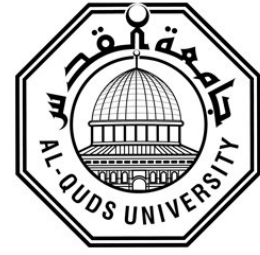


Deanship of Graduate Studies

Al- Quds University



**The Interplay of Serotonin and Clock Genes in
Mediating the Interaction Between Clinical Depression
and Chronotypes**

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M.Sc. Thesis

Jerusalem- Palestine

1440 - 2019

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Interaction Between Clinical Depression and Chronotypes**

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A Thesis Submitted in Partial Fulfillment of the Requirements for
the Degree of Master of Biochemistry and Molecular Biology -

Faculty of Medicine - Al-Quds University

1440 - 2019

Deanship of Graduate Studies

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Master Thesis Submitted and Accepted Date: 5/8/2019

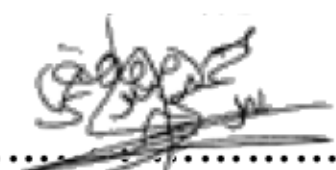
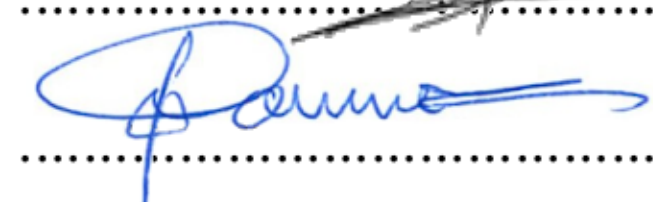
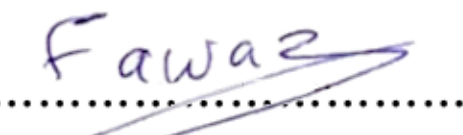
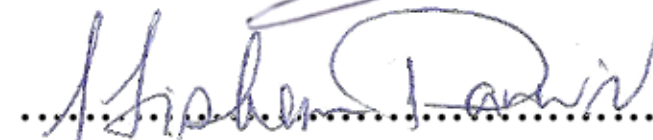
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Jerusalem – Palestine

1440 – 2019

Dedication

To my family, who supported me all the way.

To my friends, and people I met in my journey,


You were a great help and source of inspiration,

To you I dedicate my thesis.

Abdelrahman Salah Jabr Sawalma

Declaration

I certify that this thesis submitted for the degree of master, is the result of my own research, except where otherwise acknowledged, and that this study has not been submitted for a higher degree to any other university or institution.

Signed:

Abdelrahman Salah Jabr Sawalma

Date: 5 / 8 / 2019

Acknowledgment

In the beginning of this thesis, I find it very important to thank everyone who helped me finalize this thesis the way it is now. I would like to thank my supervisor, Mohammad Herzallah for his continuous support, and for showing me the way of science. I would like to thank the Palestinian Neuroscience Initiative for providing me with subjects and blood samples, and most importantly for being a second family to me. Specifically, I would like to thank Anfal Abuhilal for her invaluable help in various aspects, including optimizing the protocols for gene analysis.

Abdelrahman Salah Jabr Sawalma

Abstract

The biological clock regulates a myriad of physiological functions. It is synchronized by various environmental cues and follows a 24-hour cycle with variable start and end points that are referred to as “chronotypes”. The suprachiasmatic nucleus (SCN) in the brain orchestrates the circadian rhythm as the central clock of the body, with oscillating expression of biological clock genes, including the *PERIOD* genes. The biological rhythm is modulated by serotonergic neurotransmission, with the largest afferent projection to the SCN coming from the serotonergic median raphe nucleus. Also, disruptions of the biological rhythm contribute to the pathophysiology of various psychiatric disorders. For instance, in clinical depression (a hypo-serotonergic state), patients exhibit a generalized disruption of their biological rhythm in the form of disturbances in sleep, hormonal, mood and temperature rhythms.

The main aim of our study is to investigate the intercorrelations between four factors: genotype, depression symptoms, chronotype and brain functionality. We examined the interaction between serotonin neurotransmission, electroencephalography (EEG) brain oscillations, chronotype, and the expression of depression symptomatology in healthy subjects. In particular, we examined naturally-occurring genetic polymorphisms in the 5-HT1A receptor gene and the *PER2* clock gene as indirect measures of serotonergic neurotransmission and the circadian clock, respectively.

We recruited Sixty-three healthy subjects who underwent evaluations for biological clock phase (chronotype), clinical depression symptomatology. A subgroup of the subjects underwent EEG testing to measure their baseline brain activity and response to various stimuli. A proportion of the subjects were genotyped for 5-HT1A receptor (28 subjects) and the *PER2* polymorphisms (41 subjects).

Our results confirmed the interaction between the four studied factors. We found that subjects with the later chronotype express higher level of depression symptoms. The power of brain's theta oscillation was positively correlated with chronotype. We found that females had an earlier chronotype than males, which can be explained by the differences we found in their genotypes. This can be considered an indirect evidence for the correlation between genotype and chronotype, but a direct link that confirms these results is still lacking.

This study provides preliminary evidence for the molecular underpinnings of the interaction of biological clock functioning with serotonin as a potential mechanism for the development of clinical depression. Future studies should include a larger sample size and patients with clinical depression to clearly find the differences between healthy and clinical states in terms of chronotypes, genotypes and brain functionality. This will help build a comprehensive overview of the underlying pathophysiology of clinical depression. Ultimately, this can inform the development of novel treatment modalities that take into account not just the symptomatology of clinical depression, but also genetic, physiological, and cognitive correlates.

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Definitions

Chronotype: The individual variations in the biological clock, it appears as a personal preference of sleep and wake timing, activity timing, meal timing ... etc. Some people tend to be later chronotypes, who sleep later and wake up later, become more active at a later-than-average time. Some are early people, who tend to wake up earlier, sleep earlier and become more active at an earlier time.

Zeitgebers: German for “Time givers”, are the environmental cues that drive our biological clock, such as sunlight, which is the main zeitgeber. It also includes some social cues and behavioral cues.

Abbreviations

5-HT1A: Serotonin 1A

BMAL1: Brain and Muscle ARNT-like Protein 1

CLOCK: Circadian Locomotor Output Cycles Kaput Protein

CRY1: Cryptochrome 1

CSK-3 β : Glycogen Synthase Kinase 3 β

EEG: Electroencephalography

MDD: Major Depressive Disorder

PCR: Polymerase Chain Reaction

PER1: Period 1 protein

RFLP: Restriction Fragment Length Polymorphism

SCN: Suprachiasmatic Nucleus

SSRI: Selective Serotonin Reuptake Inhibitor

ZT: Zeitgebers (Time Givers)