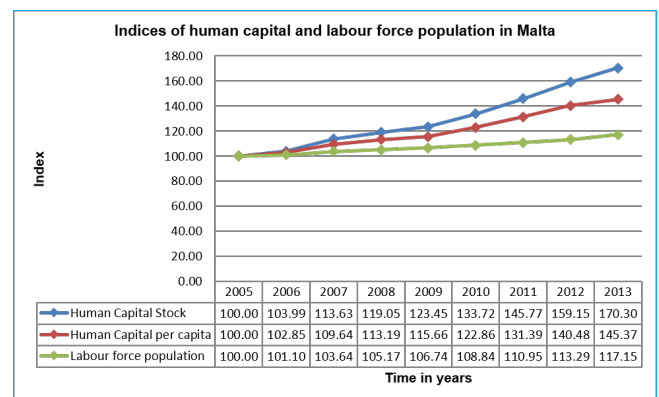


**Figure 4:** Lifetime incomes by educational attainment level in 2006. *Source: OECD Data.*

The countries recording the highest lifetime income vary across different educational attainment levels whereby New Zealand registered the highest lifetime income for the ISCED 0–2 cohort and Norway recorded the highest lifetime income for the ISCED 3–4 and ISCED 5–6 cohorts. Other countries with relatively higher lifetime incomes were Italy, the Netherlands and France.

### 4.3 Real Human Capital Stock in Malta

The indices of human capital stock, human capital per capita and labour force population were plotted so as to analyse the factors that contribute to the growth rate in nominal aggregate human capital stock for Malta.



**Figure 5:** Indices of human capital and labour force population in Malta. *Source: Authors' estimates.*

As described earlier, aggregate human capital rose at an average compound growth rate of around 7% per annum over the period 2005 to 2013. This represents the estimated nominal annual growth of Malta's human

capital stock. Fig. 5 shows that the growth rate of human capital stock can be explained by the growth in human capital per capita and the growth in the labour force population. From the indices shown in Table 4, it can be established that the average annual growth in the labour force is 2% while the average annual growth rate in nominal human capital per capita is 5%. This implies that the 7% average annual growth rate in nominal aggregate human capital stock is attributed to the growth in the labour force and to the growth in average lifetime income per capita. The latter reflects changes in an individual's productive potential, given one's age and educational level. However, this is not adjusted for changes in relative lifetime incomes<sup>5</sup>.

The real movements in the composition of the population are analysed using the Divisia quantity indices. The Divisia quantity indices, worked out using Eq. (4) explain the change in the volume of Malta's human capital stock. This can be described as the real change in human capital and is presented in Table 4.

The figures in Table 4 represent the change in the volume of human capital for all the age-education categories analysed. The total percentage figure in the last row is the change in the volume of the aggregate human capital stock. Following the methodology outlined in Gu and Wong (2010), this represents the weighted sum of the growth rates of the number of individuals across different categories of the population (age and education) using their share of the nominal value of human capital stock as weights. Thus, different from the indices analysis conducted in Fig. 5, the labour force population change is weighted by each cohort's share of human capital from the aggregate human capital stock. Table 4 reports that the estimated annual average growth rate of the volume index of the human capital is approximately equal to 3%. This can be interpreted as the real change in aggregate human capital stock since this measure abstracts from changing prices – that is, changing relative lifetime earnings across individuals. If the growth of unweighted population, that is, the growth rate of the labour force which was equal to an average of 2% per annum, is subtracted from the growth rate of weighted population counts equal to 3%, the real growth of human capital per capita can be measured. In this case, the real growth of human capital per capita is equal to approximately 1%.

OECD (Liu, 2011) also estimated the volume growth of human capital for 12 countries for the period 1997 to 2007. This growth rate varied between 0.5% to 1.3% per annum for the countries analysed. Four countries, being Israel, Korea, Norway and the US, experienced a decrease in the human capital per capita. In four other countries (Australia, Canada, France and New Zealand),

there was zero growth of human capital per capita. In three countries (Italy, Spain and the UK) it increased with 0.1% to 0.3% per year. Poland is an outlier with 0.9% increase in human capital per capita.

The findings for Malta reveal that the volume index of human capital increases throughout the whole period studied. For instance, in 2013, Table 4 reports that the volume index of human capital increased by 4.53%. This implies, either that the number of individuals in the labour force increased; or that the composition of the population moved towards those that have increasingly large remaining lifetime earnings.

The rates by which the volume of human capital stock increases represent the real increase in human capital which potentially leads to higher productivity and economic growth. By subtracting these real growth rates from the annual growth rates of the nominal aggregate human capital stock outlined in Table 1, we can deduce the human capital deflator and therefore the real aggregate human capital stock.

The second column of Table 5 below displays the nominal aggregate human capital while the third column includes the values of the deflator which reflects the growth in the prices of human capital, being the lifetime incomes. The reason for computing this deflator and not using the inflation rate for the whole economy is because the prices being examined are those of human capital, that is, the earnings of individuals. By dividing the nominal aggregate human capital stock by this deflator, the real amount of human capital stock was determined.

Whereas nominal aggregate human capital stock increased by around 70% over the 8-year period studied, the real aggregate human capital stock increased by 32%. This reflects the 3% average annual growth in the actual volume of human capital stock and the 4% average annual growth in the prices of human capital. Fig. 6 compares the nominal human capital stock and the real human capital stock. The base year is taken to be the first year under study, that is, 2005.

Fig. 6 reflects the fact that the largest increase in Malta's human capital stock can be attributed to a growth in prices rather than real increases in productivity and labour force population. In 2007, the difference between nominal and real values of the human capital stock increased by approximately 2.5 times from 2006. In 2008 and 2009, a lower growth in the price of human capital was registered. In fact, in 2009, the discrepancy between nominal and real values of the human capital stock increased by only 4% from the previous year. This may reflect the decline in wage growth that occurred in 2009. Wage growth fell to 3.8% from a peak of 4.7% in 2008 (Central Bank of Malta, 2010).

<sup>5</sup>It is expressed in nominal terms.

**Table 4:** Growth of Human Capital Divisia Indices.

Growth of Human Capital Divisia Indices								
	2006	2007	2008	2009	2010	2011	2012	2013
	%	%	%	%	%	%	%	%
<b>ISCED 0–2</b>								
15–24	0.1246	–0.7422	–0.3853	–0.7337	–0.6428	–0.1117	–0.1352	–0.2121
25–49	0.0855	0.4617	–0.0335	–1.2293	–0.596	–0.693	–0.6875	–0.0542
50–64	–0.0562	0.1643	0.1203	–0.1095	0.0754	0.0574	–0.0482	–0.0027
65+	-	-	-	-	-	-	-	-
<b>ISCED 3–4</b>								
15–24	–1.9073	1.2101	0.6193	0.2953	0.0915	–0.0514	–0.3532	1.0677
25–49	0.6851	0.0832	–0.0841	3.1059	0.7546	1.3018	1.3753	0.567
50–64	0.4854	–0.3107	0.1998	0.3733	0.3157	–0.1067	0.355	0.3145
65+	-	-	-	-	-	-	-	-
<b>ISCED 5–6</b>								
15–24	1.5876	0.5168	–1.3394	0.6031	0.7825	0.5249	–0.0025	0.0699
25–49	0.8147	2.6339	2.3226	1.3081	1.8005	3.2453	2.7339	2.6155
50–64	–0.0798	0.1316	0.0197	0.0345	0.2431	0.1167	0.2356	0.1605
65+	-	-	-	-	-	-	-	-
<b>Total</b>	<b>1.74</b>	<b>4.15</b>	<b>1.44</b>	<b>3.65</b>	<b>2.82</b>	<b>4.28</b>	<b>3.47</b>	<b>4.53</b>

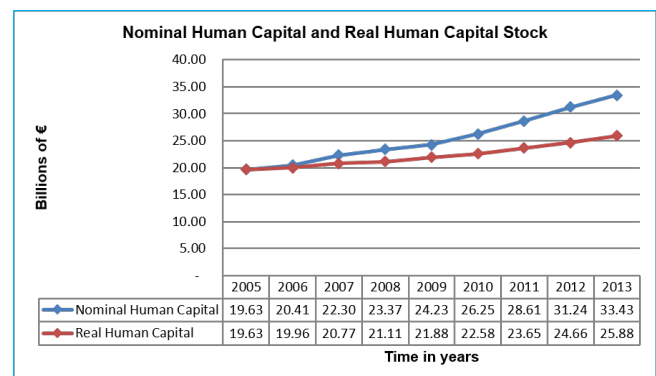
Source: Authors' estimates

**Table 5:** Real Human Capital Stock.

Real Human capital stock (Base year = 2005)			
	Nominal Human Capital	Deflator	Real Human Capital
<b>2005</b>	19,628,684,007	1.00	19,628,684,007
<b>2006</b>	20,410,997,016	1.02	19,962,629,395
<b>2007</b>	22,304,727,892	1.07	20,772,667,048
<b>2008</b>	23,367,067,182	1.11	21,108,674,965
<b>2009</b>	24,230,749,722	1.11	21,879,287,874
<b>2010</b>	26,247,338,866	1.16	22,579,261,852
<b>2011</b>	28,613,341,867	1.21	23,652,024,766
<b>2012</b>	31,239,711,317	1.27	24,659,950,536
<b>2013</b>	33,427,757,739	1.29	25,880,916,025

Source: Authors' estimates

Fig. 7 illustrates the dynamics of real human capital per capita. From 2005 to 2013, real human capital per capita increased from €122,366 to €137,727, that is, by 13%. On average, the lifetime income per capita for all individuals increased by 1% per annum. This growth rate reflects compositional shifts in the populations. Ageing is expected to have a negative impact on the growth of human capital because older people are



**Figure 6:** Nominal and Real Human Capital Stock. Source: Authors' estimates.

expected to have less remaining years of work and thus lower remaining lifetime earnings. Conversely, rising education levels improve Malta's human capital base.

#### 4.4 Human Capital relative to Physical Capital and GDP

In order to put the value of nominal human capital stock into perspective, this paper compares the value of human capital with the value of physical capital and the value of GDP.

Figure 8 plots the nominal values of the estimated aggregate human capital stock and aggregate physical

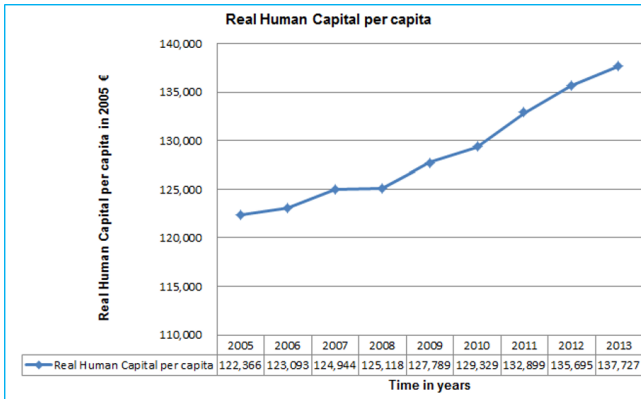


Figure 7: Real Human Capital per capita. Source: Authors' estimates.

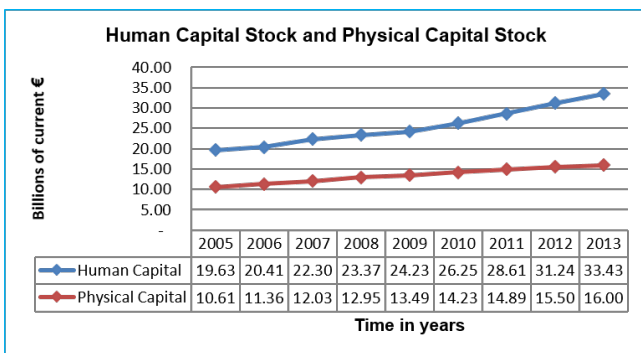


Figure 8: Human Capital Stock and Physical Capital Stock in nominal terms. Source: Authors' estimates.

capital stock for Malta. The human capital stock was approximately twice the value of the physical capital stock for the whole period 2005 to 2013. The ratio of human capital stock to physical capital stock ranged from 1.80 registered in 2006, 2008 and 2009 to 2.09, which was registered in 2013.

A comparison of the human capital stock to physical capital stock ratio across a number of countries shows that this ratio is relatively low for Malta. The OECD Human Capital study presents the ratio of human capital to physical capital and GDP for a number of countries in 2006. The data shows that ratios between human and physical capital range between 3.6 in the Netherlands and Italy and 7.0 in the United Kingdom, with a mean value of 4.7. The ratios of human capital to GDP range between 8.3 in the Netherlands and 16.3 in Korea, with an average value of around 10.6<sup>6</sup>.

Fig. 9 illustrates the ratio of Malta's estimated aggregate human capital stock to the country's GDP.

The highest human capital stock to GDP ratio was

<sup>6</sup>Measuring the Stock of Human Capital for Comparative Analysis: An Application of the Lifetime Income Approach to Selected Countries, OECD Statistics Directorate, Working Paper no. 41, page 29.

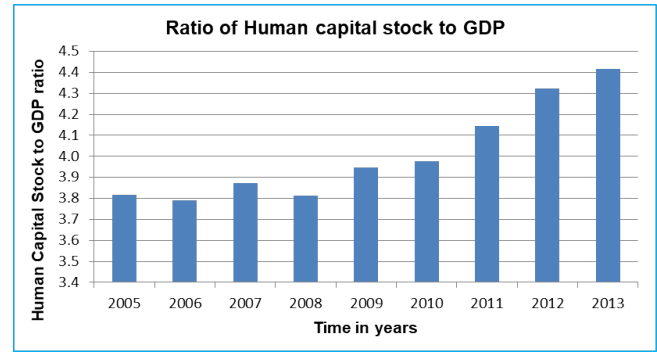


Figure 9: Ratio of Human capital stock to nominal Gross Domestic Product (GDP). Source: Authors' estimates.

recorded in 2013 with a value of 4.42 while the lowest ratio (equal to 3.79) was registered in 2006. This may be because the human capital stock increased by 4% whilst nominal GDP registered a growth rate of 5%. Thus the ratio of human capital to GDP declined marginally from 2005 to 2006. Thus this ratio is also relatively lower compared to countries considered in the OECD study.

#### 4.5 Sensitivity Analysis

The estimates of human capital depend on the expected future real income growth and the discount rate used to discount future income. In this paper, the future real income growth rate was assumed to be equal to average labour productivity growth in Malta and was taken as 0.5% per annum. The discount rate was assumed to be equal to 5% in line with the European Commission's Guidance for Cost-Benefit Analysis for investment projects (2014).

This paper examines the sensitivity of estimates for human capital stock and investment to alternative assumptions about the real income growth and the real discount rate, with the results presented in Table 6.

Table 6 reports the sensitivity of an aggregate human capital stock to changes in the real income growth rate and the real discount rate. The first row presents the baseline scenario with the initial assumptions of a 0.5% real income growth rate and a 5% real discount rate. The second row makes alternative assumptions on the real income growth rate while keeping the discount rate at 5%. Two real income growth rates are assumed: 0% and 1.05%. Finally, the third row from the bottom keeps the real income growth rate constant at 0.5% and assumes two real discount rates different from the base scenario. The rates assumed are 4% and 6%. Thus, an increase and a fall of 1% in each rate were assumed, except for the real income growth fall which was assumed not to fall below 0%.

The first column reports changes in the human capital stock for the selected year 2013, to the different assumptions made. First, the level of human capital



**Table 6:** Sensitivity analysis on aggregate human capital estimates.

Sensitivity Analysis on aggregate human capital estimates							
	Human Capital Stock at current prices			Growth in quantity of human capital stock		Growth in price of human capital stock	
	2013 Level	Relative to baseline	% $\Delta$	Annual Growth in 2013	Difference with baseline	Annual Growth in 2013	Difference with baseline
	Billions of €	Billions of €	%	Percent	Percent	Percent	Percent
Baseline estimate with 0.5% real income growth and 5% real discount rate	33.43	...	...	4.53	...	2.48	
<b>Changes in real income growth leaving the 5% discount rate constant</b>							
0% real income growth	31.68	-1.75	-5	4.52	-0.0018	2.49	0.0096
1.05% real income growth	35.54	2.11	6	4.53	0.0022	2.47	-0.011
<b>Changes in real discount rate leaving the 0.5% real income growth unchanged</b>							
4% real discount rate	37.29	3.86	12	4.53	0.0042	2.46	-0.0197
6% real discount rate	30.23	-3.2	-10	4.52	-0.0032	2.50	0.0179

Source: Authors' estimates

stock under the new assumptions are reported. The change in human capital stock from its value under the baseline scenario is then analysed in absolute and percentage terms. The growth in the volume of human capital and the growth in the price of human capital are examined in the second and third columns respectively. For each of these growth rates, the new annual growth rate and its percentage change from the baseline scenario is presented.

From Table 6, it is apparent that changes in the expected future income growth and the discount rate have only a marginal effect on the growth rate of the quantity and price of human capital. Conversely, the findings indicate that changes in the human capital stock to changes in the real income growth rate or discount rate appear to be quite significant. Eq. (2), which was employed to estimate lifetime income, indicates that an increase in real income growth has the same impact as a decline in the discount rate. In fact, the aggregate human capital stock increases by 6% when the real income growth increases to 1.05% and by 12% when the discount rate falls by one-percentage point to 4%. Con-

versely, when the real income growth falls and the discount rate increases, the aggregate human capital is expected to fall. The results in Table 6 show that when the real income growth falls to 0%, the human capital stock falls by 5% whilst when the discount rate increases to 6%, the human capital stock declines by 10%.

## 5 Conclusion

The main aim of this paper was to produce an estimate for human capital stock for Malta over the period 2005 to 2013 and to compare Malta's performance with that of other countries. The objectives of this research were to answer the following two main questions:

- i. how can one give a value to the amount of capital embodied in humans and;
- ii. what were the human capital dynamics in Malta over the years, particularly when compared with other countries.

This research was primarily motivated by the fact that human resources are Malta's major resource, in the absence of any natural endowments. The conclusions of

this study suggests that:

First, the three main approaches for estimating human capital are the education-based approach, the cost-based approach and the income-based approach. This paper concluded that while the first two approaches use indicators which may be suitable for other purposes, the lifetime income approach could provide a more reliable monetary metric.

Second, the human capital stock of Malta grew by 70% in nominal terms from 2005 to 2013. The nominal average annual growth rate was approximately equal to 7%. The real human capital stock grew by 32% over the same period and was approximately equal to €25.88 billion in 2013. The real average growth rate was around 3% per annum. This real change in human capital was attributed to a 2% increase in the labour force population and a 1% increase in real lifetime income per capita. The latter represents compositional shifts in the education and age profiles of the population. Shifts in the population towards younger and better-educated individuals are expected to have a positive impact on real human capital per capita, and thus real human capital stock.

Third, the human capital stock was estimated to be on average twice the value of physical capital stock and four times the value of Malta's GDP.

Fourth, the level of the human capital stock estimates was sensitive to the choice of the expected future income growth and the rate used to discount the future income, but the growth of the quantity and price of human capital stock was much less sensitive to these choices.

The increase in human capital stock registered over the period studied was not always reflected in higher labour productivity. Conversely, labour productivity dropped year on year from 2011 to 2013, falling to a level below that of the average Euro Area. This may be attributed to the relatively high Early School Leaving (ESL) rate registered in Malta. NSO defines early school leaving (ESL) as those students between the ages of 18 and 24 who have left compulsory schooling and who have not obtained at least 5 Secondary Education Certificate (SEC) passes grade 1 to grade 7 and who are not in education or training. This represents lost potential and more likely than not, a lower human capital base for Malta.

As depicted in Fig. 1, those individuals with a higher educational level had larger average lifetime incomes. This is because they are expected to be more productive (as measured by earnings). Moreover, the difference in average lifetime incomes between the lowest educational level ISCED 0–2 and ISCED 3–4 was higher than that between ISCED 3–4 and ISCED 5–6. This might indicate that investing in those individuals with relatively lower levels of education may be more beneficial

since the added productivity is expected to be higher. To put things into perspective, Malta's ESL rate in 2013 was equal to 20.5%. Notwithstanding the fact that from 25.7% in 2009, Malta's ESL rate went down by 5.2% in four years; in 2013 it was still classified as the second highest in the EU. The EU average stood at 11.9% in the same year.

The relatively high ESL rate for Malta is one of the main areas which should be given priority because these individuals would still be at a very early stage of their career path. Their remaining years of work and thus their productive potential is expected to be higher. With respect to the performance of Maltese students, according to the Programme for International Student Assessment (PISA) of 2009<sup>7</sup>, Malta ranked 45th position among 74 countries in reading literacy, 40th position in mathematics literacy and 41st position in science literacy. Malta's performance in these three key subjects was significantly lower than both the OECD and EU average.

The structure of the education system is an important determinant of the educational achievements of the country. The heterogeneity that exists between educational systems may somewhat hinder cross-country comparison. Some of the variances in educational systems across different countries include the school days, areas of focus, the number of mandated standardised exams and age at which students are placed at designated academic or vocational paths.

Another factor impacting on the growth of human capital is the female participation rate. Although significant progress has been made, the EU noted that Malta still has the highest gender employment gap in the EU. In fact, the female participation rate in the Maltese labour market was one of the key challenges listed by the European Union (EU) in Malta's Country-Specific Recommendations for 2013. Those women that choose to stop working represent lost human capital. Female participation is significantly affected by the flexibility of working-time arrangements, taxation, longer maternity leave and family support measures such as child care centres.

This analysis has shown that despite the significant improvement in human capital in Malta, there are still further avenues for improvement, particularly with respect to the percentage of youths who opt to leave school without having the necessary qualifications to be in demand within the labour market. This accentuates the need for more policy measures targeted at this social group.

<sup>7</sup>Malta, together with nine additional partner participants, was unable to participate within the PISA 2009 project timeframe. However, it participated in the PISA 2009+ project. Malta, together with the other nine participants administered the same assessments as their PISA 2009 counterparts, but in 2010.

## References

- Atkinson, T. (2005). *Atkinson Review: Final Report*. Palgrave Macmillan. New York.
- Barro, R. J. & Lee, J. W. (1996). International Measures of Schooling Years and Schooling Quality. *American Economic Review*, 86, 218–223.
- Becker, G. (1964). *Human Capital: A Theoretical and Empirical Analysis, with Special Reference to Education*. New York: Columbia University Press.
- Central Bank of Malta. (2010). Forty-Second Annual Report and Statement of Accounts 2009. Retrieved January 2015, from <https://www.centralbankmalta.org/annual-reports>
- Eisner, R. (1985). The Total Incomes System of Accounts. *Survey of Current Business*, 65(1), 24–48.
- Eisner, R. (1989). *The Total Incomes System of Accounts*. Chicago, I.L.: University of Chicago Press.
- European Commission. (2014). *Guide to Cost-benefit Analysis of Investment Projects: Economic appraisal tool for Cohesion Policy 2014–2020*. Luxembourg: Publications Office of the European Union.
- Fender, V. (2013). *Measuring the UK's Human Capital Stock*. London: Office for National Statistics.
- Greaker, M. & Liu, G. (2008, November). Measuring the stock of human capital for Norway: a lifetime labour income approach. In *Joint OECD – Fondazione Giovanni Agnelli Workshop on the Measurement of Human Capital*. Turin, Italy.
- Gu, W. & Wong, A. (2010). Estimates of Human Capital in Canada: The Lifetime Income Approach. *SSRN J.* (11), 1–45.
- Jorgenson, D. W. & Fraumeni, B. M. (1989). The Accumulation of Human and Nonhuman Capital, 1948–84. In R. Lipsey & H. Stone Tice (Eds.), *The Measurement of Saving, Investment, and Wealth* (1st, pp. 227–286). University of Chicago Press.
- Jorgenson, D. W. & Fraumeni, B. M. (1992a). Investment in education and U.S. economic growth. *Scandinavian Journal of Economics*, 94(0 (Supplement)), 281–302.
- Jorgenson, D. W. & Fraumeni, B. M. (1992b). The output of the education sector. In Z. Griliches (Ed.), *Output measurement in the service sectors* (pp. 303–338). Chicago: The University of Chicago Press.
- Kendrick, J. W. (1976). *The Formation and Stocks of Total Capital*. New York: Columbia University Press for the National Bureau of Economic Research.
- Kiker, B. F. (1966). The historical roots of the concept of human capital. *J. Polit. Econ.* 74(5), 481–499.
- Le, T. V. T., Gibson, J. & Oxley, L. (2002). A forward looking measure of the stock of human capital in new zealand. In *Annual conference of the New Zealand Association of Economists*. Wellington.
- Lee, J.-W. & Barro, R. J. (2001). Schooling Quality in a Cross-Section of Countries. *Economica*, 68(272), 465–488.
- Liu, G. (2011). Measuring the stock of human capital for comparative analysis: an application of the lifetime income approach to selected countries. In *OECD Statistics Working Papers* (Vol. 41, 2011/6). Paris: OECD Publishing.
- Mincer, J. (1958). Investment in Human Capital and Personal Income Distribution. *Journal of Political Economy*, 66(4 (Aug. 1958)), 281–302.
- Mincer, J. (1974). The Human Capital Earnings Function. In J. Mincer (Ed.), *Schooling, Experience, and Earnings* (1st). Columbia University Press.
- Nerdrum, L. (1998). *The Economics of Human Capital*. Oslo: Scandinavian University Press.
- O'Mahony, M. & Stevens, P. (2009). Output and productivity growth in the education sector: Comparisons for the US and UK. *Journal of Productivity Analysis*, 31, 177–194.
- Psacharopoulos, G. & Arriagada, A. M. (1986). The Educational Composition of the Labour Force: An International Comparison. *International Labour Review*, 125(5), 561–574.
- Psacharopoulos, G. & Arriagada, A. M. (1992). The Educational Composition of the Labour Force: An International Update. *Journal of Educational Planning and Administration*, 6(2), 141–159.
- Schultz, T. (1961). Investment in Human Capital. *Am. Econ. Rev.* 51(1), 1–17.
- Smith, A. (1937). *An Inquiry into the Nature and Causes of the Wealth of Nations*. New York: Modern Library.
- Wei, H. (2004). Measuring the Stock of Human Capital for Australia: A Lifetime Labour Income Approach. In *Methodology Research Papers*. Cat. No. 1351.0.55.001. Canberra: Australian Bureau of Statistics.
- Wei, H. (2007). Measuring Australia's human capital development: The role of post-school education and the impact of population ageing. *Statistical Journal of the IAOS*, 24(3/4), 183–191.
- Wei, H. (2008). Measuring Human Capital Flows for Australia: A Lifetime Labour Income. In *Methodology Research Papers*. Cat. No. 1351.0.55.023. Canberra: Australian Bureau of Statistics.

## Data Sources

Eurostat. (2015a). AMECO Database - European Commission. Retrieved February 2015, from [http://ec.europa.eu/economy\\_finance/db\\_indicators/ameco/zipped.en](http://ec.europa.eu/economy_finance/db_indicators/ameco/zipped.en).

Eurostat. (2015b). Home - Eurostat. Retrieved January 2015, from <http://ec.europa.eu/eurostat>

NSO. (2015). NSO Home. Retrieved January 2015, from <http://nso.gov.mt/en/Pages/NSO-Home.aspx>



Research Note

## Investigating the Use of UAV Systems for Photogrammetric Applications: A Case Study of Ramla Bay (Gozo, Malta)

Emanuele Colica<sup>\*1,2,3</sup>, Anton Micallef<sup>1</sup>, Sebastiano D'Amico<sup>3</sup>, Louis F. Cassar<sup>1</sup> and Charles Galdies<sup>1</sup>

<sup>1</sup>*Environmental Planning and Management Division, Institute of Earth Systems, University of Malta, Msida, Malta*

<sup>2</sup>*Department of Mathematics, IT, Physics and Earth Sciences, University of Messina, Italy*

<sup>3</sup>*Department of Geosciences, University of Malta, Msida, Malta*

**Abstract.** In this study, we present the 3D digital model of Ramla Bay (Gozo) obtained by using photographs taken from drones. The high-resolution 3D model of Ramla Bay allowed the construction of a detailed Digital Elevation Model (DEM). Comparison of an earlier LIDAR data derived DEM (ERDF 156 Data, 2013) and the photogrammetric DEM developed in this study allowed to make preliminary observations regarding the potential evolution of the coastal area over the last 5 years. This study serves as a proof of concept to demonstrate that coastal evolution can be quantitatively analysed in terms of changes of the sand dune systems. Furthermore, the technique used in this paper represents a good compromise in terms of cost effectiveness and a valid substitute for laser scanner survey. It is also useful for monitoring the dynamics of the beach-dune system and the characterization of the coast for the mitigation of coastal erosion.

**Keywords:** Photogrammetry, Ramla Bay, DEM, Drone, UAV, 3D Digital Model

### 1 Introduction

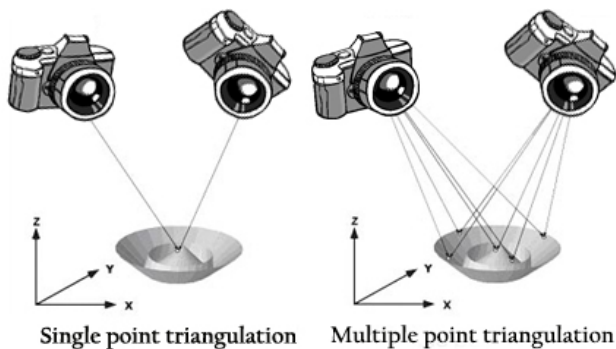
In recent years, approaches, technologies, and software for creating digital models of reality have undergone significant advancement. Acquisition time, post-processing tools and cost have also improved considerably. Digitization now allows reliable coverage of artefacts, ranging from small gauge (e.g. an archaeological prehistoric stone tool Crupi et al., 2016; D'Amico et al., 2017) to larger scales (e.g. building, urban segments or habitat areas Crupi et al., 2017). One of the 3D digitization and reconstruction techniques is known as photogrammetry. While no universally accepted definition of

photogrammetry is available, it can be described as a science to obtain reliable information about the spatial properties of land surfaces and objects, without physical contact (Schenk, 2005). Photogrammetry provides methods to obtain quantitative information and is often defined as the "science of measurement through aerial photography". However, it is traditionally part of geodesy sciences, belonging to the field of remote sensing (RS). Through its application, it is possible to determine distance, area and other geographical information, provided that reference terrain coordinates are available; from this one can then calculate geometric data or create detailed cartography.

The fundamental principle used in photogrammetry is triangulation (Figure 1). By taking photographs from at least two different locations, so-called "lines of sight" can be developed from each camera to points on the object. These lines of sight are mathematically intersected to produce the three-dimensional coordinates of the points of interest (Nisha, 2013). While from a single photo (with a two-dimensional plane) one can only obtain two-dimensional coordinates, stereoscopic viewing may be employed to obtain three-dimensional information. Essentially, if there are two (or more) photos of the same object but taken from different positions, one may easily calculate the three-dimensional coordinates of any point which is represented in both photos. Therefore, through the use of photogrammetry, it is possible to calculate the three-dimensional object coordinates for any object point represented in at least two photos. If this task is completed by using several images, it is possible to digitize points, lines and areas for map production or calculate distances, areas, volumes, slopes and much more. In addition, photogrammetry also enables one to

\*Correspondence to: Emanuele Colica (emanuele.colica@gmail.com)

measure fast moving objects. This can include running or flying animals or even waves. In industry, high-speed cameras with simultaneous activation are used to obtain data about deformation processes (such as those observed in car crash-tests). A further advantage of photogrammetric matching techniques is the fact that they are relatively fast and cheap in respect to the traditional laser scanner techniques (Nuikka et al., 2008), which are nowadays widely used in terrain models generating large amounts of 3D point data.



**Figure 1:** Schematic triangulation processes for photogrammetry.

Protection and proper management of archaeological sites are essential for studying and interpreting old cultures by preserving any artefact for the benefit of present and future generations. Photogrammetry can represent a key factor and in recent years it has been applied to planning, recording, reconstruction, and revitalization of world heritage sites (Al-Ruzouq, Al-Rawashdeh, Tommalieh & Ammar, 2012). It can also be used for supporting open-pit mine excavation stages and to plan rehabilitation strategies (Esposito, Mastrorocco, Salvini, Oliveti & Starita, 2017) as well as for forestry and management planning (Mafanya et al., 2017) and disaster management (Vetrivel, Gerke, Kerle, Nex & Vosselman, 2016; Gómez, White & Wulder, 2016). In fact, oblique aerial images offer views of both building roofs and façades and thus have been recognized as a potential source to detect severe building damages caused by destructive disaster events such as earthquakes. They, therefore, represent an important source of information for first responders or other stakeholders involved in the post-disaster response (Vetrivel et al., 2016).

### 1.1 Test Site

The test site, Ramla Bay (*Malt. Ir-Ramla*), is located on the northern coast of the island of Gozo (Figure 2). The area is characterized by the typical ‘cake-layer’ Maltese stratigraphic sequence, comprising, in the case of the study site, Miocene rocks. The islands are composed of a five-layer sequence of Oligocene–Miocene

limestones and clays, with the compact Lower Coral-line Limestone (LCL) being the oldest exposed layer, and forming steep-sided cliffs along the southern coast of Gozo. In order of decreasing age, the next four layers are the Globigerina Limestone, a fine-grained foraminiferal limestone; the Blue Clay (BC) formation, a series of carbonate-poor clays and marls that is highly erodible and plastic when wet; the Greensand, a thickly bedded, coarse, glauconitic, bioclastic limestone, which forms sharp contact with Blue Clay and a more transitional contact with the younger stratum above it; and, the Upper Coralline Limestone (UCL), a patch reef, cross-bedded oolitic bioclastic limestone that is similar to the LCL and forms a well-developed karst landscape (Pedley, House & Waugh, 1978, 2002, and references therein). Deposits of Quaternary age can be observed within the area in question in the form of consolidated hill-slope material and sheen deposits.

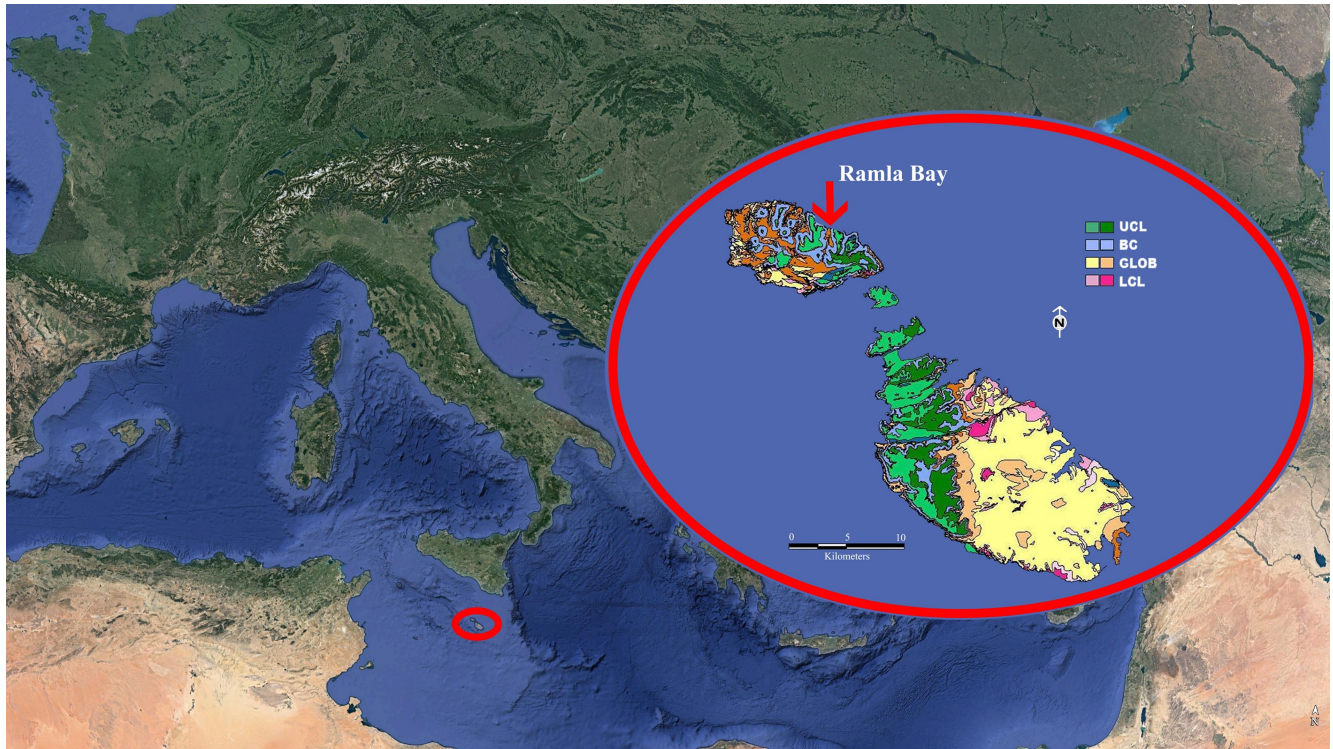
Ir-Ramla is a typical pocket embayment, nestled between two promontories, plateau extensions of the villages of Xagħra to the west and Nadur to the east. The promontories are bisected by broad valley slopes, the bed of which commences as Wied il-Hannaq at the system’s headwaters at Ta’ Hida in Nadur, snaking its way towards the coast through Blue Clay slopes and resting on Globigerina Limestone geology (Scerri, 2003). At its mouth, the bay supports a fine sand beach and Elytrigia foredunes comprising Quaternary blown material as a result of weathering processes and splash erosion of Għajn Melel Member rocks (the basal unit of the UCL, which lies atop the Greensand stratum), (Micallef, Lanfranco & Schembri, 1994; Cassar & Stevens, 2002). Mass movement on the upper Ta’ Venuta slopes (including slope failure and slippage around the base of the escarpment) is the process responsible for these scarp line fragments to accumulate nearer the shoreline, often forming boulder fields in relatively shallow waters of the bay (Scerri, 2003). A considerable amount of sand at Ir-Ramla also originates from Wied il-Pergla to the west, as sediment is transported via run-off waters during the wet season (Cassar & Stevens, 2002).

## 2 Methodology

### 2.1 Data Collection

To build a 3D model using photogrammetry, many types of images can be used such as satellite, airborne, balloon, UAVs (Unmanned Aerial Vehicle), terrestrial and even underwater images. It is, however, necessary to have at least 2 overlapping images of the same scene in order to derive 3D information. In recent years, UAV photogrammetry imaging applications have increased rapidly due to the lower costs of a UAV for aerial surveying associated with the relative simplicity in operating such systems. With GPS equipped drones, digital cameras





**Figure 2:** Geographic location of Maltese Islands and simplified geology map; modified from Oil Exploration Directorate (1993). Arrow indicates the location of the study area.

and powerful computers, surveys with an accuracy of 1 to 2 cm are possible (Corrigan, 2017).

In this study, a survey was carried out using a light drone (DJI Phantom 4) equipped with a camera. The main features of the system are reported in Table 1. The flight was performed in manual mode at a height of 50 m above sea level (Figure 3). Throughout the area of interest 10 markers were placed on the ground and the relative spatial coordinates were taken through the use of a GPS. This was done to ensure correct and precise georeferencing of the area in order to properly export the final 3D to scale. Approximately 150 images were acquired during two separate surveys. The images were acquired keeping the camera at the minimum focal length (20 mm), while the image resolution was set at the highest level ( $4000 \times 3000$  pixels) in order to acquire good quality textures. The images were taken from a nadir-looking direction, and about 70% forward overlap and 60% side overlap.

## 2.2 Data Processing

The development of the 3D model has been performed with free and open source software like VisualSFM, Meshlab and Blender. For the orthorectification process 10 ground control points collected from a GPS survey were used as the geographic references.

Generally, the final goal of photograph processing

**Table 1**

Drone features		Camera features	
Name	Model: DJI Phantom 4	Sensor	1/2.3" CMOS
Weight (Battery & Propellers Included)	1380 g	Effective pixels:	12.4 M
Max Ascent Speed mode:	6 m/s	Lens FOV	94° 20 mm (35 mm format equivalent) $f/2.8$ focus at $\infty$
Max Descent Speed mode:	4 m/s	ISO Range	100–3200 (video)
Max Speed S-mode:	20 m/s		100–1600 (photo)
Max Flight Time	approx. 28 minutes	Electronic Shutter Speed	8 – 1/8000 s
Satellite Positioning Systems	GPS/GLONASS	Image Size	4000 × 3000, Photo JPEG, DNG (RAW)

with photogrammetry software is to build a Digital Elevation Model (DEM) or/and a Digital Terrain Model (DTM). For this goal, the procedure of photograph processing and 3D model construction comprised five main stages (Figure 4):

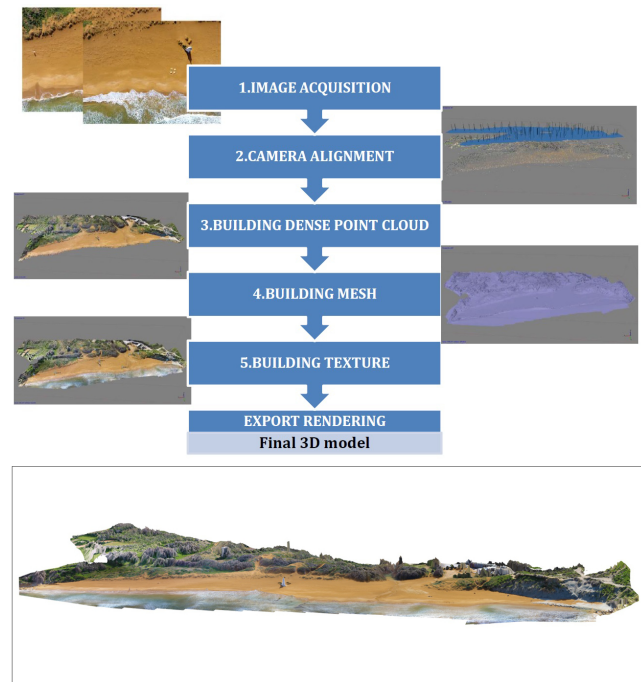


**Figure 3:** Drone flight plan during the survey. Red dots indicate the UAV position during the image acquisition.

1. *Image acquisition and selection:* Images were acquired through the use of a digital camera installed on the drone assuring a good amount of image overlapping. Preliminary processing was carried out in order to discard those of poor quality.
2. *Camera alignment:* This step consisted of searching for common points on photographs and matches through the use of appropriate software. It also identified the position of the camera for each picture and refined camera calibration parameters. As a result, a sparse point cloud and a set of camera positions were formed. The sparse point cloud represents the results of photo alignment which are not directly used in the 3D model construction procedure. On the contrary, the set of camera positions is required for further 3D model reconstruction.
3. *Building dense point cloud:* The third stage involved the building of a dense point cloud based on the estimated camera positions and pictures themselves. A dense point cloud may be edited and classified prior to export or proceeding to 3D mesh model generation.
4. *Building mesh:* At this stage the software was used to reconstruct a 3D polygonal mesh representing the object surface based on the dense or sparse point cloud according to the user's choice. Some corrections, such as mesh decimation, removal of detached components, closing of holes in the mesh, smoothing, were performed.
5. *Building texture:* After the geometry (i.e. mesh) was reconstructed, it could be textured and/or used for orthomosaic generation. After that, the 3D model was created and exported in several digital formats.

### 3 Results and Discussion

Using reality-based 3D models it was possible to derive metric data that are useful for several kinds of investigations such as the generation of ortho-images, detailed site maps, archaeological excavations and mapping, and



**Figure 4:** Workflow processing to obtain the final 3D model.

segmented high-resolution 3D models to highlight construction techniques, sequences, restorations, etc. The photogrammetric techniques require experience and a correct acquisition of images. The technique used in this paper represents a good compromise in terms of cost effectiveness and a valid substitute for laser scanner survey which can be very expensive in terms of equipment and/or external surveys. Field application of a laser scanner also requires a lot of time and experience during laboratory post-processing stage.

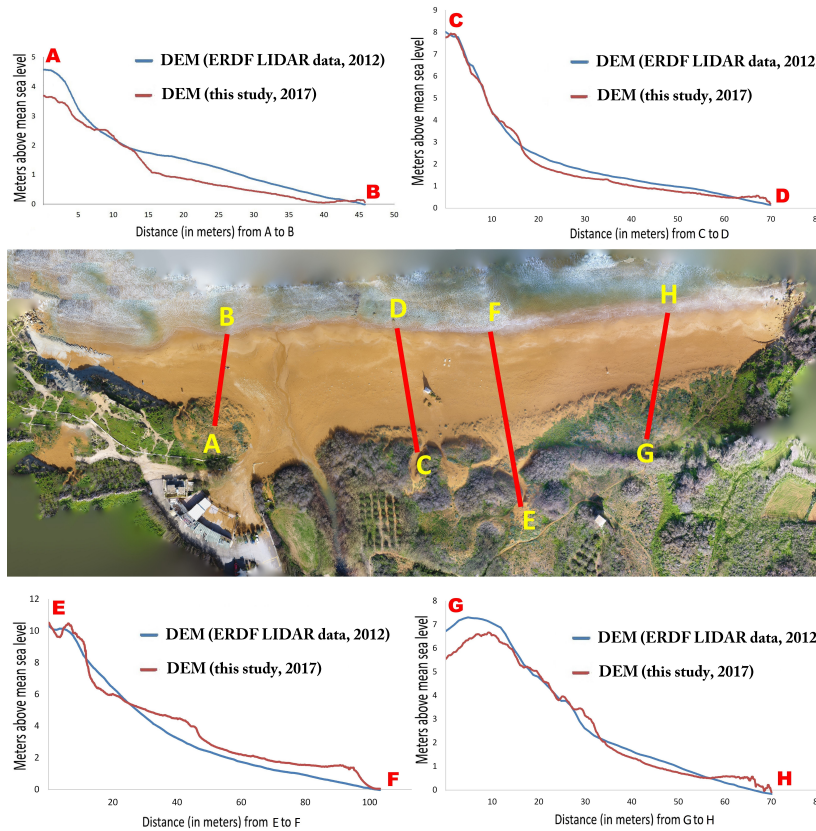
The high-resolution 3D model of Ramla Bay (Figure 5) allowed the construction of a detailed Digital Elevation Model (DEM). Comparison of this product with LiDAR-derived DEM (ERDF 156 Data, 2013) allowed the authors to make preliminary observations regarding the potential evolution of the coastal area over the last 5 years. LiDAR-derived DEM of the Ramla valley has already been used to map the degree of soil erosion in the area (Galdies, Azzopardi & Sacco, 2015).

Using the obtained 3D digital model, it was also possible to extract the profiles of the Ramla Bay's beach. DEMs obtained by LiDAR and Photogrammetry were superimposed and 4 topographical sections were tracked. Through a free and open source Geographic Information System software (QGIS) it was possible to extract 8 topographic profiles that were used for comparison. The obtained graphs have been superimposed to highlight the differences in profile elevations and it can be observed how the shape and volume of sand dune





**Figure 5:** High-resolution, oblique image of the 3D model generated for Ramla Bay.



**Figure 6:** Comparison between DEM profiles by LiDAR (A) and DEM profiles obtained in this study (B).

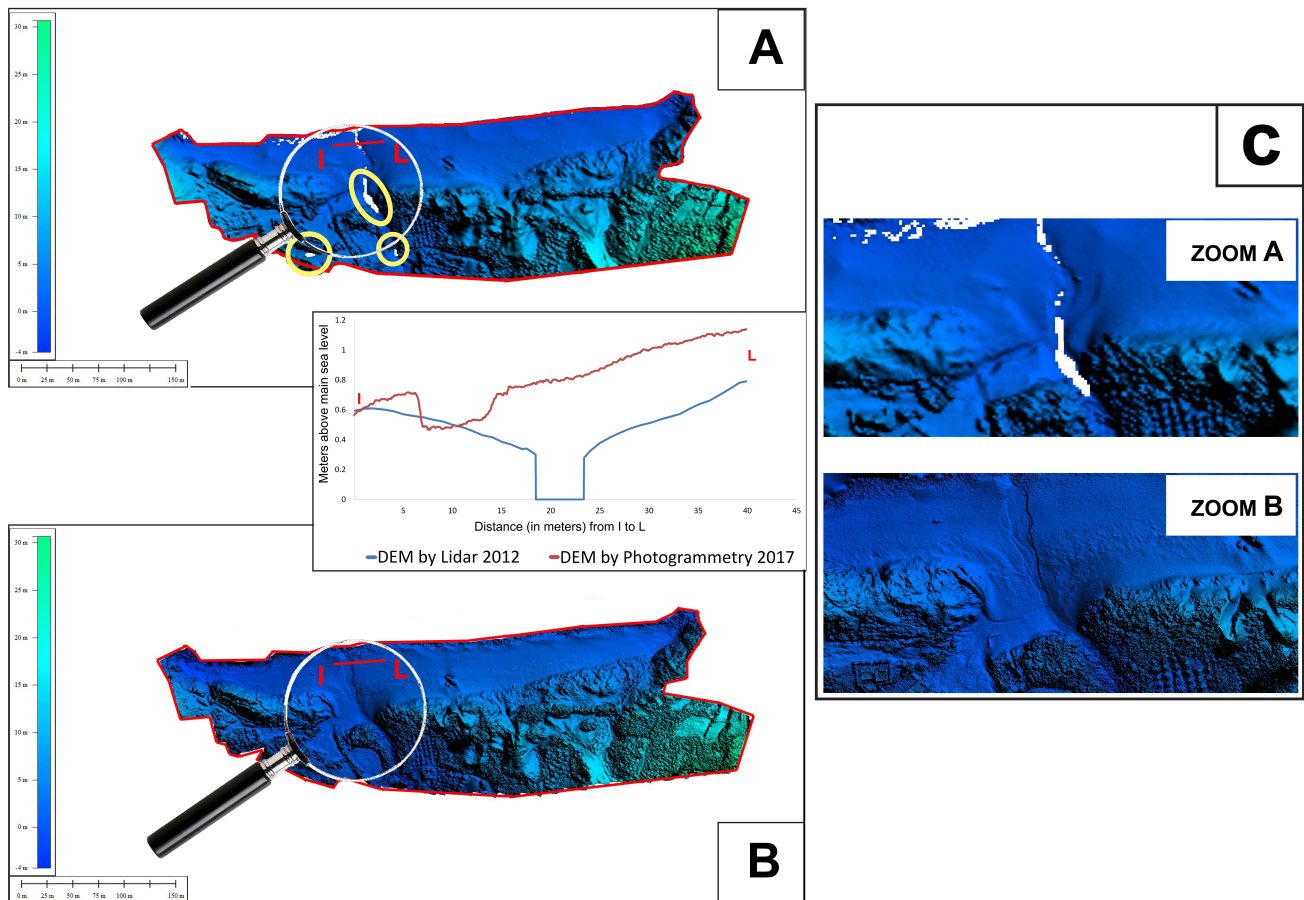
has changed from 2012 to 2017 (Figure 6). This method has been useful to quantitatively analyze coastal development.

Observing the LiDAR DEM for the study area, it is possible to identify data gaps (yellow circle in Figure 7A) where it is impossible to detect the elevation. This is problematic for the purposes of this study since tracking a topographic section across such gaps could lead to inaccuracies in topography as shown by the graph in Figure 7 in which the profiles of section I-L are compared. Furthermore, the photogrammetric DEM (Figure 7B) obtained in this study has improved the visual defini-

tion of the area at about one order of magnitude with respect to the LiDAR data that is based on  $1\text{ m} \times 1\text{ m}$  horizontal resolution (Figure 7C).

Such beach profiles can be useful for monitoring the dynamics of the beach-dune system and the characterization of the coast in the mitigation of coastal erosion.

It is important to emphasize that UAV Photogrammetry has significant advantages over ground-based survey techniques and aerial photography using manned aircrafts (Galdies, Betts, Vassallo & Micalef, 2014); specifically, in areas with difficult access, high traffic, or disaster areas, these systems can significantly improve



**Figure 7:** LiDAR DEM (A), Photogrammetric DEM (B), comparison between zoomed areas on LiDAR DEM and photogrammetric DEM.

worker safety by eliminating the need for an on-site presence.

## Acknowledgments

The authors wish to acknowledge the Operational programme I – Cohesion Policy 2007–2013 Investing in competitiveness for a better quality of life - *tender part-financed by the European Union European regional development fund (ERDF)* for the provision of LiDAR data. This research was partially supported by “ERASMUS Plus Program – Student mobility for traineeship” and by the research project funded by University of Malta “Dynamic characteristics of active coastal spreading areas: evaluation of cliff instability” (GSCR02-17).

## References

Cassar, L. F. & Stevens, D. T. (2002). *Coastal sand dunes under siege: A guide to conservation for environmental managers*. Malta: International En-

vironment Institute, Foundation for International Studies.

Corrigan, F. (2017). Introduction To UAV Photogrammetry And Lidar Mapping Basics. Retrieved May 5, 2017, from <https://www.dronezon.com/learn-about-%20drones-quadcopters/introduction-to-uav-photogrammetry-and-lidar-mapping-basics>

Crupi, V., D’Amico, S., Longo, F., Maiolino, D., Persico, R., Saccone, M., ... Venuti, V. (2016). Indagini multidisciplinari e rilievo 3D fotogrammetrico presso il sito archeologico di Scifi (Messina). In *Proceedings of the 35<sup>th</sup> National Meeting Gruppo Nazionale Geofisica della Terra Solida* (pp. 553–557). Lecce, Italy.

Crupi, V., D’Amico, S., Majolino, D., Paladini, G., Persico, R., Saccone, M., ... Venuti, V. (2017). Multidisciplinary Investigations embedded in a photogrammetric three dimensional survey in an archaeological site and St Peter and Paul Church in Agro Valley (Messina, Italy). *Geophysical Research Abstracts*, 19(EGU2017-6918).

- D'Amico, S., Crupi, V., Majolino, D., Paladini, G., Venuti, V., Spagnolo, G., ... M, S. (2017). Multidisciplinary Investigations and 3D virtual model at the Archeological Site of Scifi (Messina, Italy). In *Proceedings of the 9<sup>th</sup> International Workshop on Advanced Ground Penetrating Radar - IWAGPR 2017*. Edinburgh, Scotland: IEEE (in press).
- ERDF 156 Data. (2013). *Developing National Environmental Monitoring Infrastructure and Capacity*. Malta: Malta Environment & Planning Authority.
- Esposito, G., Mastrorocco, G., Salvini, R., Oliveti, M. & Starita, P. (2017). Application of UAV photogrammetry for the multi-temporal estimation of surface extent and volumetric excavation in the Sa Pigada Bianca open-pit mine, Sardinia, Italy. *Environ. Earth Sci.* 76(3).
- Galdies, C., Azzopardi, D. & Sacco, A. (2015). Large scale erosion mapping using LiDAR and RUSLE technique for landscape management in the island of Gozo, Malta. In *RSPSoc, NCEO and CEOI-ST Joint Annual Conference 2015*. The University of Southampton.
- Galdies, C., Betts, J., Vassallo, A. & Micallef, A. (2014). High Resolution Agriculture Land Cover Using Aerial Digital Photography and GIS - A case Study for Small Island States. In S. Formosa (Ed.), *Future Preparedness: Thematic and Spatial Issues for the Environment and Sustainability* (Chap. 7, pp. 127–151). Floriana, Malta: Department of Criminology, Faculty for Social Wellbeing, University of Malta.
- Gómez, C., White, J. C. & Wulder, M. A. (2016). Optical remotely sensed time series data for land cover classification: A review. *ISPRS J. Photogramm. Remote Sens.* 116, 55–72.
- Mafanya, M., Tsele, P., Botai, J., Manyama, P., Swart, B. & Monate, T. (2017). Evaluating pixel and object based image classification techniques for mapping plant invasions from UAV derived aerial imagery: *Harrisia pomanensis* as a case study. *ISPRS J. Photogramm. Remote Sens.* 129, 1–11.
- Micallef, S., Lanfranco, E. & Schembri, P. (1994). *An ecological survey of Ramla Bay, Gozo*. Msida, Malta: Malta University Services Ltd.
- Nisha, U. (2013). Basic of Photogrammetry. Retrieved May 5, 2017, from [http://www.gisresources.com/basic-of-photogrammetry\\_2/](http://www.gisresources.com/basic-of-photogrammetry_2/)
- Nuikka, M., Rönholm, P., Kaartinen, H., Kukku, A., Suominen, A., Salo, P., ... Hirs, H. (2008). Comparison of three accurate 3D measurement methods for evaluating as-built floor flatness. In *The International Archives of the Photogrammetry, Remote Sensing and Spatial Information Sciences* (Vol. 37, Part B5, pp. 129–134). Beijing.
- Oil Exploration Directorate. (1993). Geological Map of the Maltese Islands: Sheet 1 – Malta; Sheet 2 – Gozo and Comino. Valletta, Malta: Office of the Prime Minister.
- Pedley, H. M., Clarke, M. H. & Galea, P. (2002). *Limestone isles in a crystal sea: the geology of the Maltese Islands*. San Gwann, Malta: Publishers Enterprises Group Ltd.
- Pedley, H. M., House, M. R. & Waugh, B. (1978). *The Geology of the Pelagian Block: The Maltese Islands* (A. E. M. Nairn, W. H. Kanes & F. G. Stehli, Eds.). The Western Mediterranean. London: Plenum Press.
- Al-Ruzouq, R. I., Al-Rawashdeh, S. B., Tommalieh, O. A. & Ammar, M. S. (2012). Photogrammetry and GIS for three-dimensional modeling of the Dome of the Rock. *Appl. Geomatics*, 4(4), 257–267.
- Scerri, S. (2003). *Geo-environmental survey of Ramla Bay - Gozo*. Malta: GAIA Foundation.
- Schenk, T. (2005). *Introduction to Photogrammetry*. Department of Civil, Environmental Engineering and Geodetic Science, The Ohio State University. Ohio.
- Vetrivel, A., Gerke, M., Kerle, N., Nex, F. & Vosselman, G. (2016). Disaster damage detection through synergistic use of deep learning and 3D point cloud features derived from very high resolution oblique aerial images, and multiple-kernel-learning. *ISPRS J. Photogramm. Remote Sens.* (in press).



## Alcohol, Cannabinoids and Nicotine in Liver Pathophysiology

Manuela Radic<sup>\*1,2</sup>, Francesca Rappa<sup>1</sup>, Rosario Barone<sup>1</sup>, Francesco Cappello<sup>1</sup>, Giuseppe Crescimanno<sup>3</sup>, Maurizio Casarrubea<sup>3</sup>, Massimo Perucci<sup>2</sup>, Antonella Marino Gammazza<sup>\*1</sup>, Giuseppe Di Giovanni<sup>\*2</sup>

<sup>1</sup>Department of Experimental Biomedicine and Clinical Neuroscience (BIONECA), Section of Human Anatomy, University of Palermo, Italy

<sup>2</sup>Department of Physiology and Biochemistry, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

<sup>3</sup>Department of Experimental Biomedicine and Clinical Neuroscience (BIONECA), Section of Human Physiology, University of Palermo, Italy

**Abstract.** The liver can be affected by a wide range of therapeutic and environmental chemicals and here we want to provide a summary of the complex effects of alcohol, cannabinoids and nicotine on liver function. Alcohol is the most important agent that produces liver injury, manifesting as alcoholic fatty liver disease. In addition, it is one of the main etiologic agents for hepatocellular carcinoma development. Studies reviewed in this article regarding cannabinoids, show that  $\Delta 9$ -THC does not produce any harmful effects on the liver, while cannabidiol has hepatoprotective effects in ischemia/reperfusion and alcohol-induced liver injuries. The liver is negatively affected by nicotine exposure, but surprisingly nicotine was shown to have a positive effect on the liver in the diet-induced obese animal model, which should be confirmed by future research.

**Keywords:** liver, alcohol, cannabinoids, nicotine

### 1 Introduction

Alcohol, cannabinoids and nicotine are three major drugs of abuse, widely used especially among the youth (Johnston, O'Malley, Miech, Bachman & Schulenberg, 2017). It is important to study their effects, considering that they are common causes of preventable morbidity and mortality (Johnston et al., 2017). In this work, we want to provide a concise summary of the complex effects of alcohol, cannabinoids and nicotine on liver functions (see Table 1). The liver is a major detoxifying and drug metabolizing organ, with an enormous functional reserve (Theise, 2013). It can be affected by a wide

range of therapeutic and environmental chemicals, directly or by immune mechanisms (Theise, 2013).

Fatty liver disease (alcoholic or nonalcoholic) is a broad term which includes three liver alterations that can be present in any combination: hepatocellular steatosis, steatohepatitis and steatohepatitis with fibrosis (Theise, 2013). Hepatocellular steatosis or fat accumulation can be microvesicular (small lipid droplets) or macrovesicular (large lipid droplets) (Theise, 2013). Steatohepatitis is characterized by hepatocyte ballooning, Mallory-Denk bodies (eosinophilic cytoplasmic inclusions in degenerating hepatocytes) and inflammatory infiltration (Theise, 2013; Mandrekar & Szabo, 2010). Finally, steatohepatitis with fibrosis starts as central vein sclerosis and the scarring gradually spreads to the portal tracts forming central-portal or portal-portal bridging fibrosis (Theise, 2013; Sakhuja, 2014). Then, if the injury continues, the fibrosis and hepatocytes regeneration involves a pseudolobular or Laennec cirrhosis in which a nodular morphology is present (Theise, 2013; Sakhuja, 2014).

Among the inducers of liver diseases, alcohol is the most important agent that produces toxic liver injury and 60% of chronic liver disease in Western countries is caused by excessive ethanol intake (Theise, 2013). The Monitoring the future (MTF) survey conducted in 2016 shows that 61% of students have consumed alcohol by the end of high school and 46% of 12<sup>th</sup> graders have reported being drunk at least once in their life, which makes alcohol the most widely used substance by today's teenagers (Johnston et al., 2017). Alcohol causes lipid metabolism changes, decreases export of

\*Correspondence to: Manuela Radic (manuela.radic@outlook.com), Antonella Marino Gammazza (antonella.marino@hotmail.it), Giuseppe Di Giovanni (giuseppe.digiovanni@um.edu.mt)

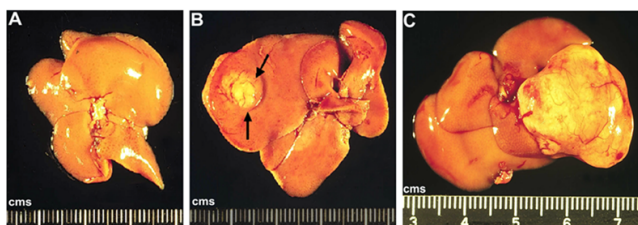
Table 1: Liver changes induced by ethanol, cannabinoids and nicotine.

DRUG	ANIMALS	ADMINISTRATION ROUTE	DOSE	DURATION	LIVER CHANGES	REFERENCES
Ethanol	Albino rats	Drinking water	2 ml (0.5 g)/100 g body weight per day of 30% v/v of an aqueous solution	8 weeks	↑ALT, ↑GGT, ↑liver weight, ↑liver volume, ↑hepatocyte size, large number of cytoplasmic vacuoles, pyknotic nuclei, periportal inflammation	Habib-ur-Rehman, Tahir, Lone and Sami (2011)
Ethanol	Wistar rats	Drinking water	Weekly increase in concentration to a 40% v/v	Up to 29 weeks	Steatosis, inflammation, hepatocyte necrosis, pericentral sclerosis	Keegan, Martini and Batey (1995)
Ethanol	Mice (ICR - Institute for Cancer Research)	Drinking water	Concentration: 5% (first week), 10% (next 8 weeks), 15% ethanol thereafter ad libitum for 60 and 70 weeks	70 weeks	Several larger nodules (5-22 mm) → trabecular HCC (eosinophilic and vacuolated cells)	Tsuchishima et al. (2013)
Δ9-THC	C57BL/6J mice	Intraperitoneal injection	10 mg/kg body weight	10 days	No harmful effects on: lipid peroxidation, protein carbonylation or DNA oxidation	Pinto, Moura, Serrão, Martins and Vieira-Coelho (2010)
Cannabidiol	Sprague-Dawley rats (exposed to ischemia/reperfusion liver injury)	Intravenous injection	5 mg/kg	1-hour following the procedure and 24 hours thereafter for two consecutive days	↓TNF-α elevation, ↓NO elevation and ↓ALT, induced by ischemia/reperfusion injury + histology comparable to the control group	Fouad and Jresat (2011)
Cannabidiol + Ethanol	C57BL/6 mice	Cannabidiol: intraperitoneal injection. Ethanol: gavage	Cannabidiol: 5 mg/kg, every 12 h, 30 min before each ethanol gavage. Ethanol: 30% v/v in saline, 4 g/kg, every 12 h	5 days	Cannabidiol prevented the ethanol-induced ↑AST and hepatic triglycerides, reversed the ethanol-induced ↓hepatic ATP levels. Cannabidiol ↓basal triglycerides levels	Yang et al. (2014)
Nicotine	Fischer 344 rats	Intraperitoneal via implanted osmotic minipumps	9 mg/(Kg d)	2 weeks	↑ALT, ↑AST, ↑ALP, ↑biliary proliferation and fibrosis	Jensen et al. (2013)
Nicotine	Sprague-Dawley rats (diet-induced obesity)	Subcutaneous injection	2 mg/kg every 12 h	17 days	↓liver steatosis, ↓inflammation, ↓ER stress	Seoane-Collazo et al. (2014)
Nicotine + Ethanol	C57BL/6 mice	Nicotine: intraperitoneal injection. Ethanol: liquid ethanol diet	Nicotine: 1 mg/kg body weight, Ethanol: from 10% gradually to 35% of total calories	3 weeks	Nicotine ↓ethanol-induced steatosis. Nicotine + Ethanol: ↑hepatic contents of collagen type I	Lu, Ward and Cederbaum (2013)



lipoproteins, and causes cell injury, which manifest as fatty liver disease (Theise, 2013). Hepatotoxicity of ethanol has been shown in experimental animals (Habibur-Rehman, Tahir, Lone & Sami, 2011; Keegan, Martini & Batey, 1995; Tsuchishima et al., 2013). Habibur-Rehman and co-workers (2011) treated albino rats with ethanol for 8 weeks and found functional and structural liver changes, such as increase in the serum alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) levels, periportal inflammation, liver weight and volume increase (Habibur-Rehman et al., 2011). Another group induced alcoholic liver injury by delivering ethanol in the drinking water (Keegan et al., 1995). They found evident hepatotoxic histological changes (i.e., steatosis, inflammation, hepatocyte necrosis and pericentral sclerosis) while maintaining a nutritionally adequate food intake (Keegan et al., 1995).

In addition, ethanol consumption is one of the main etiologic agents for hepatocellular carcinoma (Theise, 2013). For example, in the study conducted by Tsuchishima and co-workers, male mice were administered ethanol through drinking water for 70 weeks (Tsuchishima et al., 2013). 50% of those mice had several larger nodules (5–22 mm) in their liver, histologically verified as trabecular HCC composed of eosinophilic and vacuolated cells (Tsuchishima et al., 2013) (see Figure 1). The authors conclude that the tumorigenesis could occur as a result of proto-oncogenes and/or oncosuppressor genes mutations, due to repeated regeneration processes, although further studies are necessary (Tsuchishima et al., 2013).



**Figure 1:** Stereoscopic images of the liver tissue of ethanol administered mice at weeks 60 and 70. (A) Control group (60 W): no tumor. (B) Ethanol group (60 W): hepatic tumor was observed. (C) Ethanol group (70 W): large hepatic tumor measuring 22 mm was present. Adapted from Tsuchishima et al. (2013).

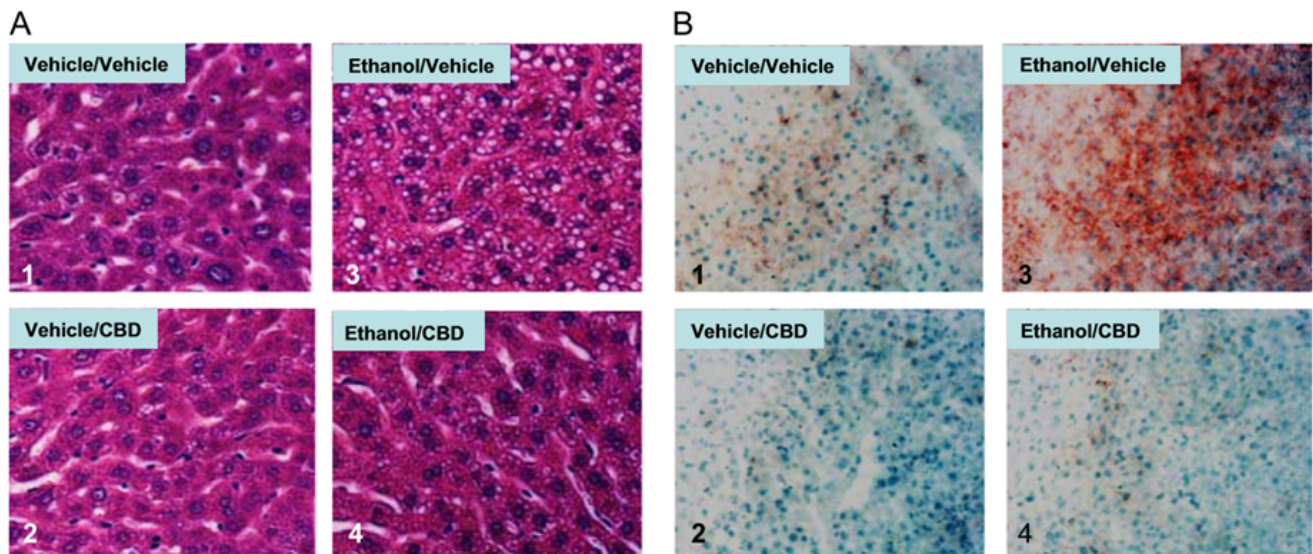
Together with alcohol, marijuana, made from leaves of the *Cannabis sativa* plant, is the most widely used illegal drug (Kumar, Abbas & Aster, 2013) and it is a popular drug of choice among young people which is mainly due to its easy availability and low cost. The MTF survey shows that one in seventeen 12<sup>th</sup> grades smoke marijuana daily (Johnston et al., 2017). Pinto and co-workers showed that  $\Delta$ -tetrahydrocannabinoid ( $\Delta$ 9-THC), marijuana's most psychoactive cannabinoid, does not produce any harmful effects on the liver of

healthy mice, when chronically administered (Pinto, Moura, Serrão, Martins & Vieira-Coelho, 2010). Mice were given intraperitoneal injections of  $\Delta$ 9-THC, in a total daily dose of 10 mg/kg body weight, for 10 days and this treatment did not produce any significant changes in the hepatic redox state (Pinto et al., 2010).

An increased expression of cannabinoid receptors type 1 (CB1) in human cirrhotic liver samples has been observed and it has been shown that CB1 signalling has a profibrogenic effect (see Parfieniuk & Flisiak, 2008). Julien and co-workers showed that cannabinoid receptors type 2 are expressed in cirrhotic human liver, predominantly in hepatic fibrogenic cells, but not in normal liver, and when activated endogenously they counteract liver fibrogenesis (Julien et al., 2005). Cannabidiol, the major non-psychoactive cannabis component, ameliorates ischemia/reperfusion-induced liver damage (Fouad & Jresat, 2011). Indeed, cannabidiol treatment resulted in significant reduction of ischemia/reperfusion-induced elevations of tumour necrosis factor- $\alpha$  and nitric oxide in liver homogenates, as well as the serum level of ALT (Fouad & Jresat, 2011). Furthermore, the hepatoprotective effect of cannabidiol was also shown on the histopathological examination, where the histological picture of the ischemia/reperfusion cannabidiol-treated group was comparable to the control group (Fouad & Jresat, 2011). Yang and co-workers showed that cannabidiol protects mouse liver from acute alcohol-induced steatosis (Yang et al., 2014). Cannabidiol prevented ethanol-induced serum aspartate aminotransferase (AST) increase and significantly attenuated the hepatic triglycerides elevation (Yang et al., 2014) (see Figure 2). Furthermore, cannabidiol lowered basal triglycerides levels and completely reversed the ethanol-induced decline in hepatic ATP levels (Yang et al., 2014).

Cigarette smoking represents another factor that increases risk or susceptibility for a lot of diseases and for liver disease as well. In particular, cigarette smoking by teenagers and young adults leads to immediate and serious health problems including respiratory and non-respiratory effects, addiction to nicotine, and the associated risk of other drug use. Several studies have found nicotine to be addictive in ways similar to heroin, cocaine, and alcohol. In fact, nicotine is a highly addictive alkaloid, found in tobacco leaves, responsible for the acute effects of smoking (i.e., increased heart rate, blood pressure, cardiac contractility and output) (Kumar et al., 2013). Thirty-day prevalence of cigarette use, for 12<sup>th</sup> graders, was 11% in 2016 (Johnston et al., 2017).

It is continuously declining from 1997 (37%), due to increases in disapproval and perceived risk (Johnston et al., 2017). A retrospective follow-up study of a 10-year interval was conducted on a total of 3,365 sub-

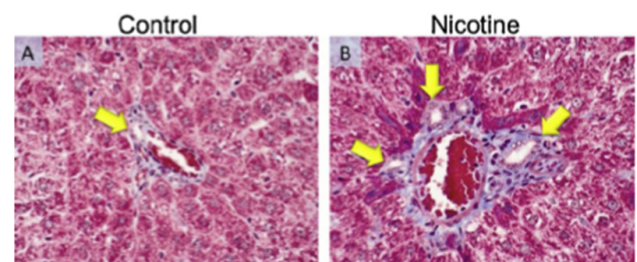


**Figure 2:** (A) H&E staining and (B) oil red O staining showing increased lipid accumulation in mouse liver after binge alcohol treatment. CBD decreases this lipid accumulation (image 4 compared to image 3 in (A) and (B)). Adopted from Yang et al. (2014).

jects, to assess the effect of cigarette smoking on the development or cure of nonalcoholic fatty liver disease (Hamabe et al., 2011). This study showed that cigarette smoking is an independent risk factor for nonalcoholic fatty liver disease development (Hamabe et al., 2011). Jensen and co-workers (2013) showed that chronic nicotine exposure induces a significant increase in ALT, AST and alkaline phosphatase (ALP) levels in rats, as well as an increase of biliary proliferation and fibrosis, which may play a role in the pathogenesis of cholangiopathies (Jensen et al., 2013) (see Figure 3). On the other hand, an interesting study was conducted by Seoane-Collazo and co-workers (Seoane-Collazo et al., 2014). They found that nicotine reduced liver steatosis, inflammation and ER stress in diet-induced obese male rats (Seoane-Collazo et al., 2014). Moreover, this effect was produced independently of nicotine's anorectic action (Seoane-Collazo et al., 2014). Finally, Lu and co-workers (2013) showed that nicotine treatment alone does not induce a necro-inflammatory response nor steatosis, while it enhances ethanol-induced steatosis (Lu, Ward & Cederbaum, 2013). In addition, nicotine and ethanol when given alone increase hepatic contents of collagen type I and this effect is enhanced by a nicotine and ethanol combination (Lu et al., 2013).

## 2 Conclusion

In conclusion, ethanol treatment deteriorates liver's function which can lead to cancer development. Nicotine exposure was shown to induce liver injury and to promote fibrosis, while its positive effect in diet-induced obese animal models should be evaluated by further research. Regarding cannabinoids,  $\Delta^9$ -THC was not



**Figure 3:** Evaluation of collagen deposition by Masson's trichrome staining in liver sections from control and nicotine-treated rats. Masson's trichrome staining in control (A) and nicotine-treated rats (B). Chronic administration of nicotine stimulated an increase in collagen deposition (blue staining) around the portal areas of nicotine-treated (B) compared with normal control rats (A). Bile ducts are indicated with yellow arrows. Adopted from Jensen et al. (2013).

shown to produce any harmful effects on the liver, while cannabidiol showed hepatoprotective effects in ischemia/reperfusion and alcohol-induced liver injuries. Therefore, cannabinoid signalling modulation could potentially be a new therapeutic approach in the liver fibrosis management.

## References

- Fouad, A. A. & Jresat, I. (2011). Therapeutic potential of cannabidiol against ischemia/reperfusion liver injury in rats. *Eur. J. Pharmacol.* 670(1), 216–223.
- Habib-ur-Rehman, M., Tahir, M., Lone, K. P. & Sami, W. (2011). Ethanol induced hepatotoxicity in albino rats. *J. Coll. Physicians Surg. Pakistan*, 21(10), 642–643.



- Hamabe, A., Uto, H., Imamura, Y., Kusano, K., Mawatari, S., Kumagai, K., ... Tsubouchi, H. (2011). Impact of cigarette smoking on onset of non-alcoholic fatty liver disease over a 10-year period. *J. Gastroenterol.* 46(6), 769–778.
- Jensen, K., Afroze, S., Ueno, Y., Rahal, K., Frenzel, A., Sterling, M., ... Glaser, S. S. (2013). Chronic nicotine exposure stimulates biliary growth and fibrosis in normal rats. *Dig. Liver Dis.* 45(9), 754–761.
- Johnston, L. D., O'Malley, P. M., Miech, R. A., Bachman, J. G. & Schulenberg, J. E. (2017). *Monitoring the Future national survey results on drug use, 1975-2016: Overview, key findings on adolescent drug use*. Institute for Social Research, The University of Michigan.
- Julien, B., Grenard, P., Teixeira-Clerc, F., Tran Van Nhieu, J., Li, L., Karsak, M., ... Lotersztajn, S. (2005). Antifibrogenic role of the cannabinoid receptor CB2 in the liver. *Gastroenterology*, 128(3), 742–755.
- Keegan, A., Martini, R. & Batey, R. (1995). Ethanol-related liver injury in the rat: a model of steatosis, inflammation and pericentral fibrosis. *J. Hepatol.* 23(5), 591–600.
- Kumar, V., Abbas, A. K. & Aster, J. C. (2013). Environmental and Nutritional Diseases. In *Robbins basic pathology* (9th ed., pp. 269–308). Philadelphia: Saunders/Elsevier.
- Lu, Y., Ward, S. C. & Cederbaum, A. I. (2013). Nicotine enhances ethanol-induced fat accumulation and collagen deposition but not inflammation in mouse liver. *Alcohol*, 47(5), 353–357.
- Mandrekar, P. & Szabo, G. (2010). Inflammation and liver injury. In S. P. S. Monga (Ed.), *Molecular pathology of liver diseases* (pp. 411–425). United States of America: Springer.
- Parfieniuk, A. & Flisiak, R. (2008). Role of cannabinoids in chronic liver diseases. *World J. Gastroenterol.* 14(40), 6109–6114.
- Pinto, C. E., Moura, E., Serrão, M., Martins, M. J. & Vieira-Coelho, M. A. (2010). Effect of (-)D - tetrahydrocannabinoid on the hepatic redox state of mice. *Brazilian J. Med. Biol. Res.* 43(4), 325–329.
- Sakhuja, P. (2014). Pathology of alcoholic liver disease, can it be differentiated from nonalcoholic steatohepatitis? *World J. Gastroenterol.* 20(44), 16474–9.
- Seoane-Collazo, P., Martínez de Morentin, P. B., Ferno, J., Diéguez, C., Nogueiras, R. & López, M. (2014). Nicotine Improves Obesity and Hepatic Steatosis and ER Stress in Diet-Induced Obese Male Rats. *Endocrinology*, 155(5), 1679–1689.
- Theise, N. D. (2013). Liver, Gallbladder, and Biliary Tract. In V. Kumar, A. K. Abbas & J. C. Aster (Eds.), *Robbins basic pathology* (9th ed., pp. 603–644). Philadelphia: Saunders/Elsevier.
- Tsuchishima, M., George, J., Shiroeda, H., Arisawa, T., Takegami, T. & Tsutsumi, M. (2013). Chronic Ingestion of Ethanol Induces Hepatocellular Carcinoma in Mice Without Additional Hepatic Insult. *Dig. Dis. Sci.* 58(7), 1923–1933.
- Yang, L., Rozenfeld, R., Wu, D., Devi, L. A., Zhang, Z. & Cederbaum, A. (2014). Cannabidiol protects liver from binge alcohol-induced steatosis by mechanisms including inhibition of oxidative stress and increase in autophagy. *Free Radic. Biol. Med.* 68, 260–267.



Research Article

## A Revised Appraisal of Scientific Names Used in the 1915 List of Lichens of the Maltese Islands by S. Sommier and A. Caruana Gatto

Jennifer Fiorentino\*<sup>1</sup>

<sup>1</sup>Department of Biology, University Junior College, Msida, Malta

**Abstract.** In 1915, Stefano Sommier and Alfredo Caruana Gatto published a list of lichens from the Maltese Islands. This author published an appraisal of the scientific names used in their list in 2002. The present work aims to replace the previous work given the important changes which have occurred in lichen nomenclature.

**Keywords:** Maltese Islands, lichens, checklist, endemism

### 1 Introduction

Stefano Sommier (1848–1922) was a traveller, collector and once-director of the Istituto Botanico, University of Firenze. In 1906 and 1907 he visited the Maltese Islands to explore the local vegetation. Alfredo Caruana Gatto, a local lawyer and naturalist, joined Sommier on his excursions to the different islands where amongst others they collected lichens. In 1915 Stefano Sommier and Alfredo Caruana Gatto included a list of 183 local lichens in the second volume of their publication *Flora Melitensis Nova* (Sommier & Caruana Gatto, 1915).

The listed lichens had been sent to Antonio Jatta for identification, as revealed in the footnote that accompanies their checklist:

*“I licheni raccolti quasi tutti da uno di noi (CG.), sono stati determinati dal compianto Dott. A. Jatta, ed una parte di essi si trova citata sia in «Materiali per un censimento generale dei Licheni Italiani» sia nella «Flora Italica Cryptogama Pars III (Lichenes)» dello stesso Jatta. Abbiamo seguito la nomenclatura e l'ordine adottati da Jatta nella Flora Italica Cryptogama, ed abbiamo citato i suddetti lavori per le specie delle quali vi é detto che si trovano nelle Isole Maltesi.”* (Sommier & Caruana Gatto, 1915).

Records of the lichen species collected by Sommier and Caruana Gatto appeared in *Flora Italica Crypto-*

*gama* (Jatta, 1909–11) four years before being published in *Flora Melitensis Nova* (Sommier & Caruana Gatto, 1915). Antonio Jatta himself died in 1912. The Herbarium Jatta at the Orto Botanico in Naples still conserves a number of lichens from Malta.

To date, Sommier and Caruana Gatto's checklist (Sommier & Caruana Gatto, 1915) remains the only local publication which gives an idea of the lichen biodiversity that existed in our islands around a century ago. In Fiorentino (2002), the present author reviewed this checklist and where relevant and possible, suggested current scientific names for the listed lichens. Since then lichen taxonomical nomenclature has undergone considerable changes, and this is likely to go on changing due to the application of molecular phylogeny to lichenised fungi. In turn, the preceding is leading to changes in the scientific name of numerous lichens.

The best way to discover which lichens were growing on our islands in 1915 would be to go through the collection deposited by Alfredo Caruana Gatto at the University Argotti Herbarium (ARG), Floriana. However, the lichens would first need to be identified since most of the labels in this Herbarium are missing or misplaced. A much smaller and well-labelled lichen collection is housed at the Museum of Natural History (NMNH) at Mdina. A note found with this collection says that the lichens had been collected by Surgeon Rear Admiral Sir Reginald Bankart in 1927 and identified by the lichenologist Annie Lorrain Smith.

This present author is involved in an ongoing project which aims to collect and identify the lichens present in the Maltese Islands. This will eventually lead to an updated lichen checklist which can only be compared to Sommier & Caruana Gatto's checklist once the scientific names of the latter are converted to current ones.

\*Correspondence to: Jennifer Fiorentino (jennifer.fiorentino@um.edu.mt)

## 2 Methodology

In this work, I have made a second attempt to review the lichen names listed in Sommier and Caruana Gatto (1915) and to replace them, where possible, with those which are currently considered valid. For obvious reasons the updated version does not correct any misidentifications, but a comment is given under the notes section whenever any identification looks dubious.

The nomenclature adopted in this work follows that found in *Lichens of Italy – a second annotated catalogue* (Nimis, 2016). Other resources used were: *A*

*Second Checklist of the Lichens of Italy* (Nimis & Martellos, 2003); *The Global Fungal Nomenclator* (Index Fungorum, 2017); *Lichens of Italy* (Nimis, 1993); *ITALIC – The Information System on Italian Lichens* (Nimis & Martellos, 2017) and *MycoBank* (Crous, Gams, Stalpers, Robert & Stegehuis, 2004). Additional references are specified in the notes section.

## 3 Results

Table 1 gives the original list of lichens in Sommier and Caruana Gatto (1915) together with the recommended current name.

**Table 1:** (Left) Numbered names of lichens as originally appearing in Sommier and Caruana Gatto (1915) and (right) their current scientific names. **D:** dubious record. **Es:** a species that in the original checklist was considered known only (endemic) for the Maltese Islands. **Ev:** a variety that was considered known only for the Maltese Islands. **Es, Ev:** original “endemic” nature ruled out. **Lf:** lichenicolous fungus. **nL:** non-lichenised fungus. **?:** indicates uncertainty which is usually but not always clarified in the comments section. **nrf:** no reference to this lichen name could be found.

1. Placynthium corallinoides (Hoffm.) Krb.	<i>Placynthium nigrum</i> (Huds.) Gray	
2. Placynthium caesium (Duf.) Mass.	<i>Psorotichia schaeereri</i> (A. Massal.) Arnold	
3. Psorotichia murorum Mass.	<i>Psorotichia murorum</i> A. Massal.	
4. Psorotichia riparia Arnd.	<i>Porocyphus rehmicus</i> (A. Massal) Zahlbr.	
5. Enchylium Rubbianum Mass.	<i>Pterygiopsis affinis</i> (A. Massal.) Henssen	
6. Collema pulposum Ach. var. granulorum (Ach.) Krb. var. compactum Ach.	<i>Enchylium tenax</i> (Sw.) Gray <i>Enchylium tenax</i> (Sw.) Gray <i>Enchylium tenax</i> (Sw.) Gray	
7. Collema cheileum (Ach.) Nyl.	<i>Blennothallia crispa</i> (Huds.) Otálora, P.M. Jørg. & Wedin	(1)
8. Collema limosum (Ach.) Nyl.	<i>Enchylium limosum</i> (Ach.) Otálora, P.M. Jørg. & Wedin	(2)
9. Collema tenax (Sw.) Ach.	<i>Enchylium tenax</i> (Sw.) Gray	
10. Collema palmatum (non DC) Schaer.	<i>Enchylium tenax</i> (Sw.) Gray	(3)
11. Collema Meliteum Jatta var. conglomeratum Jatta	<i>Enchylium tenax</i> (Sw.) Gray <i>Enchylium tenax</i> (Sw.) Gray	(4)
12. Collema granosum Wlf.	<i>Lathagrium auriforme</i> (With.) Otálora, P.M. Jørg. & Wedin	
13. Synechoblastus flaccidus Krb. var. hydrelus (Fw.) Krb.	<b>D</b> <i>Collema flaccidum</i> (Ach.) Ach.?	(5)
14. Collemodium subplicatile Nyl.	<i>Scytinium plicatile</i> (Ach.) Otálora, P.M. Jørg. & Wedin	
15. Collemodium turgidum (Schaer.) Nyl.	<i>Scytinium turgidum</i> (Ach.) Otálora, P.M. Jørg. & Wedin	(6)
16. Leptogium lacerum (Ach.) Nyl.	<i>Scytinium lichenoides</i> (L.) Otálora, P.M. Jørg. & Wedin	
17. Leptogium Schraderi Nyl.	<i>Leptogium schraderi</i> Nyl.	
18. Leptogium tenuissimum (Dcks.) Krb.	<i>Scytinium tenuissimum</i> (Hoffm.) Otálora, P.M. Jørg. & Wedin	
19. Leptogium subtile (Sm.) Nyl.	<i>Scytinium subtile</i> (Schrader.) Otálora, P.M. Jørg. & Wedin	(7)
20. Ramalina Duriaei (De Not.) Bagl.	<i>Ramalina lacera</i> (With.) J.R. Laundon	
21. Xanthoria parietina (L.) Th. var. aureola (Ach.) Fr. var. livida De Not. var. subgranulosa Nyl. var. ectanea Ach.	<i>Xanthoria parietina</i> (L.) Th. Fr. <i>Xanthoria aureola</i> (Ach.) Erichsen <i>Xanthoria parietina</i> (L.) Th. Fr. <i>Xanthoria parietina</i> (L.) Th. Fr. <i>Xanthoria calcicola</i> Oxner	
22. Physcia tenella (Sc.) Nyl.	<i>Physcia tenella</i> (Scop.) DC.	
23. Physcia obscura Fr. var. virella (Ach.) Th.	<i>Phaeophyscia orbicularis</i> (Neck.) Moberg <i>Phaeophyscia orbicularis</i> (Neck.) Moberg	
24. Lecanora crassa (Hds.) Ach. var. caespitosa (Vill.) Schaer.	<i>Squamarina cartilaginea</i> (With.) P. James var. <i>cartilaginea</i> <i>Squamarina cartilaginea</i> (With.) P. James var. <i>cartilaginea</i>	
25. Lecanora gypsacea (Sm.) Ach.	<i>Squamarina gypsacea</i> (Sm.) Poelt	
26. Lecanora lentigera (Web.) Ach.	<i>Squamarina lentigera</i> (Weber) Poelt	
27. Lecanora sublentigera Jatta	<b>Es</b> <i>Squamarina concrescens</i> (Müll. Arg.) Poelt	(8)
28. Lecanora saxicola (Poll.)	<i>Protoparmeliopsis muralis</i> (Schreb.) M. Choisy s.lat.	
29. Lecanora fulgens (Sm.) Ach.	<i>Gyalolechia fulgens</i> (Sw.) Søchting, Frödén & Arup	(9)
30. Lecanora pruinafera Nyl.	<i>Myriolecis pruinosus</i> (Chaub.) Sliwa, Zhao Xin & Lumbsch	
31. Lecanora circinata (Pers.) Ach.	<i>Lobothallia radiosa</i> (Hoffm.) Hafellner	
32. Lecanora galactina Ach. var. muralis Mass.	<i>Myriolecis albescens</i> (Hoffm.) Sliwa, Zhao Xin & Lumbsch <i>Myriolecis albescens</i> (Hoffm.) Sliwa, Zhao Xin & Lumbsch	
33. Lecanora subfusca Ach. var. allophana Ach. var. chlorona Ach.	<i>Lecanora allophana</i> (Ach.) Nyl. var. <i>allophana</i> <i>Lecanora chlorotera</i> Nyl.	

- var. *argentata* Ach.  
 forma *glabrata* Schaer.  
 f. *boeomycioides* Mass.
34. *Lecanora Hageni* Ach.  
 var. *coerulescens* (Schaer) Jatta
35. *Lecanora sulphurea* (Hffm.) Ach.
36. *Lecanora calcarea* (L) Snarf  
 var. *concreta* Schaer.  
 f. *farinosa* (Flk.) Schaer  
 var. *contorta* (Flk.) Jatta  
 f. *cinereo-virens* Mass.
- var. *viridescens* (Mass.) Krb.
37. *Lecanora lithofraga* (Mass.) Jatta
38. *Lecanora hiascens* (Mass.) Jatta
39. *Acaraspora glaucocarpa* (Wahl.) Krb.
40. *Caloplaca aurea* (Schaer.) Jatta
41. *Caloplaca murorum* (Hffm.) Th.
42. *Caloplaca pusilla* Mass.  
 var. *umbratica* Jatta
43. *Caloplaca callopisma* (Ach.) Th.  
 var. *centroleuca* Mass.
44. *Caloplaca luteo-alba* (Turn.) Th.
45. *Caloplaca ochracea* (Schaer) Mass.
46. *Caloplaca erythrocarpa* (Pers.) Th.
47. *Caloplaca Melitensis* Jatta
48. *Caloplaca aurantiaca* (Lgthf.) Th.  
 var. *Velana* Mass.  
 var. *diffRACTA* Mass.  
 var. *leucotis* Mass.  
 var. *placidia* Mass.  
 var. *Oasis* Mass.  
 var. *erythrella* (Ach) Jatta
49. *Caloplaca cerina* (Ehrh) Th.  
 var. *cyanoleptra* Krb.
50. *Caloplaca pyracea* (Ach) Th.  
 var. *confluens* Mass.  
 var. *lactea* Mass. forma *macrocarpa*  
 var. *pyrithroma* (Ach.) Ny1.
51. *Caloplaca marmorata* Bagl.  
 var. *cephaloidea* Jatta
52. *Caloplaca fulva* (Anzi)
53. *Diphrotora Cesati* Mass.  
 var. *grisea* Bagl.  
 var. *olivacea* Bagl
54. *Diphrotora spadicea* (Fw.) Jatta  
 var. *Gennari* Bagl
55. *Diphrotora olivacea* Duf.
56. *Lecaniella pseudocyrtella* Anzi  
 var. *Melitensis*
57. *Lecaniella Turicensis* Mass.
58. *Lecaniella proteiformis* Mass.  
 var. *lecideina* Mass.  
 var. *compacta* Mass.
59. *Lecaniella alocyza* Mass.  
 var. *flavidula*
60. *Lecaniella dimorpha* Mass.
61. *Lecaniella polycycla* Anzi.
62. *Lecania athrocarpa* Dub.
63. *Lecania Koerberiana* (Lhm) Krb.
64. *Haematomma cisonicum* Beltr.
65. *Rinodina metabolica* (Ach.) Krb.  
 var. *Maculiformis*
66. *Rinodina albana* Mass.
67. *Pertusaria dealbata* Ach.
68. *Pertusaria communis* DC.
69. *Pertusaria lejoplaca* Ach.
70. *Pertusaria leucostoma* Mass.
- Lecanora argentata* (Ach.) Malme? or *L. glabrata* (Ach.) Nyl.? nrf
- Myriolecis hagenii* (Ach.) Sliwa, Zhao Xin & Lumbsch  
*Myriolecis hagenii* (Ach.) Sliwa, Zhao Xin & Lumbsch  
*Lecanora sulphurea* (Hffm.) Ach.  
*Circinaria calcarea* (L.) A. Nordin, Savić & Tibell
- Circinaria calcarea* (L.) A. Nordin, Savić & Tibell (10)
- Circinaria calcarea* (L.) A. Nordin, Savić & Tibell subsp. *contorta* nrf (10)
- D *Hymenelia prevostii* (Duby) Kremp. ? (11)  
*Hymenelia coerulea* A. Massal.  
*Acaraspora glaucocarpa* (Ach.) Körb.
- D ? (12)  
*Variospora flavescens* (Huds.) Arup, Frödén & Søchting (13)
- Calogaya pusilla* (A. Massal.) Arup, Frödén & Søchting (14)  
*Variospora aurantia* (Pers.) Arup, Frödén & Søchting  
*Variospora flavescens* (Huds.) Arup, Frödén & Søchting  
*Cerothallia luteoalba* (Turner) Arup, Frödén & Søchting (15)  
*Xanthocarpia ochracea* (Schaer.) A. Massal. & De Not.  
*Caloplaca erythrocarpa* (Pers.) Zwackh
- Es *Caloplaca melitensis* Jatta ? (16)  
*Blastenia ferruginea* (Huds.) A. Massal.  
*Variospora velana* (A. Massal.) Arup, Søchting & Frödén nrf  
*Variospora velana* (A. Massal.) Arup, Søchting & Frödén  
*Variospora velana* (A. Massal.) Arup, Søchting & Frödén  
*Flavoplaca oasis* (A. Massal.) Arup, Frödén & Søchting s.str.  
*Gyalolechia flavovirescens* (Wulfen) Søchting, Frödén & Arup
- Caloplaca cerina* (Hedw.) Th. Fr. s.lat.  
*Athallia holocarpa* (Hoffm.) Arup, Frödén & Søchting  
*Athallia holocarpa* (Hoffm.) Arup, Frödén & Søchting  
 Ev *Xanthocarpia lactea* (A. Massal.) A. Massal. (17)  
*Athallia holocarpa* (Hoffm.) Arup, Frödén & Søchting  
*Caloplaca subochracea* auct.  
 ? (18)  
*Pyrenodesmia variabilis* (Pers.) A. Massal. (19)  
*Solenopsora cesatii* (A. Massal.) Zahlbr.  
*Solenopsora cesatii* (A. Massal.) Zahlbr.  
*Solenopsora cesatii* (A. Massal.) Zahlbr.
- Lecania spadicea* (Flot.) Zahlbr.  
*Solenopsora olivacea* (Fr.) H. Kiliass subsp. *olivacea*  
*Lecania cyrtella* (Ach.) Th. Fr.
- Ev ? (20)  
*Lecania turicensis* (Hepp) Müll. Arg.  
*Lecania turicensis* (Hepp) Müll. Arg.  
*Lecania turicensis* (Hepp) Müll. Arg.  
*Lecania inundata* (Körb.) M. Mayrhofer (21)  
*Pyrenodesmia alociza* (A. Massal.) Arnold
- Ev *P. alociza* (A. Massal.) Arnold ? (22)  
*Catillaria dimorpha* A. Massal.  
*Lecania polycycla* (Anzi.) Lettau  
*Lecania fuscella* (Schaer.) A. Massal. (23)  
*Lecania koerberiana* J. Lahm  
 D *Loxospora cisonica* (Beltr.) Hafellner (24)
- Rinodina exigua* (Ach.) Gray  
*Rinodina albana* (A. Massal.) A. Massal.  
 nrf (25)  
*Pertusaria pertusa* (L.) Tuck. var. *pertusa*  
*Pertusaria leioplaca* (Ach.) DC.  
*Pertusaria leioplaca* (Ach.) DC.

71. *Urceolaria scruposa* Ach. D *Diploschistes scruposus* (Schreb.) Norman (26)  
 var. *gypsacea* Smrf. *Diploschistes gypsaceus* (Ach.) Zahlbr  
 var. *bryophila* Schaer. *Diploschistes scruposus* (Schreb.) Norman (26)  
 72. *Urceolaria actinostoma* Pers. *Diploschistes candidissimus* (Ach.) Zahlbr  
 var. *tectorum* Mass. *Diploschistes candidissimus* (Kremp.) Zahlbr.  
 73. *Cladonia pungens* Flk. *Cladonia rangiformis* Hoffm.  
 74. *Cladonia muricata* Del. *Cladonia rangiformis* Hoffm.  
 75. *Cladonia pyxidata* (L) Fr. *Cladonia pyxidata* (L) Hoffm.  
 var. *neglecta* (Flk.) Krb. *Cladonia pyxidata* (L) Hoffm. (27)  
 var. *pocillum* (Ach.) Flk. *Cladonia pocillum* (Ach.) Grognot  
 76. *Cladonia fimbriata* (L.) Fr. *Cladonia fimbriata* (L.) Fr.  
 77. *Cladonia endiviaefolia* (Dcks.) Fr. *Cladonia foliacea f. convoluta* (Lam.)  
 78. *Biatora decipiens* (Ach.) Fr. *Psora decipiens* (Hedw.) Hoffm.  
 var. *dealbata* Mass. *Psora decipiens* (Hedw.) Hoffm.  
 79. *Biatora coroniformis* Krphl. D *Psora crenata* (Th. Tayl.) Reinke (28)  
 80. *Biatora fusco-nigrescens* Jatta Es nrf (29)  
 81. *Biatora chondrodes* Mass. *Clauzadea chondrodes* (A. Massal) Hafellner & Türk  
 82. *Biatora cyclicsa* Mass. *Clauzadea chondrodes* (A. Massal) Hafellner & Türk  
 83. *Biatorina sylvestris* Arnd. *Lecania sylvestris* var. *umbratica* (Arnold) M. Mayrhofer  
 84. *Biatorina lenticularis* (Ach.) Krb. *Catillaria lenticularis* (Ach.) Th. Fr.  
 var. *ecrustacea* (Krb.) Arnd. *Catillaria lenticularis* (Ach.) Th. Fr.  
 85. *Bacidia atrogrisea* (Hepp.) Krb. *Bacidia laurocerasi* (Duby) Zahlbr.  
 86. *Bacidia rosella* (Pers.) De Not. *Bacidia rosella* (Pers.) de Not.  
 87. *Lecidea auriculata* Th. var. *calicicola* Jatta Ev ? (30)  
 88. *Lecidea viridans* Fw. *Lecidella viridans* (Flot.) Körb.  
 89. *Lecidea enteroleuca* Ach. *Lecidella elaeochroma* (Ach.) M Choisy var. *elaeochroma* f.  
*elaeochroma*  
 90. *Lecidea olivacea* Mass. *Lecidella elaeochroma* (Ach.) M Choisy var. *elaeochroma* f.  
*elaeochroma*  
 91. *Lecidea glabra* Krphl. var. *viridula* Arnd. *Lecidella stigmatea* (Ach.) Hertel & Leuckert ? (31)  
 92. *Lecidea pertusariicola* Jatta Lf Es *Skyttea heterochroae* Nav.- Ros. & Muniz (32)  
 93. *Thalloedema tabacinum* (DC.) Mass. *Toninia tristis* (Th. Fr.) Th. Fr. subsp. *Tristis*  
 94. *Thalloedema paradoxum* Jatta Es *Toninia paradoxa* (Jatta) Zahlbr. (33)  
 95. *Thalloedema vesiculare* (Hffm.) Mass. *Toninia sedifolia* (Scop.) Timdal  
 var. *teretocarpum* Mass. *Toninia sedifolia* (Scop.) Timdal (34)  
 96. *Thalloedema mammillare* (Fr) Mass. Ev *Porpidinia tumidula* (Sm.) Timdal (35)  
 var. *pulchellum*  
 97. *Toninia acervulata* Nyl. *Toninia aromatica* (Sm.) A. Massal.  
 98. *Toninia aromatica* (Sm.) Mass. *Toninia aromatica* (Sm.) A. Massal.  
 99. *Toninia squalida* (Ach.) A. Massal. *Toninia squalida* (Ach.) A. Massal.  
 100. *Arthrosporium accline* Krb. *Arthrosporium populorum* A. Massal.  
 101. *Scoliciosporium Doriae* Bagl. *Bactrospora patellarioides* var. *convexa* (B. de Lesd.) Egea & Torr.  
 var. *decussatum* Ev *B. patellarioides* (B. de Lesd.) Egea & Torr variety ? (36)  
 102. *Buellia canescens* (Dcks.) De Not. *Diploicia canescens* (Dicks.) A. Massal.  
 103. *Buellia parasema* (Ach.) Krb. *Buellia disciformis* (Fr.) Mudd  
 var. *rugulosa* (Ach.) Krb. *Amandinea punctata* (Hoffm.) Coppins & Scheid.  
 104. *Buellia punctata* (Flk.) Krb. *Diplotomma alboatrum* (Hoffm.) Flot.  
 105. *Diplotomma albo-atrum* (Hffm.) Krb. *Diplotomma alboatrum* (Hoffm.) Flot.  
 var. *epilobium* (Ach.) Schaer. *Diplotomma venustum* (Körb) Körb.  
 var. *venustum* Krb. *Diplotomma alboatrum* (Hoffm.) Flot.  
 var. *corticola* Schaer. *Diplotomma alboatrum* (Hoffm.) Flot.  
 106. *Roccella tinctoria* DC. D *Roccella tinctoria* DC. ? (37)  
 107. *Roccella phycopsis* Ach. *Roccella phycopsis* Ach.  
 108. *Lecanactis lyncea* (Sm.) Eschw. *Lecanactis lyncea* (Sm.) Egea & Torrente  
 109. *Lecanactis Dilleniana* (Ach.) Krb. D *Psoronactis dilleniana* (Ach.) Ertz & Tehler (38)  
 110. *Lecanactis granulosa* (Duf.) Fr. *Paralecanographa grumulosa* (Dufour) Ertz & Tehler  
 111. *Graphis dendritica* Ach. *Arthonia medusula* (Pers.) Nyl.  
 var. *medusula* Nyl.  
 112. *Graphis scripta* (L) Ach. *Graphis scripta* (L.) Ach.  
 var. *recta* (Hmb.) Krb. *Graphis scripta* (L.) Ach.  
 var. *serpentina* (Ach.) Schaer.  
 113. *Graphina sophistica* Nyl. D Ev *Graphis inustuloides* Lücking ? (39)  
 var. *Melitensis*  
 114. *Opegrapha Duriaei* Mtg. et Brck. *Opegrapha durieui* Mont.  
 115. *Opegrapha celtidicola* Jatta *Opegrapha celtidicola* (Jatta) Jatta  
 116. *Opegrapha varia* Pers. *Alyxoria varia* (Pers.) Ertz & Tehler  
 var. *notha* (Ach.) Jatta *Alyxoria varia* (Pers.) Ertz & Tehler

- var. *rimalis* (Pers.) Ach.  
var. *violatra* (Mass.) Jatta
117. *Opegrapha rupestris* Fr.  
var. *dolomitica* Arnd.
118. *Opegrapha herpetica* Ach.  
var. *fuscata* Schaer.
119. *Opegrapha rubecula* Mass.
120. *Opegrapha lilacina* Mass.
121. *Opegrapha atra* (Pers.) Fr.
122. *Opegrapha lithyrgea* (Ach.) Krb. D *Opegrapha lithyrgea* Ach. (40)
123. *Opegrapha siderella* Ach. *Pseudoschismatomma rufescens* (Pers.) Ertz & Tehler
124. *Opegrapha saxatilis* DC. *Opegrapha rupestris* Pers.
125. *Opegrapha Mougeothii* Mass.  
var. *Pisana* Bagl. *Alyxoria mougeotii* (A. Massal.) Ertz, Frisch & G.Thor  
*Alyxoria mougeotii* (A. Massal.) Ertz, Frisch & G.Thor
126. *Arthonia caesio-pruinosa* Schaer. D *Arthonia cinereopruinosa* Schaer. (41)
127. *Arthonia galactites* (DC.) Nyl. *Arthonia galactites* (DC.) Dufour
128. *Arthonia apotheciorum* (Mass.) Almg. Lf *Arthonia clemens* (Tul.) Th. Fr. (42)
129. *Arthonia dispersa* (Schrad.) Mass. *Arthonia dispersa* (Schrad.) Nyl.
130. *Arthonia aspersa* Lgth. D *Arthonia arthonioides* (Ach.) A.L.Sm. ? (43)
131. *Arthonia coniangioides* Bagl. *Arthonia melanophthalma* Nyl.
132. *Arthonia punctiformis* Ach. *Arthonia punctiformis* Ach
133. *Arthonia epipastoides* Nyl. nL *Arthonia radiata* (Pers.) Ach. (44)  
var. *galactitella* Nyl. *Arthonia glaucella* Nyl. (45)
134. *Arthonia mediella* Nyl. D *Arthonia mediella* Nyl. ? (45)
135. *Arthonia ectropoma* Mass. *Arthonia dispersa* (Schrad.) Nyl.
136. *Arthonia didyma* Krb. D *Arthonia didyma* Krb. ? (46)
137. *Arthothelium Ru anum* Mass. *Arthonia ruana* A. Massal.
138. *Arthothelium Beltraminianum* Mass. *Arthonia ruana* A. Massal.
139. *Dirina Ceratoniae* (Ach.) De Not. *Dirina ceratoniae* (Ach.) Fr.
140. *Dirina repanda* (Fr.) Nyl. *Dirina massiliensis* Durieu & Mont.
141. *Endopyrenium rufescens* (Ach.) Krb. *Placidium rufescens* (Ach.) A. Massal.
142. *Endopyrenium hepaticum* (Ach.) Krb. *Clavascidium lacumulatum* (Ach.) M. Prieto
143. *Endopyrenium dedalaeum* (Krpplh) Krb. D *Catapyrenium cinereum* (Pers.) Körb. (47)
144. *Endopyrenium Adriaticum* Zahlbr. D *Hydropunctaria adriatica* (Zahlbr.) Orange (48)
145. *Catapyrenium Custnani* Mass. *Placidopsis custnani* (A. Massal.) Körb.
146. *Catapyrenium circinatum* Bagl. *Placidopsis cinerascens* (Nyl.) Breuss
147. *Dermatocarpon glomeruliferum* Mass. *Endocarpon pusillum* Hedwig
148. *Verrucaria lecideoides* Hepp. *Verruculopsis lecideoides* (A. Massal.) Gueidan & Cl. Roux var. *lecideoides*
- var. *minuta* Mass. *Verruculopsis minuta* (Hepp) Krzew.
149. *Verrucaria hydrela* Ach. D *Verrucaria hydrela* Ach. (49)
150. *Verrucaria ruderum* DC. *Verrucaria ruderum* DC.
151. *Verrucaria papillosa* Ach. *Verrucaria papillosa* Ach.
152. *Verrucaria rupestris* Schrad. *Verrucaria rupestris* Schrad.  
var. *calciseda* Schaer. *Bagliettoa calciseda* (DC.) Gueidan & Cl. Roux  
var. *crassa* Mass. nrf  
var. *caesia* Arnd. nrf  
var. *orbicularis* Garov. nrf
153. *Verrucaria purpurascens* Hffm. *Bagliettoa marmorea* (Scop.) Gueidan & Cl. Roux
154. *Verrucaria muralis* (Ach.) Mass. *Verrucaria muralis* (Ach.)
155. *Verrucaria anceps* Krpplh D *Verrucaria anceps* Kremp. (50)
156. *Verrucaria myriocarpa* Hepp. D *Verrucaria murina* Leight. (51)
157. *Verrucaria Baldensis* Mass. *Bagliettoa baldensis* (A. Massal.) Vězda
- var. *spilomatica* Mass. *Verrucaria veronensis* A. Massal.
158. *Verrucaria Veronensis* Mass. *Verrucaria dolomitica* (A. Massal.) Kremp.
159. *Verrucaria dolomitica* Mass. *Verrucaria foveolata* (Flörke) A. Massal.
160. *Verrucaria foveolata* (Flk.) Mass. *Verrucaria foveolata* (Flörke) A. Massal.
161. *Verrucaria macrostoma* (Duf.) DC. *Verrucaria macrostoma* DC. f. *macrostoma*
162. *Verrucaria tabacina* Mass. *Verrucaria tabacina* (A. Massal.) Trevis.
163. *Verrucaria acrotelloides* Mass. *Verrucaria nigrescens* Pers. f. *nigrescens*
164. *Verrucaria apathela* (Mass) Jatta *Verrucaria apathela* (A. Massal.) Trevis.
165. *Verrucaria fuscoatra* (Wallr.) Krb. *Verrucaria nigrescens* Pers. f. *nigrescens*  
var. *controversa* Mass. *Verrucaria nigrescens* Pers. f. *nigrescens*  
var. *collematodes* Garov. *Verrucaria collematodes* Garov.
166. *Verrucaria viridula* Ach. *Verrucaria viridula* (Schrad.) Ach
167. *Verrucaria Beltraminiana* Mass. *Verrucaria beltraminiana* (A. Massal.) Trevis
168. *Verrucaria fuscella* Turn. *Placopyrenium fuscillum* (Turner) Gueidan & Cl. Roux  
var. *cinereo-glaucula* Garov. nrf

169. <i>Verrucaria glaucina</i> (Ach.) Hepp.	D	<i>Verrucaria caerulea</i> DC. or <i>Placopyrenium fuscellum</i> (Turner) Gueidan & Cl. Roux ?	(52)
170. <i>Verrucaria tristis</i> Krypt. var. <i>depauperata</i> Mass.	D	<i>Parabagliettoa disjuncta</i> (Arnold) Krzewicka	(53)
171. <i>Thelidium galbanum</i> (Krpplh.) Krb. var. <i>acrustaceum</i> Arnd.		<i>Thelidium pyrenophorum</i> (Ach.) A. Massal.	(54)
172. <i>Thelidium crassum</i> Mass.	D	<i>Thelidium decipiens</i> (Nyl.) Kremp. ?	(55)
173. <i>Thelidium minutulum</i> Krb.	D	<i>Thelidium minutulum</i> Krb. ?	(56)
174. <i>Thelidium epipolaeum</i> (Ach.) Krb.		<i>Verrucaria rupestris</i> Schrad. ?	(57)
175. <i>Polyblastia clandestina</i> Arnd.	D	<i>Polyblastia clandestina</i> (Arnold) Jatta ?	(58)
176. <i>Acrocordia conoidea</i> Krb. var. <i>dimorpha</i> Krb.		<i>Acrocordia conoidea</i> Krb.	
177. <i>Arthopyrenia analepta</i> Ach.	D	nL <i>Naetrocymbe punctiformis</i> (Pers.) R.C. Harris	(59)
178. <i>Arthopyrenia cinereo-pruinosa</i> Schaer.		nL <i>Arthopyrenia cinereopruinosa</i> (Schaerer) Massal.	(60)
179. <i>Arthopyrenia punctiformis</i> Fr.		nL <i>Naetrocymbe punctiformis</i> (Pers.) R.C. Harris	(59)
180. <i>Sagedia oleriana</i> Mass.		<i>Porina oleriana</i> (Massal.) Lettau	
181. <i>Pyrenula nitida</i> (Schrad.) Ach. var. <i>nitidella</i> (Flk.) Schaer.	D	<i>Pyrenula nitidella</i> (Schaer.) Mull. Arg. ?	(61)
182. <i>Cyrtidula crataegina</i> Mnks.		nL <i>Cyrtidula</i> sp. ?	(62)
183. <i>Cyrtidula occulta</i> Mnks.		nL <i>Cyrtidula</i> sp. ?	(62)

Table 2: Notes.

01	<i>Blennothallia crispa</i> (Huds.) Otálora, P.M. Jørg. & Wedin is the current name for <i>Collema cheileum</i> (Ach.) Ach. (Nimis, 2016).
02	<i>Enchylium limosum</i> (Ach.) Otálora, P.M. Jørg. & Wedin is the current name for <i>Collema limosum</i> (Ach.) Ach. (Nimis, 2016).
03	According to Carvalho (2012), <i>Collema palmatum</i> Ach. is a synonym of <i>Collema tenax</i> (Sw.) Ach. <i>Enchylium tenax</i> (Sw.) Gray is the current name for <i>Collema tenax</i> (Sw.) Ach.
04	In Sommier and Caruana Gatto (1915), the type is quoted as being present in Sardegna and Malta while the var. <i>conglomeratum</i> is quoted as being known from Malta only. These are both synonyms of <i>Collema tenax</i> (Sw.) Ach currently <i>Enchylium tenax</i> (Sw.) Gray.
05	In Jatta (1909-11), <i>Lethagriium rupestre</i> (Swartz.) Massal is given as a synonym of <i>Synechoblastus flaccidus</i> Krb. while in Nimis (1993) the current name <i>Collema flaccidum</i> (Ach.) Ach. is given for <i>Lethagriium rupestre</i> (Swartz.) Massal. In Nimis (2016), <i>C. flaccidum</i> is described as a boreal-montane lichen. This casts doubt on the correct identification of this lichen. Jatta (1909-11) also includes and describes the var. <i>hydrelus</i> (Fw.) Krb. but does not report it from Malta. No current name for this variety could be traced.
06	<i>Scytinium turgidum</i> (Ach.) Otálora, P.M. Jørg. & Wedin was found as the current name of <i>Collemodium turgidum</i> (Ach.) Nyl.
07	<i>Scytinium subtile</i> (Schrad.) Otálora, P.M. Jørg. & Wedi was found as the current name of <i>Leptogium subtile</i> (Schrad.) Torss.
08	<i>Lecanora sublentigera</i> Jatta is currently known as <i>Squamarina concrescens</i> . This lichen is not restricted to the Maltese Islands.
09	<i>Lecanora fulgens</i> (Sm.) Ach. should read <i>Lecanora fulgens</i> (Sw.) Ach. The current name proposed here has recently replaced that of <i>Fulgensia fulgens</i> (Sw.) Elenkin.
10	The current names being suggested here do not refer to f. <i>farinosa</i> and to f. <i>contorta</i> but to their respective varieties only. No reference to <i>Lecanora calcarea</i> var. <i>viridescens</i> could be traced.
11	This saxicolous lichen of hard stone is frequent in the Alps but is also found in the Mediterranean mountains (Nimis, 2016). The record from Malta is dubious.
12	Jatta (1909-11) and several authors had a wrong concept of <i>Caloplaca aurea</i> (Schaer.) which is more of an upland region lichen (Nimis, 1993). Records of <i>C. aurea</i> by various authors probably refer to a <i>Fulgensia</i> species (Nimis, 1993).
13	<i>Caloplaca flavescens</i> (currently <i>Variospora flavescens</i> ) was frequently called <i>Caloplaca murorum</i> by early Italian authors. The name <i>C. murorum</i> was also used albeit less frequently for <i>Caloplaca aurantia</i> (currently <i>Variospora aurantia</i> ) (Nimis, 1993).
14	The current name being suggested does not refer to the var. <i>umbriatica</i> to which no reference was found.



- 15 In Sommier and Caruana Gatto (1915), *Caloplaca luteo alba* was quoted as found growing on rocks, stone and bark. *Cerothallia luteoalba* grows on bark in temperate regions. The name “luteoalba” was frequently used by early Italian authors, including Jatta, to refer to taxa of the *C. pyracea-holocarpa* complex. Old records collected on rock could refer to *Xanthocarpia* [*Caloplaca*] *lactea* and related species (Nimis, 1993). Several old corticolous records reported in Nimis (1993) might actually be *Athallia pyracea* (Nimis, 2016).
- 16 The identification of this lichen needs clarification.
- 17 According to Sommier and Caruana Gatto (1915) var. *lactea* f. *macrocarpa* was found on rocks in Gozo only. (Jatta, 1909-11) reports f. *macrocarpa* from the island of Malta but does not refer to it as being known only from Malta (or Gozo).
- 18 *C. marmorata* var. *cephaloidea* was collected by Sommier & Caruana Gatto from Girgenti (Malta). Though Jatta had suggested the name *cephaloidea* for this variety he never published this record (Sommier & Caruana Gatto, 1915).
- 19 If the specimen sent to Jatta was correctly identified it is surprising that the authors report that this lichen was found at Fort Manoel only (Sommier & Caruana Gatto, 1915). *Pyrenodesmia variabilis* [*Caloplaca variabilis*] is more widespread in the Maltese Islands.
- 20 Sommier and Caruana Gatto (1915) report that they had found a different form of *Lecania pseudocyrtella* growing on pine trees at Buskett. Jatta had suggested calling this variety *Melitensis*. However, he never wrote any description for this variety and there is no mention of it in Flora Cryptogama Italica (Jatta, 1909-11).
- 21 In the past *Lecania inundata* was often confused with *L. erysibe* and *L. turiciensis* (Nimis, 2016).
- 22 Sommier and Caruana Gatto (1915) report that the variety *flavidula* was known from Malta only. Jatta (1909-11) mentions it as a variety found on coastal cliffs in Malta. He gives a description but does not say it is endemic. *Pyrenodesmia alociza* [*Caloplaca alociza*; *Lecaniella alociza*] is one of the black-fruited “*Caloplacas*” and can be rather variable from a morphological point of view (Muggia, Grube & Tretiach, 2007).
- 23 Jatta (1909-11) includes *Lecania fuscella* as a synonym of *Lecania athroocarpa* Dub.
- 24 *Haemotomma cisonicum* Beltr. is the basionym of *Loxospora cisonica* (Beltr.) Hafellner. This epiphytic lichen of old forests is mostly found in the montane belt. Here it is reported as having been found only once growing on *Datura* in a garden in Mosta. This identification is rather dubious.
- 25 No valid current name for *P. dealbata* Ach. could be found.
- 26 *Diploschistes scruposus* grows on siliceous rocks and rarely on soil (Nimis, 2016). The authors (Sommier & Caruana Gatto, 1915) quote that the lichen was found growing on *Cladonia* and other lichens. According to Nimis (1993), old records of *D. scruposus* should be viewed with caution as they might refer to *D. muscorum*. All this sheds doubt on the correct identification of this lichen.
- 27 *Cladonia pyxidata* is the current name for both *Cladonia neglecta* (Flörke) Spreng. and *Cladonia pyxidata* var. *neglecta* (Flörke) A. Massal.
- 28 The records of *Psora crenata* [*Biatora coroniformis*] from Sardegna and Sicily by Jatta (1909-11) most probably refer to *Psora decipiens* (Nimis, 2016). In his addenda section Jatta (1909-11) mentions *B. coroniformis* as having also been found in Malta.
- 29 Jatta (1909-11) reports *B. fusco-nigrescens* a new species known from trees in Malta but does not write “known only from Malta”. Sommier and Caruana Gatto (1915) specify that it was found on carob trees at Wied Babu and add that the species was known only from Malta. No further information could be found about this species.
- 30 *Lecidea auriculata* subsp. *auriculata* Th. Fr. is found on siliceous rocks in wind-exposed, sunny situations, in the high-Alpine belt of humid mountains (Nimis, 2016). A high percentage of the older herbarium specimens are misidentified (Hertel, 2001). According to Nimis (1993), the var. *calcicola* described by Jatta (1909-11) from Malta is probably not related to this species.
- 31 The current name *Lecidella stigmatea* applies to *Lecidea glabra* and not to *L. glabra* var. *viridula*.

- 32 *Lecidea pertusariicola* is not a lichen but a lichenicolous fungus (a fungus growing on lichens). Jatta (1909-11) quotes this “lichen” from Malta as having been found growing on *Pertusaria communis* while in Sommier and Caruana Gatto (1915) it is quoted as growing on *Pertusaria*, carobs, fig trees and on *Crataegus*. The type material of *L. pertusariicola* Jatta is housed at the Jatta herbarium in Naples. Navarro-Rosinés and Muñiz (2009) examined the host of *L. pertusariicola* in the type specimen from Malta and found it to be *Pertusaria heterochroa* rather than *P. communis* as had been reported in Jatta (1909-11). A new name *Skyttea heterochroae* was proposed for this lichenicolous fungus (Navarro-Rosinés & Muñiz, 2009) to include *Lecidea pertusariicola* Jatta in the genus *Skyttea*, in order to avoid the homonymy with *Skyttea pertusariicola* Diederich et Etayo. *S. heterochroae* is a non-lichenized lichenicolous fungus that grows specifically on *Pertusaria heterochroa*, and it is only known from a few European Mediterranean localities which are Catalonia, Ibiza, Majorca and Malta (Navarro-Rosinés & Muñiz, 2009).
- 33 Sommier and Caruana Gatto (1915) treat this as an endemic terricolous lichen while Jatta (1909-11) does not refer to it as being endemic to Malta but only that it is was found on soil in Malta.
- 34 *Toninia sedifolia* [*T. vesiculare*] is morphologically very variable. Preliminary investigations using morphology, chemistry and DNA sequence data show that *T. sedifolia* needs to be revised (Westberg, Fernandez-Brime, Timdal, Williams & Wedin, 2016). The variety *teretocarpum* being mentioned here (Sommier & Caruana Gatto, 1915) may reflect the findings of Westberg et al. (2016).
- 35 *Thalloedema mammillare* (Fr.) Mass. (but not the variety *pulchellum*) is reported as a saxicolous calciferous lichen from Italy and Malta by Jatta (1909-11). This species is not reported in Sommier and Caruana Gatto (1915). Instead they report the terricolous variety *pulchellum* known from Malta only. Up to some years ago *Thalloedema mammillare* (Fr.) Mass. was *Toninia timidula* (Sm.) Zahlbr. Timdal (2010) described a new genus *Porpidinia* for *Toninia timidula* due to differences in the microscopical sections of the hymenium. The lichen is currently *Porpidinia timidula* (Sm.) Timdal.
- 36 *Bactrospora patellarioides* is the only *Bactrospora* species to be found in the Mediterranean (Egea & Torrente, 1993). *B. patellarioides* var. *convexa* is known from all over Italy. One can tentatively suggest that the specimens of *Scolicosporum doriae* collected from the bark of different trees and mentioned in Sommier and Caruana Gatto (1915) represent this variety. Could the variety *decussatum* in Sommier and Caruana Gatto (1915) – described as known only from Malta – be referring to *Bactrospora patellarioides* (Nyl.) Almq. var. *patellarioides*? This variety has been collected in different parts of Italy though.
- 37 The existence of *R. tinctoria* in the Mediterranean region is dubious. Old Italian authors used this name for *Roccella phycopsis* (Nimis, 1993). All specimens labelled as *R. tinctoria* present in the herbaria of ARG and NMNH and were examined by this author and all were found to be *R. phycopsis* (Fiorentino, 2015).
- 38 This lichen grows on siliceous rocks of upland regions. Records from the South of Italy are dubious (Nimis, 1993). This species is not expected to be found growing on rocks in Malta as reported.
- 39 Sommier and Caruana Gatto (1915) report that the specimen from Malta, found growing on the bark of fig trees at Balluta, was considered a local variety of the species and was given the name var. *Melitensis*. A short description of its spores is included. However in *Flora Italica Cryptogama* (Jatta, 1909-11) there is no mention of var. *melitensis*. Instead only *Graphina sophistica* from Malta is mentioned. The description and spore size given in Jatta (1909-11) does not exclude the “variety” from Malta. In Europe *G. inustuloides* [*G. sophistica*] has an Atlantic distribution. There are only two dubious records of this lichen from Italy (Nimis, 1993). This sheds doubt on the presence of this lichen in Malta.
- 40 *O. lithyrga* is usually found on hard siliceous rocks in deep gorges or in mature forests (Nimis, 2016). Jatta (1909-11) reports it growing on siliceous, calcareous and volcanic rock. Sommier and Caruana Gatto (1915) found the lichen on stones of walls and on rocks (calcareous substrates). The habitat preferred by this species (Nimis, 2016) makes its presence in Malta unlikely.
- 41 This corticolous lichen occurs in shaded, humid situations especially dense woodlands. According to Nimis (1993), the records by Jatta from Southern Italy appear dubious thus making its presence on cypress trees at the Addolorata cemetery equally dubious.

- 42 *Arthonia clemens* is a lichenicolous fungus (a fungus which parasitises lichens) and not a lichen. It grows only on the apothecia of the lichen *Rhizoplaca chrysoleuca* a mountain lichen of siliceous rocks (Nimis, 2016). In Sommier and Caruana Gatto (1915), *A. clemens* is reported to have been found on the saxicolous lichen *Lecanora galactina* (currently *Myriolecis albescens*). According to Nimis (2016), references to *Arthonia clemens* on epilithic *Lecanora* species may be referring either to the lichenicolous fungus *A. galactinaria* which grows on lichens of the *Myriolecis dispersa*-group or to *A. apotheciorum* which grows on *Myriolecis albescens*.
- 43 Nimis (1993) quotes Redinger (1936) who claims that the record of *A. aspersa* Leight. from Malta by Jatta (1900) in *Sylloge Lichenum Italicorum* is most probably *Arthonia melanophthalma* Nyl. *Arthonia arthonioides* [*Arthonia aspersa*] grows on acidic rocks, on exposed roots in dry underhangs as well as on dry undersides of trees in sheltered, humid situations, such as in forests (Nimis, 2016).
- 44 *A. glaucella* is probably a non-lichenised fungus (Nimis, 2016).
- 45 *A. mediella* is a cool-temperate to boreal-montane epiphytic lichen (Nimis, 2016). It is not expected from Malta.
- 46 *A. didyma* is a cool-temperate species found on smooth, acid bark in humid areas. Not likely to be present on olive trees in Malta.
- 47 *Catapyrenium cinereum* is a lichen of very cold climates and may also be found on mountains near or above treeline. It grows on siliceous, base-rich soil or amongst terricolous bryophytes. Some records from low elevations in Sicily appear dubious (Nimis, 2016). This makes the record from Malta equally dubious.
- 48 *H. adriatica* is a rather poorly known species of maritime, mostly calcareous rocks in the supralittoral zone (Nimis, 2016). In Sommier and Caruana Gatto (1915), the lichen is quoted as having been found growing on the bastions in Valletta. This makes the record of this lichen rather dubious.
- 49 *V. hydrela* grows on siliceous pebbles which are periodically submerged by fresh water usually in upland regions. Several records, especially those from southern Italy, need confirmation (Nimis, 2016). The record from Malta – being quoted as found growing on walls – is rather dubious.
- 50 *Verrucaria anceps* is a saxicolous lichen found on mountains. Its presence on rock, walls and bastions in Malta is therefore dubious.
- 51 *Verrucaria murina* is a saxicolous lichen of limestone and dolomite in upland areas. Records of this species from Southern Italy being dubious are not accepted (Nimis, 2016). This doubt can be extended to records from Malta.
- 52 *Verrucaria caerulea* DC is the current name of *Verrucaria glaucina* Ach. non auct. In Southern Italy, *V. caerulea* is restricted to upland regions when present (Nimis, 2016). Hence the record of its presence on the bastions of Valletta is dubious. Jatta (1909-11) does not include the record from Malta of *Verrucaria glaucina* (Ach.) Hepp. and gives *Verrucaria fuscella* v. *subviridula* Garov. as its synonym. However, according to Nimis (2016), *Verrucaria fuscella* v. *subviridula* Garov. is a synonym of *Placopyrenium fuscillum* (Turner) Gueidan & Cl. Roux which up to recently was known as *Verrucaria fuscella* (Turner) Winch and was the accepted name of *V. glaucina sensu* Zetterst. et auct p.p. non Ach. (Nimis, 2016). According to Nimis (2016), *P. fuscillum* is a polymorphic taxon in need of revision.
- 53 *Parabagliettoa disjuncta* is a saxicolous lichen typical of mountains. The record from Malta is dubious.
- 54 In Jatta (1909-11), *Thelidium galbanum* and *T. pyrenophorum* are treated as two separate species and the latter is described as having 3-septate spores. In actual fact *T. pyrenophorum* has 1-septate spores (Smith, 2009). Jatta (1909-11) mentions *T. galbanum* var. *acrustaceum* from Malta citing differences in thallus and spore size between the species and its variety. The collection of lichens at NMNH includes one saxicolous specimen carrying the label *Thelidium galbanum* from Imtahleb as well as a second saxicolous specimen carrying a label with two names *Thelidium pyrenophorum* Krb. and *Thelidium galbanum* Jatta. Both specimens were examined by the present author and both were found to be *T. pyrenophorum*. This lichen is typically a high altitude lichen (Nimis, 2016) and its presence at Imtahleb which is 186 m above sea level is rather unexpected.
- 55 The current name of *T. crassum* is *Thelidium decipiens*. Jatta (1909-11) reports *T. crassum* as growing on calcareous cliffs in Veneto, Abruzzo, Puglia and Malta. Nimis (2016) describes it as a species of calcareous rocks, including large pebbles, in rather sheltered situations in upland regions. However, Sommier and Caruana Gatto (1915) report the lichen from maritime rocks in the splash zone. This sheds great doubt on the correct identification of the specimen from Malta.

- 56 *T. minutulum* is reported as having been found on maritime rock (Sommier & Caruana Gatto, 1915). However, *T. minutulum* is a cold-climate lichen which sometimes occurs in the splash zone of creeks (Nimis, 2016). This throws doubt on the correct identification of this lichen.
- 57 In Flora Italica Cryptogama (Jatta, 1909-11) a description of *Thelidium epipolaeum* (Ach.) Krb. with 3-septate spores is given without any mention of Malta as provenance. Jatta (1909-11) probably made a mistake in citing Acharius (Ach.) as a basionym. Instead he should have used *Thelidium epipolaeum* A. Massal. When examining the specimen from Gozo (Malta), Jatta might have been probably dealing with *Verrucaria epipolaea* Ach. whose current name is *Verrucaria rupestris* Schrad. (Pier Luigi Nimis, personal communication).
- 58 *P. clandestina* is found on limestone and dolomite at high altitudes in rather humid situations. The record of Jatta (1909-11) from Malta seems very dubious (Nimis, 1993).
- 59 *Naetrocymbe punctiformis* (Pers.) R.C. Harris (formerly *Arthropyrenia punctiformis* (Pers.) Massal.) colonises smooth bark in temperate to boreal-mountain regions. It is very rarely found in dry areas. It is probably a non-lichenised fungus (Nimis, 2016).
- 60 Probably a non-lichenised fungus (Nimis, 2016).
- 61 This record should be *Pyrenula chlorospila* Arnold (Fiorentino, 2007).
- 62 The fungal genus *Cyrtidula* is very poorly understood. The thallus of this fungus is saprobic, doubtfully lichenised, mostly immersed in bark which is discoloured in the process (Smith, 2009).

The list of lichens in Sommier and Caruana Gatto (1915) is followed by a footnote in Italian accompanied by a short list of new lichens quoted in Gulia (1858–59). A loose translation of the note from Italian is given below.

“*Observation: Pages 213–214 of the Repertorio di Storia Naturale by Gavino Gulia give a number of local lichens which we have not included in our list as we were not very sure of their correct identification.*”

Table 3 gives the original names of these lichens together with their current names.

#### 4 Conclusion

The list of lichens appearing in Sommier and Caruana Gatto (1915) has reduced to about 150 lichens from the original 183. This is due to a number of reasons. There are instances where a number of different species in Sommier and Caruana Gatto (1915) point to the same lichen species. Some records are highly dubious as they refer to lichens which are not expected to be found in the Maltese Islands while a small number of records refer to non-lichenised or lichenicolous fungi. These reasons have contributed to a reduction in the count. On the other hand, some lichen varieties appearing in Sommier and Caruana Gatto (1915) have been raised to species rank thus adding to species number.

All lichens mentioned in Gulia (1858–59) except for *Lecanora flavescens* (currently *Lecanora rupicola* subsp. *sulphurata*) and *Endocarpon panduraeforme* are also included in the checklist of Sommier and Caruana Gatto (1915). No information or current name for *E. panduraeforme* could be found by the present author.

Sommier and Caruana Gatto (1915) used the term ‘endemic’ twice only – for the lichenicolous fungus *Skyttea heterochroae* [No. 92: *Lecidea pertusariicola*] and

**Table 3:** Left: names of lichens originally listed by Gulia (1858–59) as quoted in Sommier and Caruana Gatto (1915) and right: current names of lichens.

<i>Collema plicatile</i>	<i>Scytinium plicatile</i> (Ach.) Otálora, P.M. Jørg. & Wedin
<i>C. crispum</i>	<i>Blennothallia crispa</i> (Huds.) Otálora, P.M. Jørg. & Wedin
<i>Lecanora flavescens</i>	<i>Lecanora rupicola</i> subsp. <i>sulphurata</i> (Ach.) Leuckert & Poelt
<i>L. subimbricata</i>	<i>Lobothallia radiosa</i> (Hoffm.) Hafellner
<i>L. canescens</i>	<i>Diploicia canescens</i> (Dicks.) A. Massal
<i>L. crassa</i>	<i>Squamarina cartilaginea</i> (With.) P. James var. <i>cartilaginea</i>
<i>Scynophorus pyxidatus</i>	<i>Cladonia pyxidata</i> (L.) Hoffm.
<i>Endocarpon panduraeforme</i> species nova	?

for *Toninia paradoxa* [No. 94: *Thalloedema paradoxum*]. For ten other species the term “known only from Malta (or Gozo)” was used. For two lichen varieties also quoted as known from Malta only [No. 51: *Caloplaca marmorata* var. *cephaloidea* and No. 56: *Lecaniella pseudocyrtella* var. *Melitensis*] no description was published in Jatta (1909-11).

In Lanfranco (1989), twelve lichen species and varieties were listed. These were considered ‘presumably endemic’ since at that time the lichens of the Maltese Is-

lands were still awaiting a thorough investigation (Lanfranco, 1989) and the only significant information available was that of Sommier and Caruana Gatto (1915).

This work has revealed that seven out of the eleven truly lichen species that were reported in Sommier and Caruana Gatto (1915) as being present in Malta (or Gozo) only, have in fact been reported from places other than the Maltese Islands (Table 1 & 2).

Out of the remaining four lichens No. 87: *Lecideia auriculata* var. *calcicola* has been considered a misidentification (see Table 2 note 30). Consequently, only three lichen species listed in Sommier and Caruana Gatto (1915) still hold the description of being ‘presumably endemic’ (Lanfranco, 1989) until this is confirmed. These are No. 47: *Caloplaca melitensis*, No. 80: *Biatora fusconigrescens* and No. 94: *Toninia paradoxa* [*Thalloedema paradoxum*]. Their status will be clarified once lichen material from Malta deposited in the Herbarium Jatta in Naples is examined.

## References

- Carvalho, P. (2012). *Flora Liquenológica Ibérica X*. Pontevedra: Sociedad Española de Liquenología, Imprenta El Pueblo.
- Crous, P. W., Gams, W., Stalpers, J. A., Robert, V. & Stegehuis, G. (2004). MycoBank: an online initiative to launch mycology into the 21st century. *Stud. Mycol.* 50, 19–22.
- Egea, J. M. & Torrente, P. (1993). The lichen genus *Bactrospora* Massal. *Lichenologist*, 25(3), 211–255.
- Fiorentino, J. (2002). An appraisal of scientific names used in the 1915 list of lichens of the Maltese Islands by Stefano Sommier and Alfredo Caruana Gatto. *Cent. Mediterr. Nat.* 3(4), 189–196.
- Fiorentino, J. (2007). First record of *Pyrenula chlorospila* Arnold (Pyrenulales: Pyrenulaceae) from the Maltese Islands (Central Mediterranean). *Cent. Mediterr. Nat.* 4(3), 191–195.
- Fiorentino, J. (2015). Clarification regarding old records of *Rocella* in the Maltese Islands. *Mycosphere*, 6(6), 673–680.
- Gulia, G. (1858–59). *Repertorio di Storia Naturale*. Malta III. Valletta, Malta: Anglo-Maltese.
- Hertel, H. (2001). Floristic and taxonomic notes on saxicolous lecideoid lichens. *Sendtnera*, 7, 93–136.
- Index Fungorum. (2017). The global fungal nomenclator. Retrieved July 1, 2017, from <http://www.indexfungorum.org/>
- Jatta, A. (1900). *Sylloge Licheneum Italicorum*. Trano: V. Vecchi.
- Jatta, A. (1909–11). *Flora Italica Cryptogama. Pars III. Lichenes*. Rocca di S. Casciano: Societa Botanica Italiana, L. Cappelli.
- Lanfranco, E. (1989). Lichens. In P. J. Schembri & J. Sultana (Eds.), *Red data book for the maltese islands* (p. 64). Malta: Department of Information, Malta.
- Muggia, L., Grube, M. & Tretiach, M. (2007). A combined molecular and morphological approach to species definition in black-fruited, endolithic *Caloplaca*: high genetic and low morphological diversity. *Mycol. Res.* 112, 1:36–49.
- Navarro-Rosinés, P. & Muñoz, D. (2009). *Skyttea heterochroae* comb. et nom. nov. (Helotiales) un hongo liquenícola propio de *Pertusaria heterochroa*, presente en Cataluña, Islas Baleares y Malta. *Rev. Catalana Micol.* 31, 71–85.
- Nimis, P. L. (1993). *Lichens of Italy. An annotated catalogue*. Monografie XII. Torino: Museo Regionali di Scienze Naturali.
- Nimis, P. L. (2016). *The Lichens of Italy. A Second Annotated Catalogue*. Trieste: EUT.
- Nimis, P. L. & Martellos, S. (2003). *A second checklist of the lichens of Italy, with a thesaurus of synonyms*. Monografie IV. Valle d’Aosta: Museo Regionali di Scienze Naturali St. Pierre.
- Nimis, P. L. & Martellos, S. (2017). *ITALIC - The Information System on Italian Lichens. Version 5.0*. University of Trieste, Department of Biology.
- Redinger, K. (1936). Arthoniaceae, Graphidaceae, Chiodectionaceae, Dirinaceae, Roccellaceae, Lecanactidaceae, Thelotremaaceae, Diploschistaceae, Gyalectaceae und Coenogoniaceae. *Rabenhorst’s Kryptogamenflora*, 9(2), 1–404.
- Smith, C. W. (2009). *The Lichens of Great Britain and Ireland* (C. W. Smith, A. Aptroot, B. J. Coppins, A. Fletcher, O. L. Gilbert, P. W. James & P. A. Wolseley, Eds.). London: British Lichen Society.
- Sommier, S. & Caruana Gatto, A. (1915). *Flora Melitensis Nova*. Firenze: Stabilimento Pellas.
- Timdal, E. (2010). *Porpidinia* (Porpidiaceae), a new genus for *Toninia tumidula*. *Bibl. Lichenol.* 104, 333–337.
- Westberg, M., Fernandez-Brime, S., Timdal, E., Williams, L. & Wedin, M. (2016). Species-delimitations in the *Toninia sedifolia* group. In *IAL8, Book of Abstracts* (p. 176). Helsinki.



*Research Note*

## The Social Impact of the American University of Malta on the Cottonera Region

Yanica Ellul\*<sup>1</sup> and Katya De Giovanni<sup>1</sup>

<sup>1</sup>*Cottonera Resource Centre, University of Malta, Vittoriosa, Malta*

**Abstract.** The American University of Malta (AUM) is a private university in the South Eastern Region of Malta. This article aims to look at the social impact of the American University of Malta's Cospicua site on the Cottonera and the surrounding localities.

**Keywords:** Social impact assessment, community infrastructure, Population change

### 1 Introduction

The Cottonera is a collective description of the three cities of Cospicua, Vittoriosa, and Senglea. The three cities of Cottonera and Kalkara form the hub of the maritime history of Malta. The Dockyard apprenticeship school was the main producer of skilled tradesmen in Malta and for many young people from Cottonera, the dockyards were their main source of employment (Cutajar, 2014). During the Second World War, Cottonera experienced massive outmigration as its inhabitants had to seek refuge in less exposed towns and villages. After the war, the professional and educated people of Cottonera were replaced by a poorer working class (Attard, 2015).

Data from 2011 Census revealed that 9.3% of people in the Southern harbour are illiterate (National Statistics Office, 2014); figure reflecting the highest percentage rate when compared to other regions. In addition, Cottonera students are under-represented in post-secondary educational institutions, even when these provide vocational education (Cutajar, 2014). This leads to the fact that a substantial number of people in the Cottonera area are more likely to be employed in unskilled occupations (Cutajar, 2014). Moreover, data obtained from Jobsplus show that over the past decade (2005–2016), the Southern harbour had the highest percentage of job seekers, on average 29% (Jobsplus, 2017). This has led

the Cottonera region to be over-represented by people who are welfare recipients and who have a high demand for social housing (Formosa & Gerada, 2015).

A series of regeneration projects in the Cottonera and the surrounding localities started in the 1990s and are still ongoing. Such projects include the opening of the National Maritime Museum in Vittoriosa, the revitalisation of the Vittoriosa Marina Grande, Smart City in Kalkara, and the new promenade in Cospicua which “transformed the environment from a noisy, polluting and dirty ship repairing yard to a modern waterfront accompanied by excellent landscaping and a serene atmosphere” (Formosa & Gerada, 2015, p. 9) and currently the regeneration of Dock 1 in Cospicua for the AUM.

### 2 Methodology

This article aims to identify possible social impacts as a result of the setting up of the American University of Malta in Cottonera.

This article utilised both primary and secondary sources of data. Secondary data analysis is “an empirical exercise carried out on data that has already been gathered or compiled in some way” (Dale, Arber & Procter, 1988, p. 3). For the purpose of this article, the Social Impact Assessment – American University of Malta Campus – Cottonera Site conducted by Formosa and Gerada (2015) was mainly consulted. On the other hand, primary sources consist of data collected by researchers themselves during the course of their research, in this case, semi-structured interviews.

Interviews were conducted with:

- Ms Alison Zerafa - Mayor, Cospicua Local Council;
- Fr Anton Cassar - Parish Priest, Cospicua;
- Mr Ivan Buttigieg - President Regatta Club, Cospicua.

Notes were taken during the interview and a more detailed description of their responses was written soon

\*Correspondence to: Yanica Ellul (yanica.ellul@um.edu.mt)

after every interview. Phrases and sentences which have been repeated in different interviews; concepts which are already pointed out in literature and other relevant sections were labelled. The social impact assessment was written in light of previous studies on the American University of Malta and studies on Cottonera.

### 3 Assessing the Social Impact

In their Social Impact Assessment (SIA), Formosa and Gerada (2015) asked residents in Cospicua, Kalkara, Senglea and Vittoriosa whether they are in favour or against the American University of Malta situated in Cospicua. Formosa and Gerada (2015) summarised the participants' responses in a favouring sentiment towards the American University of Malta:

*“Stakeholders and residents were receptive to large-scale international investments that would introduce much needed financial capital in the area - as this would not only increase the available range of **job opportunities** for residents in the Cottonera and adjoining localities but would also have a spill-over positive economic effect on **business ventures** and even **renting prospects** (p. 1).”*

Ms Alison Zerafa, Mayor of Cospicua, reaffirms the positive view stakeholders and residents have regarding the American University of Malta. Ms Zerafa added that since the dockyard closed, Dock 1 was left in a neglected state. This, together with the stigma and negative perceptions the Cottonera area struggles with, worsened the image of Cospicua and the surrounding localities. Many residents believe that the presence of a foreign university in Cottonera will minimise the disparaging image of Cottonera and prejudice towards its residents. The regeneration of Dock 1 is giving a different image to Cospicua, in Ms Zerafa's words, *“ir-residenti qed jergħu jaraw lill-Bormla tiegħu l-ħajja - residents are witnessing the rebirth of Cospicua”*. Moreover, as mentioned in Formosa and Gerada (2015) and by Mr Buttigieg, the prejudice towards Cottonera residents will possibly decrease since residents believe that the American University of Malta has a strong potential towards bringing about new job opportunities and hence lowering unemployment rates in the Cottonera region. Mr Buttigieg added that the presence of a University in Cospicua might also stimulate the interest of youths to continue furthering their education.

Fr Anton mentioned that the American University of Malta will attract affluent students which will further create more business in the area. Formosa and Gerada (2015) mentioned that the establishment of a campus situated in Cospicua means that students will opt for guest houses and rental accommodation in Cospicua and nearby localities. In fact, Fr Anton and Ms Zerafa claimed that homeowners are benefiting by renting and

selling property. Considering the small size of Malta, visiting relatives might not only opt for accommodation in the Cottonera but will have a positive effect on the island (Formosa & Gerada, 2015). In fact, Fr Anton and Ms Zerafa agreed that guest houses and boutique hotels are on the increase.

Ms Zerafa and Fr Anton stated that while some time ago, one found a lot of unsold property in Cospicua, this is no longer the case, as people are selling and restructuring their houses to rent them to students. As a result of this, Maltese citizens are finding that renting prices increased. Ms Zerafa, however, explained that cheap renting used to attract people with social problems to the area; contributing more to the stigma that Cospicua has carried with it for many years. According to Attard (2015), the accumulation of social problems in urbanised cities causes disadvantage to individuals and hinders the development of the city; hence the increase in renting price means that the burden of people with social problems will be distributed onto different localities.

Interviewees added that residents of the area will also benefit from retail, grocery and coffee shops since most businesses are run by locals and opens possibilities of new business ventures targeting the needs of students. In fact, one can already notice the number of cafeterias and pastizzi shops which opened recently in the area.

While the majority of residents and stakeholders agreed with the American University of Malta in Cospicua, they mentioned the following concerns - an increase in traffic, a decrease in parking spaces, and a surge in air pollution (Formosa & Gerada, 2015). These concerns were also pointed out by Fr Anton, adding also possible unpleasant noise from recreational activities to his list - a consequence of economic growth, as he stated in his own words *“l-ekonomija tmexxi kollox - everything is run through economy”*. While Dun Anton does not mention this in a negative tone, Mr Buttigieg added that recreational activities have a positive impact on Cospicua as lately it has become too quiet. He, in fact, stated *“Bormla saret wisq kwieta... aħna nafu Bormla aktar movimentata - Cospicua is too quiet... we know a Cospicua which was more active”*.

With regards to the issue of the introduction of a new group with different religious values and beliefs from the majority of the people residing in Cottonera, Ms Zerafa mentioned that residents were worried about different religions and cultures. Mr Buttigieg is of the opinion that such interaction will enrich the multi-cultural character of the locality. Fr Anton believes that it is inevitable that youths from the area interact with students from the American University of Malta, similar to when in the past the British forces in Malta left a particular impact on the Cottonera region.



Furthermore, Ms Zerafa explained that the announcement of the opening of the American University of Malta led residents to resist change. Taking also into consideration that Cottonera is an ageing population, Ms Zerafa claimed that, residents felt that what is theirs – hence Cospicua – will be taken from them. However, Ms Zerafa explained that the authorities involved the community from the beginning of the project, kept ongoing communication during the planning stage and made them part of the process. This enabled residents to develop a trusting relationship in order to let go of their fears. This enabled them to visualise a direct link between the project and a possibility of an improved quality of life. This has been confirmed by Mr Buttigieg. He stated that the American University of Malta is the main sponsors of the Cospicua Regatta Club for the year 2017. He also stated that other stakeholders in the community should benefit in the years to come, which ultimately all the Cottonera area is benefitting from.

#### 4 Conclusion

This article aimed to look at the social impact of the American University of Malta's Cospicua site on the Cottonera and the surrounding localities. This article concluded that stakeholders and residents believe that the presence of a foreign university in Cottonera will minimise the disparaging image of Cottonera and prejudice towards its residents, due to the regeneration and business created in the area including job opportunities, business ventures and renting prospects.

Residents and stakeholders pointed out four key concerns with regards the social impact of the American University of Malta on the Cottonera, including - an increase in traffic, a decrease in parking spaces, a surge in air pollution and worries regarding students of different religions and cultures. However, the authorities involved the community from the beginning of the project and this enabled residents and stakeholders to develop a trusting relationship and to visualise a direct link between the project and a possibility of an improved quality of life.

#### References

- Attard, T. (2015). *Career Barriers faced by People from Cospicua: The Case of Higher Status Jobs* (Doctoral dissertation, University of Malta).
- Cutajar, J. (2014). *Bormla: A struggling community*. Rabat, Malta: Faraxa Publisher.
- Dale, A., Arber, S. & Procter, M. (1988). *Doing Secondary Analysis*. London, United Kingdom: Unwin Hyman.
- Formosa, M. & Gerada, J. (2015). Social impact assessment – American University of Malta campus – Cottonera site. Retrieved November 7, 2017, from <https://opm.gov.mt/en/Documents/AUM/AUM-SIA-Cottonera.pdf>
- Jobsplus. (2017). Registered jobseekers segmented by region. Retrieved November 20, 2017, from <https://jobsplus.gov.mt/resources/publication-statistics-mt-mt-en-gb/labour-market-information/jobseekers-data>
- National Statistics Office. (2014). Census of population and housing 2011. Retrieved November 20, 2017, from [https://nso.gov.mt/en/publications/Publications\\_by\\_Unit/Documents/01\\_Methodology\\_and\\_Research/Census2011\\_FinalReport.pdf](https://nso.gov.mt/en/publications/Publications_by_Unit/Documents/01_Methodology_and_Research/Census2011_FinalReport.pdf)

#### Appendix A

Interview Guide (adapted from Formosa & Gerada, 2015)

##### Wide-ranging impacts

- Community's views on AUM
- Key issues driving the community's perception
- Concerns of residents and stakeholders

##### Population impacts

- Population change – Influx of young persons
- Seasonal residents

##### Conflicts between local residents and new comers

- Culture differences/introduction of new social classes
- Change in commercial focus of the community

##### Community infrastructure & Arrangements

- Change in community infrastructure
- Change in occupational opportunities



Commentary

## Parkinson's Disease Motor Disorganization and Temporal Processing

Tiziana M. Florio\*<sup>1,2</sup>

<sup>1</sup>Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy

<sup>2</sup>INFN-LNGS, Assergi, L'Aquila, Italy

Motor control is essential for everyday life and highly contributes to the development and organisation of higher cognitive functions. Embodied cognition endemically approaches cognitive activities, grounding on sensory-motor processes and the ability to switch from each other in response to specific context and situations. In this view, it is possible to deliberate higher functions such as “expertise” and “decision making” as the ability to reactivate, deconstruct and reconstruct different motor plans in their subroutines to plastically react to external or internal environmental requirements (Leisman, Moustafa & Shafir, 2016).

Automation is the best way through which different neural patterns work to execute motor skills. A sequence of motor acts could be successfully and efficiently executed when sensory-motor associations are acquired and timed to relate each other to a specific outcome. Skills derive from the possibility to perform motor acts in sequences after the establishment of the sensory-motor rules in terms of temporally associated outcomes, and then disrupt it in subroutines and reconstruct it in different ways supporting many motor strategy, something known as plastic behaviour (Kim & Hikosaka, 2015; Liljeholm, Dunne & O'Doherty, 2015). On the contrary, a failure to predict sensory consequences of one's actions may underlie agency disturbances characterising many psychotic symptoms (Takkar, Diwadkar & Rolfs, 2017).

Such a comprehensive knowledge about intimate sensory-motor processing and higher functions was compelled by important studies aimed to clarify the motoric organisation of movements, their sequencing, and the temporal attributes (Wu, Hallett & Chan, 2015). Movement disorders are characterised by impairments spreading from hypokinetic disorders characterized by poverty of movement up to include hyperkinetic disorders associated with abnormal, involuntary movements (Dickson,

2018). On the other hand, psychiatric disorders share many symptoms and common aetiological factors with movement disorders, suggesting a degree of common or overlapping pathogenic mechanisms (Patel, Jankovic & Hallett, 2014; Peall et al., 2017). Psychiatric symptoms are part of the clinical spectrum of movement disorders and often are the premotor symptom of the disease, such as Huntington disease or Parkinson's disease (PD) (Williams-Gray & Worth, 2016; Asakawa et al., 2016). Postural and locomotor impairments of PD develop when degeneration of the dopamine (DA) releasing cells in *Substantia Nigra pars compacta* induces a near complete loss of DA in striatal tissue (Schapira, Chaudhuri & Jenner, 2017).

In patients with advanced PD, the substitutive therapy is accomplished through L-DOPA administration, providing a long-lasting improvement in motor abilities. When the loss of DA nerve terminals is almost complete, the DA striatal supply depends on the plasma level of L-DOPA. Unfortunately, the therapeutic window of L-DOPA narrows during the progression of PD with the development of L-DOPA-induced dyskinesia (LID) and a spectrum of abnormal involuntary movements (Stefani, Pierantozzi, Koch, Galati & Stanzione, 2010; Cenci, 2014). Despite recent progress, the pharmacodynamics, presynaptic and postsynaptic pathogenesis of LID is still unknown. It is hypothesised that both alteration in the regulation of DA release and clearance and neurovascular mechanism acting during L-DOPA treatment are related with LID pathogenesis (Hirano et al., 2008; Brehm et al., 2015).

It is worthy to note that motor complications are characterised by dysfunctions in temporal processing (Harrington & Rao, 2015; Avanzino, Pelosin & Vicario, 2016). PD is characterised by an increased of brain oscillatory activity in the  $\beta$  band range (12–35 Hz), and new bursts of pathologically synchronised activity seem to

\*Correspondence to: Tiziana M. Florio (tizianamarilena.florio@univaq.it)

be associated with delayed or impaired conscious movement (Little & Brown, 2014). The development of LID is accompanied by opposite effect on the  $\beta$  band and largely increasing the  $\gamma$  band frequency (60–80 Hz) (Salvadè et al., 2016).

Therapeutic interventions such as the deep brain stimulation or DA continues therapies are used to manage the motor fluctuation deriving from the long-lasting L-DOPA therapy and to suppress pathologically synchronised oscillations. In the unilaterally 6-OHDA lesioned rat, the repeated administration of DA agonist, apomorphine, induces an exacerbating repetitive, evolving into a compulsive, behaviour that probably is dependent on a disruption of the temporal coherence of the pre-frontal cortices deriving from the two hemispheres (Wu et al., 2015; Florio, 2017).

In impulse motor control deficits, in which explicit temporal constraints are needed, an impaired inhibitory role of pre-motor-basal ganglia dysfunction (subthalamic nucleus, hyperdirect connecting pathway) is hypothesised (Graybiel & Smith, 2016). Alternatively, it is supposed that temporal coding, needed to inhibit inappropriate motor acts, are missing because of the pre-frontal cortex-basal ganglia dysfunction (Gu, van Rijn & Meck, 2015). Temporal processing occurs across different timescales. Millisecond timing is referred to speech perception and motor control, whereas milliseconds to minutes timing is important for computational learning and decision-making. In addition, cycling reoccurring stimuli can be predicted in their temporal sequence if motor movements define the duration. As a consequence, two-timing systems were proposed that engage different neuronal circuits, one that is automatic and another that is cognitively controlled (Avanzino et al., 2016).

Undoubtedly, switching between automatic and voluntary controlled movements is a function of basal ganglia (Florio, Confalone, Sciarra, Sotgiu & Alecci, 2013). Switching movements throughout different scale of time is the prerequisite through which it is possible to organize motor behaviour in response to significant environmental stimuli. We can conclude that any imbalance between sequencing and temporal processing involves impairment in the possibility to organise behaviour from the subtle and accurate imagery of thinking to the perfect execution of skilled movement, resulting in both movement and cognitive impairment.

## References

- Asakawa, T., Fang, H., Sugiyama, K., Nozaki, T., Kobayashi, S., Hong, Z., ... Xia, Y. (2016). Human behavioral assessments in current research of Parkinson's disease. *Neurosci. Biobehav. Rev.* *68*, 741–772.
- Avanzino, L., Pelosin, E. & Vicario, C. M. (2016). Time Processing and Motor Control in Movement Disorders. *Front. Hum. Neurosci.* *10*(631).
- Brehm, N., Bez, F., Carlsson, T., Kern, B., Gispert, S., Auburger, G. & Cenci, M. A. (2015). A Genetic Mouse Model of Parkinson's Disease Shows Involuntary Movements and Increased Postsynaptic Sensitivity to Apomorphine. *Mol. Neurobiol.* *52*, 1152–1164.
- Cenci, M. A. (2014). Presynaptic mechanisms of L-DOPA-induced dyskinesia: the findings, the debate, and the therapeutic implications. *Front. Neurol.* *5*(242).
- Dickson, D. W. (2018). Neuropathology of Parkinson disease. *Parkinsonism Relat. Disord.* *46*, S30–S33.
- Florio, T. M. (2017). The 6-OHDA Hemiparkinsonian Rat Model: Evidence of Early Stage Degeneration of the Nigrostriatal Pathway. In *6<sup>th</sup> Mediterranean Neuroscience Conference* (pp. 169–170). Malta.
- Florio, T. M., Confalone, G., Sciarra, A., Sotgiu, A. & Alecci, M. (2013). Switching ability of over trained movements in a Parkinson's disease rat model. *Behav. Brain Res.* *250*, 326–333.
- Graybiel, A. & Smith, K. S. (2016). Habit Formation. *Dialogues Clin. Neurosci.* *18*(1), 33–43.
- Gu, B. M., van Rijn, H. & Meck, W. H. (2015). Oscillatory multiplexing of neural population codes for interval timing and working memory. *Neurosci. Biobehav. Rev.* *48*(160–185).
- Harrington, D. L. & Rao, S. M. (2015). Timing in Neurogenerative Disorders of the Basal Ganglia. In A. Vatakis & M. Allman (Eds.), *Time Distortions in Mind: Temporal Processing in Clinical Populations* (Chap. 8, pp. 190–225). Leiden, The Netherlands: Brill.
- Hirano, S., Asanuma, K., Ma, Y., Tang, C., Feigin, A., Dhawan, V., ... Eidelberg, D. (2008). Dissociation of Metabolic and Neurovascular Responses to Levodopa in the Treatment of Parkinson's Disease. *J. Neurosci.* *28*(16), 4201–4209.
- Kim, H. F. & Hikosaka, O. (2015). Parallel basal ganglia circuits for voluntary and automatic behaviour to reach rewards. *Brain*, *138*(7), 1776–1800.
- Leisman, G., Moustafa, A. A. & Shafir, T. (2016). Thinking, Walking, Talking: Integratory Motor and Cognitive Brain Function. *Front Public Heal.* *4*(94).
- Liljeholm, M., Dunne, S. & O'Doherty, J. P. (2015). Differentiating neural systems mediating the acquisition versus expression of goal-directed and habitual behavioral control. *Eur. J. Neurosci.* *41*(10), 1358–1371.
- Little, S. & Brown, P. (2014). Focusing Brain Therapeutic Interventions in Space and Time for Parkinson's Disease. *Curr. Biol.* *24*(18), 898–909.

- Patel, N., Jankovic, J. & Hallett, M. (2014). Sensory aspects of movement disorders. *Lancet Neurol.* *13*(1), 100–112.
- Peall, K. J., Lorentzos, M. S., Heyman, I., Tijssene, M. A. J., Owena, M. J., Daley, R. C. & Kuriand, M. A. (2017). A review of psychiatric co-morbidity described in genetic and immune mediated movement disorders. *Neurosci. Biobehav. Rev.* *80*(23–25).
- Salvadè, A., D'Angelo, V., Di Giovanni, G., Tinkhauser, G., Sancesario, G., Städler, C., ... Galati, S. (2016). Distinct roles of cortical and pallidal  $\beta$  and  $\gamma$  frequencies in hemiparkinsonian and dyskinetic rats. *Exp. Neurol.* *275*(1), 199–208.
- Schapira, A. H. V., Chaudhuri, K. R. & Jenner, P. (2017). Non-motor features of Parkinson disease. *Nat. Rev.* *18*, 435–451.
- Stefani, A., Pierantozzi, P., Koch, G., Galati, G. & Stanzione, P. (2010). Therapy for Dyskinesias in Parkinson's Disease Patients. *Future Neurol.* *5*(2), 277–299.
- Takkar, K. N., Diwadkar, V. A. & Rolf, V. (2017). Oculomotor Prediction: A Window into the Psychotic Mind. *Trends Cogn. Sci.* *21*(5), 344–356.
- Williams-Gray, C. H. & Worth, P. F. (2016). Parkinson's disease. Movement Disorders. *Medicine (Baltimore)*. *44*(9), 542–546.
- Wu, T., Hallett, M. & Chan, P. (2015). Motor automaticity in Parkinson's disease. *Neurobiol. Dis.* *82*, 226–234.



Commentary

## Electrical Impedance Mammography: the key to low-cost, portable and non-invasive breast cancer screening?

Cristiana Sebu\*<sup>1</sup>

<sup>1</sup>*Department of Mathematics, Faculty of Science, University of Malta, Msida, Malta*

Breast cancer is a major public health problem with 1.7 million cases diagnosed per year and is the leading cause of cancer deaths in women worldwide (Siegel, Miller & Jemal, 2016). The two main determinants of survival are early detection and optimal treatment. Despite the advances in medicine, breast cancer is detected at advanced stages in developing countries (DCs) because early detection, diagnosis and treatment cannot be efficiently promoted. Thus, disease burden is particularly high in DCs, where more than half of breast cancer cases and 62% of the deaths now occur. The “Breast Health Global Initiative” (BHGI) evaluated the complexity of healthcare systems in relation to breast cancer. Specifically, at the basic level, breast self-examination is encouraged, whereas diagnostic ultrasound and X-ray mammography are available at a limited level. At the increased level, patients have access to diagnostic mammography with opportunistic breast screening, and at a maximum level, the population undergoes organized screening for breast cancer (Anderson et al., 2006).

X-ray mammography detects breast cancer with sensitivity rates of up to 90%. This classical diagnostic method, however, yields rather unspecific results. Only one in five biopsies of suspicious lesions leads to a malignant histological diagnosis (Lee et al., 2010), which causes unnecessary distress amongst the patients and significant delays in establishing a diagnosis. Despite the unacceptably high rate of false positives, high-income countries initiated population based mammographic screening programs, but there continues to be a heated debate regarding their possible benefits as X-ray mammography is harmful due to the radiation exposure and very costly. Thus, many national cancer control programs recommend later and less frequent mammograms. In UK, for example, women who are aged 50–

70 and registered with a GP are automatically invited for breast cancer screening every three years. However, the incidence of the disease in younger women is not rare. Breast cancer is the most diagnosed cancer in women between the ages of 25 and 35 and tends to be more aggressive and harder to treat (Cancer Mondial, <http://ci5.iarc.fr/ci5plus/ci5plus.htm>). According to World Health Organisation (WHO), if breast cancer can be detected and treated in its early stage, the mortality due to this disease can be decreased by one-third, and 400,000 lives could be saved every year globally. Current research is therefore aimed at developing alternative techniques to detect breast cancer more accurately and possibly earlier.

Electrical impedance tomography (EIT) is a non-invasive, portable, low-cost technology developed to image the distribution of electrical properties, conductivity and/or permittivity, within an object from measurements of electric currents and voltages on its surface (Borcea, 2002). Since *in vivo* studies discovered a difference of three times or more in the specific electrical conductivity between healthy and cancerous tissue (Rigaud, Morucci & Chauveau, 1996), EIT has been actively studied as a complementary imaging modality for early detection of breast cancer (Holder, 2004).

The EIT estimation problem is mathematically challenging being both nonlinear and extremely ill-posed in the Hadamard sense, thus requiring the measured data to have a high degree of precision. Substantial progress has been made in determining the class of conductivity distributions that can be recovered from the boundary data (Astala & Päivärinta, 2006; Calderón, 1980; Nachman, 1996), as well as in designing practical reconstruction algorithms applicable to noisy measurement data (Holder, 2004). Reconstruction procedures addressing the full nonlinear problem include a wide

\*Correspondence to: Cristiana Sebu (cristiana.sebu@um.edu.mt)

range of iterative methods based on formulating the inverse problem in the framework of nonlinear optimization (Gehre, Kluth, Sebu & Maass, 2014; Halter, Hartov & Paulsen, 2008; Hong et al., 2015; Pak et al., 2012; Sze, 2012; Ye et al., 2008). While these techniques are promising for obtaining accurate reconstructed conductivity values, they are often slow to converge and are quite demanding computationally particularly when addressing the three-dimensional problem. These concerns have encouraged the search for reconstruction algorithms which reduce the computational demands. Some use a priori information to reconstruct piecewise constant conductivity distributions (e.g. Harrach, 2013), while others are based on reformulating the inverse problems in terms of integral equations and/or linearization (Delbary, Hansen & Knudsen, 2012; Georgi, Hähnlein, Schilcher, Sebu & Spiesberger, 2013; Hähnlein, Schilcher, Sebu & Spiesberger, 2011; Perez, Pidcock & Sebu, 2017). This list is by no means exhaustive and new approaches are constantly being presented (Hauptmann, Santacesaria & Siltanen, 2017).

Several electrical impedance mammographic systems have been developed over the years: fixed 3D EIT systems (Halter et al., 2008; Sze, 2012; Ye et al., 2008), bedside data-acquisition systems (Georgi et al., 2013; Pak et al., 2012), and a fully portable and autonomous EIT IC system (Hong et al., 2015). The EIT device developed at Dartmouth College (Halter et al., 2008) has 64 electrodes incorporated into a mechanical framework optimized for breast imaging. The mechanical assembly uses multiple rings of electrodes that conform the breast to a specific geometry which provides information on both the location of electrodes ( $\pm 1$  mm) and the shape of the breast. In contrast, the EIT system designed at Duke University (Ye et al., 2008) has a 3D applicator with 128 electrodes on a cone-shaped surface which is filled with liquid electrolyte whose electrical properties are similar to that of normal breast tissue and which encases the breast to be imaged. The principle behind the Sussex EIM Mk4 system (Sze, 2012) is very similar, the only difference being that the array of 85 electrodes is planar and is fixed at the bottom of the examination tank. The devices described in (Assenheimer et al., 2001; Georgi et al., 2013; Pak et al., 2012) are in some aspects similar in the sense that all of them use planar electrode arrays in a handheld probe geometry which is pressed against the breast during the examination (see Figure 1). Note, however, that the T-Scan technology (Assenheimer et al., 2001) does not produce tomographic reconstructions, it just maps the surface impedance using 256 electrodes. In all the aforementioned bed type and probe type systems, the electronic circuitry is contained in a big box, and a PC is used as the imaging device. The compact brassiere-shaped EIT

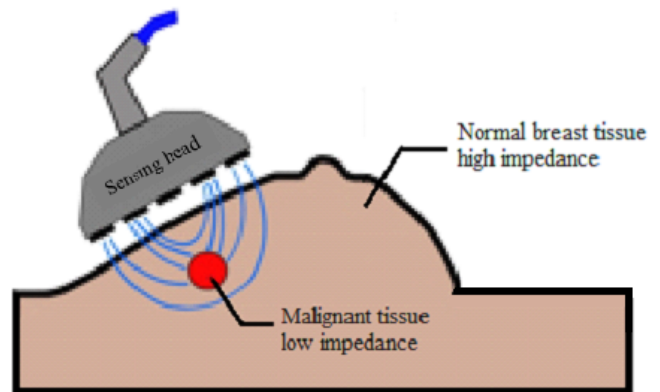


Figure 1: Data collection setup for EIM.

system introduced in (Hong et al., 2015) was designed for personal use at home without expertise. The EIT IC is integrated onto a fabric which has 90 soft electrodes fabricated using Planar-Fashionable Circuit Board technology. In addition, a portable smart device which can be connected via the USB port is used for imaging and displaying.

In spite of the tremendous development of electronic technologies, which has enabled a continuous modernisation and miniaturisation of electronic circuits (Hong et al., 2015), a higher degree of precision in the collected data (Terzopoulos, Hayatleh, Hart, Lidgley & McLeod, 2005), an extension of the operating frequency range of the EIT systems at lower power and improvements of the signal-to-noise ratios (SNRs) (Halter et al., 2008; Hong et al., 2015), Electrical Impedance Mammography (EIT) has raised only moderate interest in the medical community and has not yet made the transition from an exciting medical physics discipline into widespread routine clinical use. This is mainly due to its sensitivity to measurement errors and high computational demands, and to practical issues: errors in electrode positions or boundary shape, high and uncontrollable contact impedance of the skin (variations of 20% or more). While errors due to electrode position and boundary shape are of a technical nature, the problem of the contact impedance in medical applications is more fundamental.

Almost all previous EIT systems use the same electrodes for current injection and voltage measurement (Halter et al., 2008; Pak et al., 2012; Sze, 2012; Ye et al., 2008). The excitation current is injected (extracted) at one pair of electrodes at each time and the resulting voltage is measured at all or some of the remaining electrodes, e.g. (Halter et al., 2008; Pak et al., 2012). In this way, the problem with the high and uncontrollable skin-electrode contact impedance is avoided but at the price of aggravating the ill-posedness of the reconstruct-

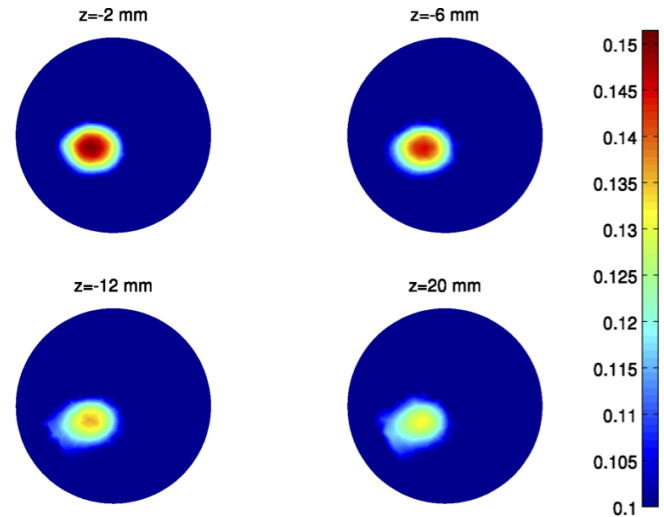


tion. In other cases, the current is dispersed into the liquid before entering into the breast, which results in a low image resolution (Sze, 2012; Ye et al., 2008), or dry flexible electrodes are used (Hong et al., 2015) at the detriment of introducing errors in the electrode positions and boundary shape.

The novelty of the EIM devices designed by the author in collaboration with colleagues from University of Mainz, Germany, and Oxford Brookes University, UK, and hence of the image reconstructions proposed, consists in the distinct use of active and passive electrodes (Gehre et al., 2014; Georgi et al., 2013; Hähnlein et al., 2011; Perez et al., 2017). The active electrodes are used only for current injection while the passive electrodes only for voltage measurements, and thus there are no issues related to the contact impedance. The device has a fixed geometry and the positions of the electrodes are exactly known. Recently, this collaborative research group has made significant technical advances in EIM technology which could potentially bring breakthroughs to clinical acceptance. More precisely, the latest research project of the group funded by the Higher Education Innovation Fund HEIF5 (UK) was devoted to the design, construction and testing of a near-to-market electrical impedance mammographic sensor (see Figure 2) and to the development of computationally efficient image reconstruction algorithms which could be used to detect the size and the location of breast tumours in real-time. The numerical reconstructions obtained using data from *in vitro* experiments had very good spatial resolutions, and the algorithms were robust with respect to errors in the data (see Figure 3). The researchers are now establishing the experimental protocols for preliminary clinical trials. The next challenge though will be to embed the EIM system into a bra for home use whose results will be sent regularly via internet to a medical practitioner.



**Figure 2:** Sensing head of the EIM device developed at the University of Mainz in collaboration with the University of Malta and Oxford Brookes University.



**Figure 3:** Cross-sections of 3D numerical reconstructions obtained from *in vitro* experimental data.

To summarize, the state of art of EIM research is still healthy and considerable efforts are continuously invested into the clinical trials and pilot studies to achieve widespread clinical acceptance. The advantages of EIM over traditional X-ray mammography - portability, low cost, little or zero patient discomfort, no known patient risk and no known side effects – will make this technology a welcome addition to the tools available in the fight against breast cancer. It will reduce the number of invasive X-ray and MRI mammograms, although of course, it will not fully replace them. Moreover, since the investigation could be performed by every medical practitioner without special training, EIM could be the key to mass breast cancer screening especially in the countries with underdeveloped medical facilities where it could even be used for provisional biopsy examinations.

## References

- Anderson, B. O., Shyyan, R., Eniu, A., Smith, R. A., Yip, C.-H., Bese, N. S., ... Carlson, R. W. (2006). Breast Cancer in Limited-Resource Countries: An Overview of the Breast Health Global Initiative 2005 Guidelines. *Breast J.* 12, S3–S15.
- Assenheimer, M., Laver-Moskovitz, O., Malonek, D., Manor, D., Nahaliel, U., Nitzan, R. & Saad, A. (2001). The T-SCANTM technology: electrical impedance as a diagnostic tool for breast cancer detection. *Physiol. Meas.* 22(1), 1.
- Astala, K. & Päivärinta, L. (2006). Calderón's inverse conductivity problem in the plane. *Ann. Math.* 265–299.
- Borcea, L. (2002). Electrical impedance tomography. *Inverse Probl.* 18(6), R99.

- Calderón, A. P. (1980). Seminar on numerical analysis and its applications to continuum physics, Soc. *Bras. Mat. Rio Janeiro*, 65.
- Delbary, F., Hansen, P. C. & Knudsen, K. (2012). Electrical impedance tomography: 3D reconstructions using scattering transforms. *Appl. Anal.* 91(4), 737–755.
- Gehre, M., Kluth, T., Sebu, C. & Maass, P. (2014). Sparse 3D reconstructions in electrical impedance tomography using real data. *Inverse Probl. Sci. Eng.* 22(1), 31–44.
- Georgi, K.-H., Hähnlein, C., Schilcher, K., Sebu, C. & Spiesberger, H. (2013). Conductivity reconstructions using real data from a new planar electrical impedance tomography device. *Inverse Probl. Sci. Eng.* 21(5), 801–822.
- Hähnlein, C., Schilcher, K., Sebu, C. & Spiesberger, H. (2011). Conductivity imaging with interior potential measurements. *Inverse Probl. Sci. Eng.* 19(5), 729–750.
- Halter, R. J., Hartov, A. & Paulsen, K. D. (2008). A broadband high-frequency electrical impedance tomography system for breast imaging. *IEEE Trans. Biomed. Eng.* 55(2), 650–659.
- Harrach, B. (2013). Recent progress on the factorization method for electrical impedance tomography. *Comput. Math. Methods Med.* 2013.
- Hauptmann, A., Santacesaria, M. & Siltanen, S. (2017). Direct inversion from partial-boundary data in electrical impedance tomography. *Inverse Probl.* 33(2), 25009.
- Holder, D. S. (2004). *Electrical impedance tomography: methods, history and applications*. CRC Press.
- Hong, S., Lee, K., Ha, U., Kim, H., Lee, Y., Kim, Y. & Yoo, H.-J. (2015). A 4.9 m $\Omega$ -sensitivity mobile electrical impedance tomography IC for early breast-cancer detection system. *IEEE J. Solid-State Circuits*, 50(1), 245–257.
- Lee, C. H., Dershaw, D. D., Kopans, D., Evans, P., Monsees, B., Monticciolo, D., ... Burhenne, L. W. (2010). Breast Cancer Screening With Imaging: Recommendations From the Society of Breast Imaging and the ACR on the Use of Mammography, Breast MRI, Breast Ultrasound, and Other Technologies for the Detection of Clinically Occult Breast Cancer. *J. Am. Coll. Radiol.* 7(1), 18–27.
- Nachman, A. I. (1996). Global uniqueness for a two-dimensional inverse boundary value problem. *Ann. Math.* 71–96.
- Pak, D. D., Rozhkova, N. I., Kireeva, M. N., Ermoshchenkova, M. V., Nazarov, A. A., Fomin, D. K. & Rubtsova, N. A. (2012). Diagnosis of breast cancer using electrical impedance tomography. *Bio-med. Eng. (NY)*. 46(4), 154–157.
- Perez, H., Pidcock, M. & Sebu, C. (2017). A three-dimensional image reconstruction algorithm for electrical impedance tomography using planar electrode arrays. *Inverse Probl. Sci. Eng.* 25(4), 471–491.
- Rigaud, B., Morucci, J. P. & Chauveau, N. (1996). Bioelectrical impedance techniques in medicine. Part I: Bioimpedance measurement. Second section: impedance spectrometry. *Crit. Rev. Biomed. Eng.* 24(4-6), 257–351.
- Siegel, R. L., Miller, K. D. & Jemal, A. (2016). Cancer statistics, 2016. *CA. Cancer J. Clin.* 66(1), 7–30.
- Sze, G. (2012). *Detection of breast cancer with electrical impedance mammography*. Engineering. University of Sussex.
- Terzopoulos, N., Hayatleh, K., Hart, B., Lidgley, F. J. & McLeod, C. (2005). A novel bipolar-drive circuit for medical applications. *Physiol. Meas.* 26(5), N21.
- Ye, G., Lim, K. H., George, R. T., Ybarra, G. A., Joines, W. T. & Liu, Q. H. (2008). 3D EIT for breast cancer imaging: System, measurements, and reconstruction. *Microw. Opt. Technol. Lett.* 50(12), 3261–3271.



## 6<sup>th</sup> Annual *Science in the House* Exhibition

David C. Magri\*<sup>1</sup>

<sup>1</sup>Department of Chemistry, Faculty of Science, University of Malta, Msida, Malta

The *Science in the House* media exhibition was held on Friday 29<sup>th</sup> September 2017 at 5:00 pm in the main foyer of the Parliament Building in Valletta. The event opened with a personal brief welcome followed by an opening address by Prof. Alex Felice, Chairman of the *Science in the City/European Researchers' Night* consortium and followed by Prof. Joseph Cilia, Rector's Delegate of the University of Malta. This year short oral speeches were also contributed from four researchers: Dr Maria Briguglio, Dr Ruben Gatt, Prof. Ing. Cyril Spiteri Staines and Prof. Neville Vassallo. They presented an overview of research they will be conducting with funds awarded by the University of Malta. The inauguration closed with an address by the Hon. Anglu Farrugia M.P., Speaker of the House of Representatives, Parliament of Malta. After 6:00 pm the Parliament Building was opened to the general public for viewing until midnight. An interactive exhibition allowing the general public to use microscopes was also on display (Figure 1).

Various research projects not limited to the Faculties of ICT, Science, Medicine and Surgery, and Health Sciences from the University of Malta were on display (Figure 2). Twenty posters were showcased on five four-sided display panels. The topics included microbial degradation of plastics, online hate speech, non-invasive analysis of cultural heritage sites, face image enhancement technology, cystic fibrosis research, algorithm development of subatomic particle detection, photovoltaics, Maltese Human genome, stroke research with animals models, limestone geological dating, quantum communication technologies, exploration of groundwater beneath the sea, and blood analysis using electromagnetic fields. There were also poster contributions from the Malta Life Science Park, the University Research Trust (RIDT), the Malta Medicines Authority, and Malta College of Arts Science and Technology (MCAST) on the mapping of ecosystems by Mario Balzan.



**Figure 1:** A mother with her two boys viewing through a microscope in Parliament. In the background is Dr Shawn Baldacchino, a researcher in the Department of Pathology at the University of Malta, who set-up the interactive microscope exhibition.

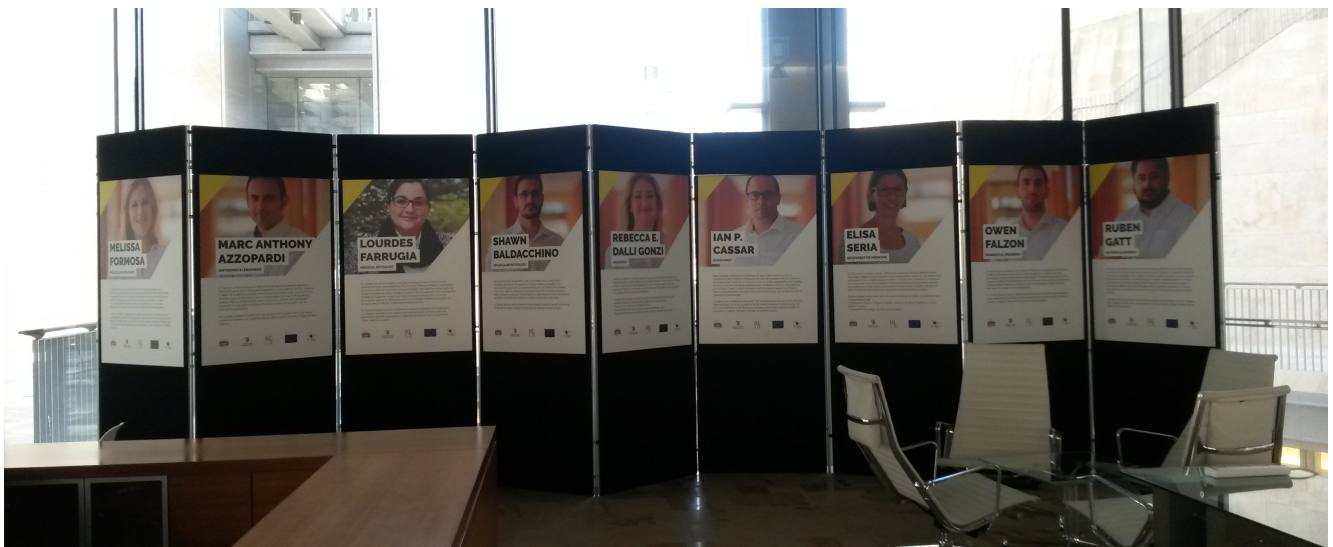
This year's event also showcased a cross-section of early career researchers (Figure 3). Nine biographical posters were on display of local scholars from the University of Malta. Highlighted in the collection were Dr Ing Marc Anthony Azzopardi, Dr Owen Falzon, Dr Elisa Seria, Dr Ian P. Cassar, Dr Ruben Gatt, Dr Rebecca Dalli Gonzi, Dr Lourdes Farrugia, Dr Melissa Formosa and Dr Shawn Baldacchino.

*Science in the House* is organised by the Malta Chamber of Scientists, the University Research Trust (RIDT) and the *European Researchers' Night – Science in the City* consortium. The consortium is supported by the European Commission's Research and Innovation Framework Programme Horizon 2020 (H2020, 2014–2020) by the Marie Skłodowska-Curie actions. The event is organised by the University of Malta, the Malta Chamber of Scientists and the Research Trust of the

\*Correspondence to: David C. Magri (david.magri@um.edu.mt)



**Figure 2:** The media exhibition at the main entrance of the Parliament Building before the commencement of the 6<sup>th</sup> annual *Science in the House* exhibition on 29<sup>th</sup> September 2017.



**Figure 3:** Biography posters of nine early career researchers at the *Science in the House* exhibition.

University of Malta, in partnership with the Ministry for Education and Employment, Parliamentary Secretary for Financial Services, Digital Economy and Innovation, Jugs Malta, Studio 7, MEUSAC, MCST, Esplora, Valetta Local Council, Malta College for Arts, Science and Technology, PBS, BPC International, Notte Bianca, Spazju Kreativ, Pjazza Teatru Rjal, the AquaBioTech

Group, the Central Bank of Malta, Wasteserv and a number of other partners. The festival has been recognised by EFFE International Jury to receive the EFFE Label 2017–2018. The programme can be viewed on [www.scienceinthecity.org.mt](http://www.scienceinthecity.org.mt) or follow the festival on Facebook for regular updates: [www.facebook.com/ScienceInTheCityMalta](https://www.facebook.com/ScienceInTheCityMalta).

## 2017 *Science in the House* Posters by Title and Contributing Researchers/Partners

Contributors are from the University of Malta unless otherwise stated.

1. The Dielectric Properties of Blood – Prof. Charles Sammut, Prof. Pierre Schembri-Wismayer, Dr Lourdes Farrugia, Julian Bonello; Saqib Salahuddin, Martin O’Holloran and Emily Porter (National University of Ireland, Galway).
2. The Malta NGSProject – Dr Stephanie Bezzina Wettinger, Dr Rosienne Farrugia, Dr Ritienne Attard, Francesca Borg Carbott, Dr Philip Dingli, Dr Tiziana Felice, Dr Karen Cassar, Adrian Pleven, Dr Valerie Said Conti and Prof Josanne Vassallo.
3. Finding Groundwater Beneath the Sea – Prof. Aaron Micallef, Prof. JoAnn Cassar, Adrian Mifsud, Adam Gauci; Dr Marion Jegen (GEOMAR, Germany), Prof Mark Person (New Mexico Institute of Mining & Technology, USA) and Dr Joshu Mountjoy (NIWA, New Zealand).
4. Quantum Islands – Dr André Xuereb; Sören Wengerowsky, Siddarth Joshi and Dr Rupert Ursin (University of Vienna and IQOQI); Davide Calonico and Alberto Mura (INRIM, Italy); Roderick Cassar (Melita Ltd).
5. The Maltese Human Genome Project – Prof. Alex E. Felice, Dr Joseph Borg, Dr Lidia Ryabova, Joanna Vella, Laura Grech, Malcolm Pace, Dr Nikolai Pace, Dr Graziella Zahra, Mark Briffa, Rebecca Borg, Dr Jerry Lu (Genomics Co. Ltd); Dr Rade Drmanac and Dr Brock Peters (Complete Genomics) and Prof. Sjaak Philipsen (Erasmus MC, Rotterdam, The Netherlands).
6. *L*-Lactate Protects the Brain from Stroke – Prof. Mario Valentino, Jasmine Vella, Christian Zammit, Ing. Robert Zammit; Prof. Robert Fern (University of Plymouth).
7. Maltese Limestone as a Window into Ancient Climates – Ray Zammit, Prof. Aaron Micallef; Prof. Caroline H. Lear and Prof. Paul N. Pearson (Cardiff University).
8. Photovoltaic Research – Prof. Luciano Mule Stagno, Dr Ing. Maurizio Fenech, Bonnie Attard, Ryan Bugeja and Mark Anthony Callus.
9. Finding Subatomic Particles – Dr Gianluca Valentino, Dr Johann A. Briffa; Dr Marian Ivanov (GSI), Dr Kai Schweda (University of Heidelberg), Dr Giacinto de Cataldo (CERN and INFN Bari) and Dr Giacomo Volpe (University of Bari).
10. Structural Bioinformatics in Disease – Prof. Gary J. Hunter, Prof. Therese Hunter, Dr Maria Cristina D’Adamo, Prof. Mauro Pessia, Dr Rosalin Bonetta, Marita Vella and Brandon Seychell.
11. Glutamate and Aspirin in Cellular Life and Death – Prof. Rena Balzan, Dr Gianluca Farrugia and Maria Azzopardi.
12. A New Therapy for Cystic Fibrosis? – Dr Maria Cristina D’Adamo, Prof. Mauro Pessia.
13. Face Image Enhancement from CCTV Images – Dr Reuben Farrugia, Prof. Kenneth Camilleri and Amped Software.
14. Revealing the Buried Past by Non-invasive Analysis – Dr Sebastiano D’Amico, Prof. Pauline Galea and Daniela Farrugia.
15. Understanding Online Hate Speech – Dr Stavros Assimakopoulos, Dr Albert Gatt, Rebecca Vella Muskat, Dr Colin Calleja, Dr Barbara Baschiera.
16. The Microbial Degradation of Plastics – Dr Gabrielle Zammit, Dr Daniel Vella, Prof. Joseph Grima, Megan Borg and Andrea Farrugia.
17. Malta Medicines Authority – Partners include University of Malta, Malta Enterprise, Malta Life Sciences Park, EU Network Training Centre, European Medicines Regulatory Network and the EU Innovation Network.
18. Malta Life Sciences Park – BioDNA Laboratory Services Ltd, SUNLAB Group Ltd, BuiltinMT.
19. Research, Innovation and Development Trust (RIDT)
20. Measuring Nature’s Benefits – Dr Mario Balzan (MCAST Water Research and Training Centre).



## Table of Contents

---

### ARTICLES

86 The Last Editorial

#### Editorial

**G. Di Giovanni**

87 Molecular Mechanisms of the Sleep Wake Cycle:  
Therapeutic Applications to Insomnia

#### Review Article

**M. Grima, T. Hunter and Y. Zhang**

98 Erosive Tooth Wear in Children and Adolescents

#### Research Article

**G. Gatt, M. Schembri, P. Vassallo, M. Luisa  
Gainza-Cirauqui, E. Vento Zahra and N. Attard**

110 Measuring Human Capital: A Comparative Study  
with Emphasis on Malta

#### Research Article

**P. von Brockdorff and B. Amaira**

125 Investigating the Use of UAV Systems for  
Photogrammetric Applications: A Case Study of  
Ramla Bay (Gozo, Malta)

#### Research Note

**E. Colica, A. Micallef, S. D'Amico, L. F. Cassar  
and C. Galdies**

132 Alcohol, Cannabinoids and Nicotine in Liver  
Pathophysiology

#### Mini Review Article

**M. Radic, F. Rappa, R. Barone, F. Cappello, G.  
Crescimanno, M. Casarrubea, M. Perucci, A.  
Marino Gammazza, G. Di Giovanni**

137 A Revised Appraisal of Scientific Names Used in  
the 1915 List of Lichens of the Maltese Islands  
by S. Sommier and A. Caruana Gatto

#### Research Article

**J. Fiorentino**

148 The Social Impact of the American University of  
Malta on the Cottonera Region

#### Research Note

**Y. Ellul and K. De Giovanni**

151 Parkinson's Disease Motor Disorganization and  
Temporal Processing

#### Commentary

**T. M. Florio**

154 Electrical Impedance Mammography: the key  
to low-cost, portable and non-invasive breast  
cancer screening?

#### Commentary

**C. Sebu**

178 6th Annual Science in the House Exhibition

#### News Article

**D. C. Magri**