

COST ACTION CA16210 TRAINING SCHOOL

IMAGING AND CLINICAL PHENOTYPING

3RD - 5TH December 2018



Venue: Macedonian Academy of Sciences and Arts, Skopje, Macedonia

Local organizer: Macedonian Association of Psychophysiology

МАКЕДОНСКО ЗДРУЖЕНИЕ ЗА ПСИХОФИЗИОЛОГИЈА



MACEDONIAN ASSOCIATION OF PSYCHOPHYSIOLOGY

WELCOME

I would like to thank you for joining this MINDDS Phenotyping Training School in Skopje, Macedonia.

This training school will cover clinical care of patients with Copy Number Variation (CNV; small chromosomal deletions or duplications) causing neurodevelopmental disorder as well as the development of research studies of these patients. Sessions will focus on the clinical implications of carrying these CNVs, counselling of patients and their families, recommendations for genetic testing and clinical care, the neurodevelopmental and wider phenotype of child CNV carriers over time, and the psychiatric profiles of child and adult carriers. Furthermore, there will be sessions on how to develop research studies of these CNV carriers, including neuro-imaging and EEG studies.

Please use this opportunity to ask the trainers about their work, form new connections and develop new ideas and collaborations.

I would like to thank all the trainers: Ann Swillen, Beate Nowakowska, Therese van Amelsvoort, Silvana Markovska Simoska, Hayley Moss, Samuel Chawner, Andrew Cuthbert and Hayley Moulding for putting together this wonderful training programme. Furthermore I would also like to thank Local Host Organiser Silvana Markovska Simoska, Macedonian Association of Psychophysiology and the Macedonian Academy of Sciences and Arts for hosting this event, Hayley Moss and Samuel Chawner for organising the event, and the MINDDS COST action for funding this training school.



Marianne van den Bree

Professor of Psychological Medicine
Cardiff University
MINDDS Working Group 2 Lead

CLINICAL CASE STUDIES

We invite all trainees to present a clinical or research case study on Day 2 in session 6. This is an opportunity to discuss a complex patient case in front of a multidisciplinary pan-european audience.

Guidelines:

- The patient has to have a pathogenic genetic variant related to developmental disorder
- No more than 2 powerpoint slides should be presented.
- If the patient is identifiable from the presentation, the presenter needs to make sure they have the appropriate consent to disclose patient identifiable information. If in doubt please consult with you supervisor or manager.



TRAINING PROGRAMME

Day 1: Monday 3rd December, 2018

09:00 - 09:15 Welcome and Introduction to the training school

09:15 - 10:00 Introductions to get to know Trainers and Trainees

Session 1

10:00 - 11:15 Introduction to clinical implications (Lead Trainer: Beata Nowakowska)

- Introduction to CNVs
- CNV Interpretation
- Phenotypic Consequences
- Penetrance
- Recommendations for genetic testing (when and which tests)
- Recommendations of clinical care of CNV carriers

Coffee break: 11:15-11:45

Session 2

11:45 - 13:00 Essentials of genetic counselling (Lead Trainer: Andrew Cuthbert)

- Principles of Genetic Counselling
- Consent, capacity and confidentiality in clinical practice
- The role of Genetics Counsellors in clinical practice
- Distinguishing between research and clinical care
- Ethical issues in returning additional findings
- Disclosing variants of uncertain significance

Lunch: 13:00-14:00

Session 3

14:00 – 15:15 Developmental characteristics of child carriers (Lead: Ann Swillen)

- Physical health phenotype
- Developmental phenotype
- Psychological phenotype
- The phenomenological presentation: importance of considering all aspects of presentation, the importance of a holistic approach and of developmental perspective
- Co-occurrence of psychiatric disorder with motor coordination and sleep problems, seizures and cognitive impairment (Marianne van den Bree)

Coffee break: 15:15-15:45

Session 4

15:45-17:15

Tour of the Centre for Genetics genotyping facilities (Dijana Plasheska-Karanfilska)

Day 2: Tuesday 4th December, 2018

Session 5

9:00-10:15 Psychiatric profile of carriers (Lead Trainer: Therese van Amelsvoort)

- Psychiatric diagnostic systems
- Psychiatric diagnosis of child carriers
- Psychiatric diagnosis of adult carriers
- Intervention and treatment
- The transition from adolescence to adulthood
- Psychosocial implications of carrying a CNV on the patient and their environment

Coffee break: 10:15-10:45

Session 6

10:45-12.45 Presentation of complicated case studies by trainees and group discussion

Lunch 12:45-13:45

Session 7

13:45-16:00 Developing research studies of CNV carriers, Part 1

(Lead Trainer: Marianne van den Bree)

- A story of developing a research programme of CNV carriers (Marianne van den Bree)
- The practicalities of setting up CNV research (Hayley Moss)
- Conducting semi-structured psychiatric interviews with patients or their carers (Hayley Moss and Hayley Moulding)

Coffee break: 16:00-16:30

Session 8

16:30-18:00 Neuro-imaging and EEG/ERP studies (Lead Trainer: Therese van Amelsvoort with Silvana Markovska Simoska and Hayley Moulding)

- Introduction and methodology
- Findings in CNV carriers

Networking dinner: 20:00

Day 3: Wednesday 5th December, 2018

Session 9

9:00-10:15 Developing research studies of CNV carriers, Part 2

(Lead Trainer: Samuel Chawner with Marianne van den Bree)

- Neurocognitive testing in a CNV cohort
- Following a cohort of CNV carriers overtime
- Databases and statistical analysis

Session 10

10:15-11:30 Discussion with trainees, questions about how to set-up successful research studies

Coffee break 11:30-12:00

Session 11

12:00-13:15 Embedding research studies of CNV carriers in the larger social and clinical setting (Lead: Marianne van den Bree with all trainers)

- Contacts with patients and their families
- Contacts with healthcare organisations, clinics and clinicians
- Contacts with patient support groups/organisations

Lunch 13:15-14:15

Session 12

14:15-15:00 Discussion, summary and completion of evaluation forms.

TRAINING SCHOOL LOCATION

All the activities will take place at the Macedonian Academy of Sciences and Arts, Street Krste Misirkov number 2 . This is a link to the venue: <http://manu.edu.mk/en/>. There will be signs to guide you but should you need any assistance you may also inquire at the Main Reception in the Central Building.

See map below



ADDITIONAL INFORMATION

1. Bus from the airport: <https://www.manoragroup.com/en>

For the city center your final stop is Holiday Inn.

From Holiday Inn you can take taxi to your chosen hotel.

The taxi is cheap and for 2km you should not pay more than 3 euros (180 denars)

2. The taxi from airport to the city centre is around 15 to 20 euros.
3. Technical info: free WiFi, computer, projector, camera (probably all the talks will be captured by video recording). Speakers can send me the presentations until 30 November 12 pm, so I could upload them before registration on Monday. Format of presentations: Power Point.
4. Registration: Registration will start at 8am on Monday. We do not have registration fee.

REMEMBER: You will need to sign every day - it is very important for reimbursement.

5. Dinner: could you please let me know if you have some special food requirements. The main course will be meat, so fish or other special requirements will be optional. I would need to have approximate number of special meals.
6. At the end of this document I have included some useful touristic information about Skopje

Please do not hesitate to contact me or my colleague Vladimir Dinkovski by e-mail or cell phone if you need any additional information.

Silvana silvana@manu.edu.mk +389 70 837375

Vladimir vlado@manu.edu.mk +389 70 272640

I hope you all have a safe trip and I look forward to welcoming you all soon!

Best regards,

Silvana Markovska-Simoska
Local Organizer

MEET THE TRAINERS

Marianne van den Bree

Cardiff University (<https://www.cardiff.ac.uk/people/view/126811-van-den-bree-marianne>)



Prof Marianne van den Bree studies the developmental pathways of mental health. Her work focuses on the genetic and environmental factors that increase or decrease risk of the development of mental health problems. She has a background in psychology, human genetics and epidemiology/ methodology. She started studying patients with Copy Number associated with high risk of neurodevelopmental disorder ~10 years ago. Her ExperienCes of people with cOpy number variation (ECHO) study at Cardiff University has since developed into one of the largest longitudinal research programmes of its kind (>800 individuals carrying high-risk CNVs as well as their unaffected family

members have to date been phenotyped in great detail; >150 participants have been assessed two or more times and Wave Four assessments are ongoing). She is part of a number of national and international collaborations. She is Lead of one of five Working Groups of MINDDS Consortium, which has brought together >30 EU countries and affiliated nations to spearhead research into CNVs and improve care for these patients. She furthermore leads one of five Subsites of the 22q11.2DS International Brain and Behavior Consortium (IBBC). She is also a PI of the IMAGINE study; the Medical Research Council (MRC) Centre for Neuropsychiatric Genetics and Genomics at Cardiff University; and the Cardiff National Centre for Mental Health. Marianne has published ~115 peer-reviewed papers, which have yielded >4520 citations on Scopus. Her research has won several impact-related awards, including the RCUK Societal Impact Award (2015) and the Cardiff University Social Innovation Award (2015).

Silvana Markovska Simoska

Macedonian Academy of Sciences and Arts



Her research interests are focused in the field of QEEG, Event Related Potentials (ERPs), brain mapping, biofeedback and neurofeedback applications in many psychiatric disorders. Implementation of neuromarkers in the clinical context to evaluate brain function and information flow, and use of neuromodulation techniques in clinical practice becomes her main professional goal in the following working years. She has participate in several national and international projects related to the brain electrical oscillations and cognition, defining of consciousness, advanced methods for estimation of human brain activity and connectivity, autism, forensic psychiatry and individualized psychotherapy. She has published more than 90 peer reviewed papers in the International and national journals and Conferences proceedings.

She is a visiting Associate Professor of Neuroscience. She serves in several International boards and scientific societies. She is also a co-founder of the Macedonian Association of Psychophysiology.

Ann Swillen

University of Leuven



Ann Swillen is professor at the Department of Human Genetics, KU Leuven and at the Department of Rehabilitation Sciences, KU Leuven (University of Leuven, Belgium). Trained as an educational psychologist, she is also affiliated to CME-UZ (the clinical unit of the Department of Human genetics), an international centre of excellence in the field of clinical and molecular genetics. A particular focus is on individuals with genetic, neuropsychiatric, and neurodevelopmental conditions that affect learning and behavior. Through a multifaceted collaborative approach with many disciplines, we aim for four goals:

1. Better define the studied neuro-genetic syndromes (e.g. 22q11.2 DS, 22q11 dupl., 22q13.3 DS, other CNV's ...);
2. Identify mechanisms of cognitive impairment;
3. Identify mechanisms for increased psychiatric risk;
4. Using specific neuro-genetic conditions as homogeneous genetic models to better understand the interaction among genetic, behavioral and environmental factors in developmental disorders.

Ultimately, a better knowledge of neuropsychiatric and neurodevelopmental conditions will help us to refine our treatment strategies and improve the life of affected children and their families.

Besides her research, Prof. Ann Swillen is (since 1994) the coordinator of the multidisciplinary 22q11 DS clinic, and is actively involved in sharing knowledge on the implications of genetic syndromes on cognition and behaviour and the practical implications for education/teaching etc... by giving multiple lectures to professionals on national and international meetings, and to national and international parent-patient associations. Prof. Ann Swillen is an international recognized authority in the field of development, cognition and behaviour in 22q11 DS and other CNV's, and she is author of more than 90 peer-reviewed scientific publications in the field of medical genetics and behavioral phenotypes. She is member of different international expert panels (e.g. international 22q11 DS Foundation, European 22q11 Alliance,...), and co-founder of the International Brain-Behavior 22q11 DS Consortium (2011) and the 22q11 DS Society (2014). She received the Angelo DiGeorge Medal (Award) during The 10th Biennial International 22q11.2 Deletion Syndrome Meeting in Sirmione, Italy (July 2016), for her outstanding and exceptional contribution to the understanding and treatment of the 22q11.2 deletion syndrome and for her commitment to patients. Prof. Swillen is holder of the recent inaugurated 22q11 DS/Vecarfa fund at the KU Leuven:

<https://gbiomed.kuleuven.be/english/research/50000622/exceptionalkids/22Q11DS>

Therese van Amelsvoort

Maastricht University



Professor van Amelsvoort is professor of Transitional Psychiatry and consultant Psychiatrist at Maastricht UMC. After finishing her medical studies in Rotterdam (1991), she worked as a medical and scientific advisor in Basel (Switzerland, 1991-1993) and as a medical doctor in Luxembourg (1993-1994). Subsequently, she trained as an academic psychiatrist at The Maudsley Hospital / Institute of Psychiatry in London (UK, 1994-2001).

She has had a longstanding interest in neurobiological mechanisms underlying psychosis and neurodevelopmental disorders, with a special interest in 22q11.2 deletion syndrome (22q11DS) which she has been studying for more than 20 years. She obtained her PhD in 2004 at the University of Amsterdam. Since 2012 she is working at The Department of Psychiatry and Psychology at Maastricht University Medical Centre, expanding the scope of her research and clinical work to youth mental health. She is co-founder of the Dutch Headspace centres, which opened its doors in January 2018.

Beate Nowakowska

Institute of Mother and Child in Warsaw



Beata Nowakowska is a Head of the Laboratory of Cytogenetics at the Department of Medical Genetics, Institute of Mother and Child in Warsaw. In 2009 she obtained her PhD degree in Medical Genetics at the Warsaw Medical University. She gained the experience in the field of genetics at the Universities of Toronto, Rockefeller in New York, Baylor College of Medicine in Houston (where she performed part of the doctoral thesis) and KU Leuven in Belgium (as a postdoc). Her research is focused on studying the basic mechanisms underlying genomic disease, with particular interest in role of copy number variation in common diseases such as intellectual disability or autism. The main area of current research is the identification of genes and networks causing constitutional developmental disorders with particular emphasis on phenotypic variability in patients with 22q11 Deletion Syndrome. She is an author and co-author of more than 50 peer review publications and a team member in several national and international projects related to these topics.

Samuel Chawner
Cardiff University



Dr Samuel Chawner is a postdoctoral research associate in psychiatric genetics at Cardiff University. He studied Natural Sciences at Cambridge University where he specialised in Experimental Psychology. He then completed his PhD at Cardiff University's MRC centre for Neuropsychiatric Genetics and Genomics, during which he examined the neurodevelopmental trajectories of children at high genomic risk of developing schizophrenia. He currently works as part of the IMAGINE-ID study, an MRC funded collaboration between Cardiff, UCL and Cambridge universities which investigates the impact of genomics on child development and mental health (www.imagine-id.org).

Hayley Moss
Cardiff University



I began working on the ExperienCes of people with cOpy number variation (ECHO) study at Cardiff University at the beginning of 2010. I have been involved in deep-phenotyping individuals with rare CNVs since then, firstly as a Research Technician where I saw our very first participating family, to co-ordinating and underpinning our CNV research programme. The study has grown into one of the largest longitudinal research programmes of its kind. I have extensive experience in collecting phenotypic data, securing ethical applications, and the day-to-day running of CNV research. For this training school I hope to give advice from the practical perspective of being involved in large multi-disciplinary rare CNV projects.

Hayley Moulding
Cardiff University



Hayley started her PhD in 2014 and during her first year she undertook three different research projects investigating various different psychiatric and genetic disorders including 22q11.2 deletion syndrome, attention-deficit hyperactivity disorder (ADHD) and schizophrenia. In 2015, she began her PhD with Professor Marianne van den Bree exploring sleep problems in children and adolescents with 22q11.2 deletion syndrome. This genetic syndrome puts individuals at high risk for psychiatric disorders, namely schizophrenia. Hayley has experience of using ambulatory sleep electroencephalography and actigraphy in young people. Her work sets out to inform and help families of individuals with sleep problems and 22q11.2 deletion syndrome. It could be used to help determine the likelihood of mental health problems, to identify those who are at risk and implement interventions with these families.

Andrew Cuthbert

Cardiff University



Andrew has been a postdoctoral researcher in genetic counselling at Cardiff University since 2014. Working in human genetics for over 30 years he has nearly 50 peer review publications including articles in Nature Genetics and The Lancet. His work now focuses on developing health information and services to improve care for people with developmental disorders. Taking a break from research in 2003 to retrain as a genetic counsellor for families with rare diseases made him appreciate the challenge of communicating complex medical genetic information to empower people to make informed choices about genetic testing, comprehend facts and adjust to the diagnosis.

A long interest in mental health issues drove Andrew's research towards addressing concerns about recognising psychiatric disorders in individuals with rare genetic disorders, particularly children with intellectual disabilities where mental illness is frequently undiagnosed and untreated. Andrew's work, therefore, prioritises improving information and support for families concerning psychiatric risks and impacts of genomic variants. His research links with his role as liaison psychiatry genetic counsellor, where he provides genetic counselling and triage for adults with neurodevelopmental disorders through joint clinical genetics-psychiatry clinics supported by a large multidisciplinary clinical team which he runs.

SKOPJE

Skopje is the capital of the Republic of Macedonia, the City that lies in the heart of the Balkan Peninsula, at the crossroad of important communications, a city with a 2000 years old tradition. Skopje is a modern city with population of almost one million and presents Macedonia's major political, economic, educational and cultural center. It continues to be a focus for new residents, economic development, construction and refurbishment. Skopje urban area extends across the Skopje valley for approximately 30 kilometers (18.75 mi) in width and comprises 10 municipalities. Skopje also is a very attractive tourist destination with its fortress, cultural and historical monuments, archaeological sites, sport halls, caves in the canyon of the River Treska and Lake Matka and a health spa in the eastern part of the city.

Skopje is steadily becoming a vital regional route for international flight operators. The town with the beautiful quay of the Macedonian river "Vardar", the narrow streets in the Old Bazaar which is the biggest bazaar preserved in the Balkans today, the town is internationally famous for being the birthplace of Mother Teresa. He has blossomed into a thriving, stimulating city to explore, defining itself as an exciting tourist destination with the 1500 years old fortress Kale and monastery St. Pantelejmon with the fresco "Lamentation of Christ", with the first signs of the Renaissance, the Islamic monuments Sultan Murat's- Hjukar Mosque, the Daut Pasha's bath.

Places to visit:

Fortress "Kale"

The Skopje Fortress, commonly referred to as Kale Fortress, or simply Kale (from kale, the Turkish word for 'fortress'), is a historic fortress located in Skopje, the capital of the Republic of Macedonia. It is situated on the highest point in the city overlooking the Vardar River. The fortress is depicted on the coat of arms of Skopje, which in turn is incorporated in the city's flag. The first fortress, according to research and available data, is believed to have been built amidst the 6th century A.D., on land that had been inhabited during the Neolithic and Bronze ages or roughly 4000 B.C. It was constructed with yellow limestone and travertine and along with fragments of Latin inscriptions, asserts the idea that the fortress originated from the Roman city of Skupi, which was completely destroyed by an earthquake in 518. The fortress is thought to have been reconstructed during the rule of emperor Justinian I and constructed further during the 10th and 11th centuries over the remains of emperor Justinian's Byzantine fortress which may have been destroyed due to a number of wars and battles in the region, such as that of the uprising of the Bulgarian Empire against the Byzantine Empire under the rule of Peter Delyan. Not much is known about the Medieval fortress apart from a few documents which outline minor characteristics in the fortress' appearance.

<http://www.exploringmacedonia.com/fortress-kale.nspj>

Memorial house of Mother Teresa

The Memorial House of Mother Teresa stands in the center of Skopje, the city the missionary was born in and called home until she was 18. Built to the east of Macedonia Square on the land where the Sacred Heart of Jesus Roman Catholic Church once stood, and where Mother Teresa was baptized, the house opened to the public in 2009.

Travelers can visit to explore the museum and its displays of life-like sculptures depicting Mother Teresa and her family, including the one of the humanitarian as a 10 year old sitting on a stone and holding a pigeon. Exhibits also include memorabilia such as letters, awards, relics and photographs, while an upper-level glass-walled chapel holds mass twice a week. Visitors can head to the gift shop on the main floor to browse books and Macedonian souvenirs. The memorial house also occasionally hosts cultural exhibits <http://exploringmacedonia.com/memorial-house-of-mother-teresa.nspj>.

Millenium Cross

The Millennium Cross (Macedonian: Милениумски крст, Latinic: Mileniumski krst) is a 66 metre-high cross situated on the top of the Vodno Mountain in Skopje, Republic of Macedonia. It was constructed to serve as a memorial of 2,000 years of Christianity in Macedonia and the world. The construction of the cross began in 2002 and was funded by the Macedonian Orthodox Church, the Macedonian government and donations from Macedonians from all over the world. The cross was built on the highest point of the Vodno mountain on a place known since the time of the Ottoman Empire as "Krstovar", meaning "Place of the cross", as there was a smaller cross situated there. On 8 September 2008, the independence day of the Republic of Macedonia, an elevator was installed inside the cross. In 2009, a restaurant and a souvenir shop were opened next to the cross. In 2011 the Millennium Cross ropeway was opened. The ropeway is three and a half km long. At night the cross shines down over the city <http://www.exploringmacedonia.com/millennium-cross.nspix>.

Old Bazaar

The Old Bazaar (Macedonian: Стара Чаршија, Stara Čaršija from the Turkish: Çarşı meaning marketplace, Albanian: Çarshia e Vjetër) in Skopje is the largest bazaar in the Balkans outside Istanbul. It is situated on the eastern bank of the Vardar River, stretching from the Stone Bridge to the Bit-Pazar and from the Skopje Fortress to the Serava river.

The Old Bazaar falls within the borders of Centar and Čair municipalities and is a protected national landmark. The earliest known documented sources that point out to the existence of a merchant quarter on the bazaar's territory date back to the 12th century. During the Ottoman rule with the city, the place underwent a rapid development to become city's main economic and merchant centre, evidenced by about 30 mosques, numerous caravanserais and hans, as well as other Ottoman buildings and monuments. The bazaar was heavily damaged by the earthquakes that occurred in 1555 and 1963, and the destructions caused during the First and the Second World War. Subsequently, it was reconstructed on several occasions and nowadays represents the only remaining cultural monument in the Republic of Macedonia, which has kept its multicultural heritage of different civilizations.

The Ottoman architecture is predominant in the Old Bazaar, although remains of the Byzantine architecture are evident as well, while the most recent reconstructions lead to the application of elements specific to the Modern architecture. Most of the buildings that once were used to host the travellers or as hamams [disambiguation needed] for the political dignitaries were transformed into museums and galleries, which today are used with the main purpose to host art exhibitions, concerts and other cultural events. Nowadays, however, the place and its proximity are still home to several mosques, türbes, two churches and a clock tower, that together with the buildings of the Museum of Macedonia and the Museum of Modern Art form the core of the modern bazaar. The Museum of the Skopje Old Bazaar, situated in Suli Han, includes collections of artifacts that evidence the life within the bazaar, its development, and the crafts that were practiced during its history. On 13 October 2008, the Macedonian Parliament adopted a law recognising the Skopje Old Bazaar as a cultural heritage of particular importance for the country with a permanent protection.

<http://www.exploringmacedonia.com/old-bazaar.nspix>

Canyon "Matka"

Matka - A gorge in which a rich complex of mediaeval building survives, including churches, monasteries and remnants of a fortress (the mediaeval town of Matka). There are dozens of caves and large number of endemic plants and animals. The Canyon covers an area of around 5.000ha and is located 15km south-west of Skopje. By its morphogenetic characteristic, it is a breakthrough gorge. Krastic form deserve particular attention here-ten caves with their length ranging between 20 and 176 meters and two vertical chasms with a depth up to 35 meters. Matka was one of the largest refugee centers during the glacial period resulting in the presence of high number of relic and endemic plants, 20% are endemic or relic spices. Among Tertiary relics, the most significant are the Kosani violet and Nataya's Ramonda (*Ramonda natalie*). It is also important to mention that there are 77 species of Balkan endemic small butterflies in area of Matka Canyon, while 18 other species are new to the science. The Treska canyon is vertically cut into the massive of Suva Mountain. The different formations in the canyon like the karrens, flutes, valleys, cracks, crevices and caves have been formed by a long term impact of the mountain rivers, as well as by great temperature oscillations. In the surroundings of the Treska Canyon one can find dozens of caves, the most beautiful ones being Vrelo, Krshtalna and Ubava. The caves are filled with numerous stalagmites, stalactites and dripstone pillars and some of them are illuminated. The diversity of dripstone adornments has been captured by a well deployed illumination. Visiting tours are organized by an official guide. The Treska Canyon is the most important alpine climbing center in northern Macedonia. The major climbing season in Matka begins in spring, round the Easter holidays when visitors come from countries from all over Europe. The season continues throughout summer and fall until the end of November. The Treska Canyon is also open for kayaking. Built in 1389 the Monastery of St. Andrew's is located on Lake Matka (17 km away from Skopje) and contains frescos of great artistic importance. The Monastery of St. Nicholas Shishovski is situated on top of a cliff above Lake Matka giving the visitor a spectacular view of the lake and its surroundings. There is no precise information when this monastery was built, however it is known that it was first mentioned in the 17th century. Unfortunately, during the 18th century the monastery was abandoned, only to be resettled the following century. Close to both monasteries of St. Andrew's and of St. Nicholas is the Matka Monastery dating from the 14th century, its frescos dating from the 15th century. The monastery is located on the left side of river Treska at a distance of about 12 km from Skopje. Church of St. Andreas - built and decorated with frescoes in the 14th century. The compositions - "Last Supper", "Descent from the Cross", and "Prayer on the Mount of Olives" deserve a special attention <http://www.exploringmacedonia.com/matka-canyon.nspix>

There are many other places to visit. For more information:

<http://www.exploringmacedonia.com/skopje.nspix>

<http://www.visitskopje.mk/>

Macedonian Food

The traditional Macedonian cuisine combines Balkan and Mediterranean characteristics, inherited largely from Turkish tastes that prevailed during long centuries of Ottoman rule. The travelers are delighted with the taste of Macedonian tomato, carrots, lettuces, parsley, onions, an garlic, and not to mention the rich flavor and aroma of fresh fruit, such as watermelons, melons, cherries, apricots, grapes, peaches, and others. Most herbs are collected in the local mountains and in the countryside, and these herbs are renowned for their taste, have scent and healing properties. Try some of the most famous, traditional Macedonian specialties such as Tavche Gravche, ajvar, sarma and burek while having a glass of the best beer or wine. For more information:

<https://www.likealocalguide.com/skopje/eating>

<https://www.lonelyplanet.com/macedonia/skopje/restaurants/a/poi-eat/360132>