Thinking in network terms

Brain functional networks in migraine and the analogy with the patient's social network

Master of Science Thesis

by

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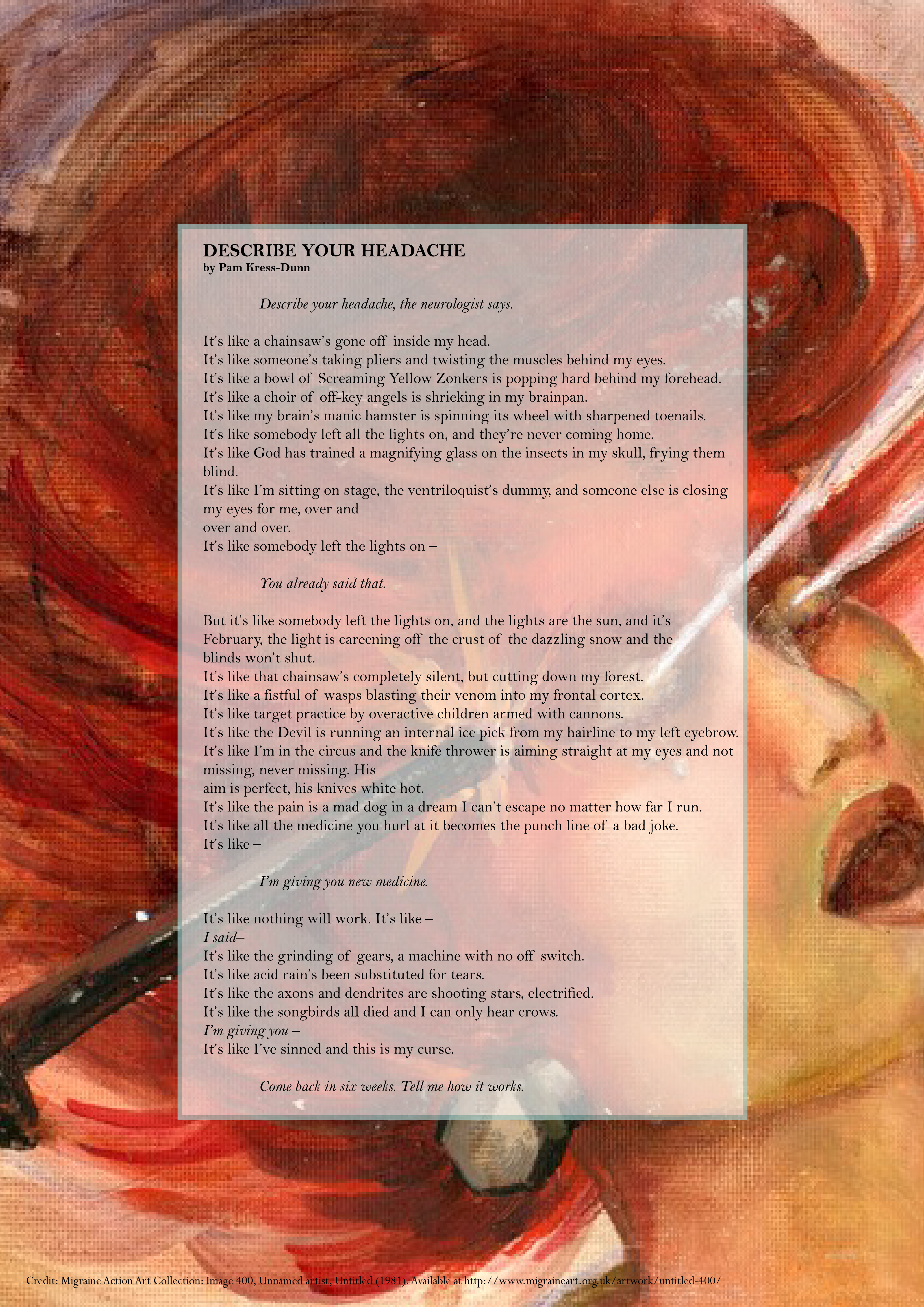


DESCRIBE YOUR HEADACHE

by Pam Kress-Dunn

Describe your headache, the neurologist says.

It's like a chainsaw's gone off inside my head.
It's like someone's taking pliers and twisting the muscles behind my eyes.
It's like a bowl of Screaming Yellow Zonkers is popping hard behind my forehead.
It's like a choir of off-key angels is shrieking in my brainpan.
It's like my brain's manic hamster is spinning its wheel with sharpened toenails.
It's like somebody left all the lights on, and they're never coming home.
It's like God has trained a magnifying glass on the insects in my skull, frying them blind.
It's like I'm sitting on stage, the ventriloquist's dummy, and someone else is closing my eyes for me, over and
over and over.
It's like somebody left the lights on –

You already said that.

But it's like somebody left the lights on, and the lights are the sun, and it's February, the light is careening off the crust of the dazzling snow and the blinds won't shut.
It's like that chainsaw's completely silent, but cutting down my forest.
It's like a fistful of wasps blasting their venom into my frontal cortex.
It's like target practice by overactive children armed with cannons.
It's like the Devil is running an internal ice pick from my hairline to my left eyebrow.
It's like I'm in the circus and the knife thrower is aiming straight at my eyes and not missing, never missing. His
aim is perfect, his knives white hot.
It's like the pain is a mad dog in a dream I can't escape no matter how far I run.
It's like all the medicine you hurl at it becomes the punch line of a bad joke.
It's like –

I'm giving you new medicine.

It's like nothing will work. It's like –
I said–
It's like the grinding of gears, a machine with no off switch.
It's like acid rain's been substituted for tears.
It's like the axons and dendrites are shooting stars, electrified.
It's like the songbirds all died and I can only hear crows.
I'm giving you –
It's like I've sinned and this is my curse.

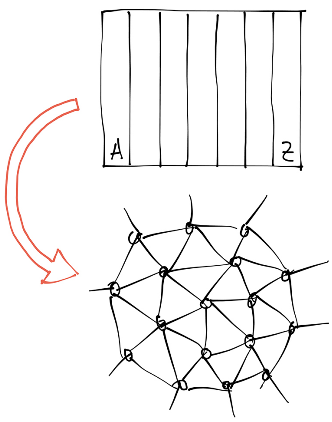
Come back in six weeks. Tell me how it works.

Credit: Migraine Action Art Collection: Image 400, Unnamed artist, Untitled (1981). Available at http://www.migraineart.org.uk/artwork/untitled-400/

Preface

We have always lived in an interconnected world, but we have been remarkably unaware of it for a long time. Surely human kind knew that it was not independent of other systems within its environment, like social systems, the economy or the forces of the Universe. Yet the prevailing manner of observing and explaining the world has been as a collection of separate and isolated systems, such as the aforementioned. It is a way of thinking that is linear and systematic, like a multipart encyclopedia with a sorting order from A to Z.

However, this view has changed drastically over the last decades. Globalization and innovations like wireless technologies, have forced us to become aware of economical, social, cultural and political connectedness. For example, cars are no longer merely produced by classic car manufacturers, as well as by IT companies like Google.



The prevailing way of thinking is changing from linear and systematic to a network way of thinking. Image by Weinberg (2015).

Network connectedness slowly became part of our world. Consequently, the categorized and systematic "encyclopedia" way of thinking might become an obstacle, hindering the flow of communication instead of supporting it. The increasing awareness of the world's connectedness requires a new way of thinking, one that supports our changing thoughts and actions: a way of thinking in network terms.

This thesis combines two research projects on networks; a project about the migraine brain and a project about the migraine patient. The analogy and synthesis of the two will bring the projects together, resulting in new lessons for network thinking.

Summary

In this thesis, two seemingly completely different systems were analyzed: the migraine brain and the migraine patient. However, similar issues can be seen by representing both as *networks*, which are abstract representations of the system. The *neuronal network* of the migraine brain most likely deviates from healthy brain networks, but it is unknown through what mechanisms possible deviations affect the brain (and hence what interventions to perform). Similarly, interventions in the social network might be beneficial for reducing the expectation gap between the patient and physician, as good communication between the two may influence health outcomes. However, it is unknown through what *psychosocial* mechanisms in the social network of the migraine patient these interventions could work. The overlap between the two therefore arises from similar blind spots. As such, an analogy was used to adopt one way of thinking for two different systems, ultimately to fill in the blind spots. The two projects were carried out separately, after which the synthesis of the two revealed new insights on both the systems and network thinking in general.

The neuronal network
Migraine is associated with brain dysfunction, which possibly originates from disturbances in the interactions between dynamical neuronal assemblies. Such abnormalities have been observed outside of attacks (in the *interictal state*) by means of external stimulation of the brain, but it is not clear yet whether these disturbances are also present without any stimulation. Therefore, the topology of the functional network of the brain (i.e., the network representing the interaction between the assemblies) was mapped in the *resting state* by means of EEG, functional connectivity measures and graph analysis subsequently. We revealed the functioning of the network on a global and a local level, which yielded no significant differences between functional networks of migraineurs and those of healthy controls. Therefore, we concluded: "this type of graph analyses are not sensitive to any possible abnormalities in the interictal migraine functional network in resting state. Brain dysfunction in migraine might occur only on a local level, making EEG-based graph analysis a less suitable technique to uncover such abnormalities."

The social network
A gap between patient and physician arises when expectations are not (correctly) aligned, possibly resulting in poor medication adherence and poor treatment outcome. The headache-specific locus of control underlies the expectations of patients, and hence was the topic of this research. In order to discover possible interventions to increase internal headache-specific locus of control, the patient's social network was mapped by means of a survey. We assessed the functioning of the network by means of graph theory based on a dichotomy of the sample in profiles with high versus low internal headache-specific locus of control. However, the sample was too small to divide. Hence, we assessed the link between the three subscales of locus of control (internal, medical professional and chance) and the graph theory measures. This yielded a significant positive correlation between node importance and internal locus of control. The significance was disputed due to the small sample size. Interventions in the social network were therefore sought on face value. We argued that these type of graph analyses are not suitable for complex social networks, and that social network analysis as such has too little resolution to accurately model the system.

The synthesis of the two projects revealed that migraine might work through multiple brain functional networks simultaneously, and that possibly not all psychosocial mechanisms in the social network are known. Furthermore, we argued that network analysis filters the complex part out of complex systems, and, as such, is an unsuitable tool to point out deviations and associated interventions in the complex network.

Contents

PART I

GENERAL INTRODUCTION

1 Introduction

This thesis combines two research projects, as a partial fulfillment of two Master of Science programs (Mechanical Engineering and Science Communication). The two projects each concentrate on the analysis of a different system, but using the same method: graph theory. As such, the focus of this research will be on the analogy between both.
To start, this chapter begins with an introduction of the two systems, which are the migraine brain and the migraine patient. Then, relevant background knowledge is presented in Section 1.2 and the research aim (Section 1.3) and approach (Section 1.4) are discussed. Finally, Section 1.5 presents the thesis outline.

1.1 Introduction

The working of the human brain has been a mystery for centuries and today, the brain is still regarded as one of the most complex objects in our Universe. It consists of dozens of brain regions and billions of *neurons* (brain cells) that are all interrelated in order to communicate, either directly or indirectly. In this way, even complicated higher-order brain functions can be established. With an estimated amount of a quadrillion connections in the brain, the corresponding *neuronal network* (the wiring pattern of interconnections) is massive. Although it is known that its structure enables rapid and cost-efficient information transfer between the brain's elements, the neuronal network remains poorly understood. Nevertheless, strong evidence implies that the network is abnormal in case of brain disorders, like migraine (Dance, 2015; Bullmore and Sporns, 2012; Liu et al., 2012). Migraine is a recurrent headache disorder, but it is unknown what biological mechanisms contribute to the development of attacks (Scheffer et al., 2013). Therefore, one of the ultimate goals in migraine research is to understand *where* the neuronal network deviates from healthy structures. A better understanding of the mechanisms underlying migraine will improve our understanding of migraine pathophysiology and thereby improve treatment.

Such knowledge is highly in demand, as migraine treatment today continues to be a matter of customization: the complexity of the disorder requires the cooperation of both patient and health care provider (hereafter: physician) to find a suitable solution. Therefore, the patient-physician relationship has a direct impact on the achievement of successful treatment, hence communication plays a pivotal role in migraine management (Peters et al., 2004; Leroux et al., 2017). However, patient expectations might differ greatly from those of physicians, which creates an expectation gap (Lipton and Stewart, 1999; Gallagher, 2004). As expectations have a major influence on treatment satisfaction (Patrick et al., 2003), the gap between patient and physician might be detrimental and lead to aborting treatment; ineffective communication has demonstrated to decrease satisfaction with care and medication adherence (Cottrell et al., 2002). In other chronic conditions, effective physician communication has led to better patient understanding and thereby better outcome (Patwardhan et al., 2007). Knowledge on how to close the gap and increase effective communication might therefore be beneficial for migraine treatment too.

This research combines a project on the migraine neuronal network with a project on the migraine patient's *social network*. Ultimately, an analogy and the corresponding synthesis of the two projects will show how we can use one way of thinking for two seemingly completely different challenges.

Why an analogy?

Our world is getting more and more aware of the advantages of interconnectedness. As such, the concept of multidisciplinary teamwork is a well-known way of working nowadays, especially in healthcare: health professionals from various disciplines integrate their separate knowledge and approaches, with the aim to collaboratively make a patient-centered treatment plan. The team enriches its understanding of the patient's situation by exchanging perspectives and experiences, in order to align their aims and harmonize a common outcome. Multidisciplinary team care is especially important in migraine to enhance the quality of headache treatment (Gunreben-Stempfle et al., 2009; Gaul et al., 2011).

However, multiple barriers are faced in multidisciplinary teamwork and one such barrier can be found in communication. Communication barriers can originate from a lack of shared aim, as the health professionals feel that their own approach or field of expertise should be prioritized. Instead of concentrating on the best practice to the patient by combining forces, the professionals might only focus on their individual perspectives (Roncaglia, 2016). Possibly, communication barriers exist due to the fact that the professionals do not speak the same language. According to Roncaglia (2016), "language used by professionals can have its own syntax and definitions which are closed to the particular professional group in question. On the surfaces this phenomenon can be underestimated whilst in effect it can lead to a number of misinterpretations and confusion." Therefore, the analogy can serve as a powerful tool to fill the blind spots among professionals.

In this research, the blind spots are the routes of communication in both networks. That is, migraine affects the functioning of the neuronal network, but it is unknown where the network deviates and what routes are affected. Therefore, it is not exactly known what interventions by means of medication to apply. Similarly, patient-physician communication (the "migraine") may affect the patient's health outcomes, but most likely via indirect routes. Similar to the brain, the mechanisms through which patient-physician communication influence the patient are unknown. Therefore, it is not clear what interventions in the social network could contribute to improve patient-physician communication and close the expectation gap.

1.2 Background

Background knowledge about migraine and knowledge about network thinking, especially about the brain and the patient, is provided in this section.

What is migraine?

Migraine is characterized by attacks of severe, throbbing headache, often at one side of the head. Rather than a normal headache, migraine is a *chronic brain disorder* and an attack can temporarily disable the migraineur to the point of complete invalidity. As such, it has a huge impact on the sufferer's normal daily functioning: migraine causes absenteeism and reduced productivity at home, school or work (Lipton et al., 2003). With around 5 million working days yearly missed in the Netherlands due to migraine, the economic burden is substantial (Carpay, 2013).

Migraine usually first occurs during childhood, after which attacks are lifelong recurring with a frequency ranging from once a year to every week. One attack can last for a few hours up to several days, during which movements or external stimuli can exacerbate the pain (Pompili et al., 2010). Most *migraineurs* (individuals suffering from migraine) experience associated symptoms during an attack, like nausea or an extreme sensitivity to light, sound and/or smell. Prior to the headache, approximately one-third of migraineurs endure visual disturbances, known as an *aura*. The aura causes temporary loss of sight (Goadsby, 2003). A typical migraine aura is depicted in an art painting by a migraineur in Figure 1.1.

The Global Burden of Disease survey (GBD) ranked migraine as the seventh most disabling disorder in the world in 2015 and even the third most disabling for people between 15-49 years old. Not only the attack itself has a huge impact on the life of sufferers, but the fear of an attack also contributes a large part of the burden (Giannini et al., 2013). Furthermore, migraine has an impact on the social and family life, and a sense of guilt towards family members is inherent to the disorder (Antonaci et al., 2008). Migraine therefore has a considerable effect on the individual, the family and society.

Figure 1.1: Image depicting migraine aura. The image was made by a participant in the third migraine art competition (rewarded the consolation prize). Credit: Migraine Action Art Collection: Image 315, Unnamed artist, Untitled (1985). Available at http://www.migraineart.org.uk/artwork/untitled-315/

Thinking in network terms

Due to the growing availability of data on a wide range of (complex) systems, the network perspective as an approach to understand systems (e.g., the neuronal network or the social network) is increasingly applied. Network thinking suggests that the connections between the parts of a system are more important than the parts themselves. The power of this perspective lies in the high degree of abstraction; thinking in terms of networks helps us recognize patterns, processes and principles that apply to a wide range of structures around us. That is, even though the elements and mechanisms of interaction can be completely distinct, systems often share common network structures and show similar macroscopic behavior (Bullmore and Sporns, 2009). Consequently, adopting a network perspective helps us understand better how systems unfold over time (Weinberg, 2015).

The language of networks in order to characterize patterns is *graph theory*. Graph theory originates from the problem of the seven bridges of Königsberg, resolved by Euler in 1736 (see Figure 1.2). In Königsberg, Russia (now known as Kaliningrad), two islands in the Pregel river were connected with the mainland by seven bridges. The challenge was to cross all seven bridges only once and ultimately finish at the starting point. Euler transformed the problem into an abstract network by representing the land as nodes and the bridges as connections, or a so-called graph. In this way, he could quantify mathematical characteristics and prove that the Königsberg challenge is impossible to solve (Bullmore and Sporns, 2009; Stam and Reijneveld, 2007).

A graph is an abstract representation of a real-world system, in terms of *nodes* (the elements) and *edges* (the connections between the elements). In case of social networks, we speak of *alters* and *ties*. Together, the nodes and edges form a spatial representation of the network. Typical behavior of any network can be mathematically described with the general principles of graph theory. The power of graph theory lies in its generalized application, because we can freely designate

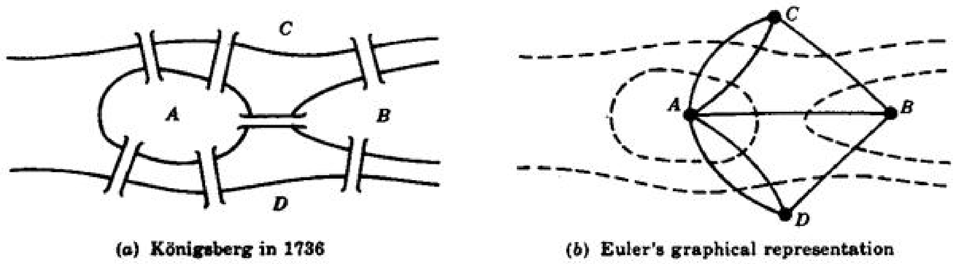


Figure 1.2: Euler proved that the challenge of the seven bridges of Königsberg (a) is impossible to solve by means of graph theory (b). A, B, C and D represent land surrounded by water (Source: McCormick, 2013).

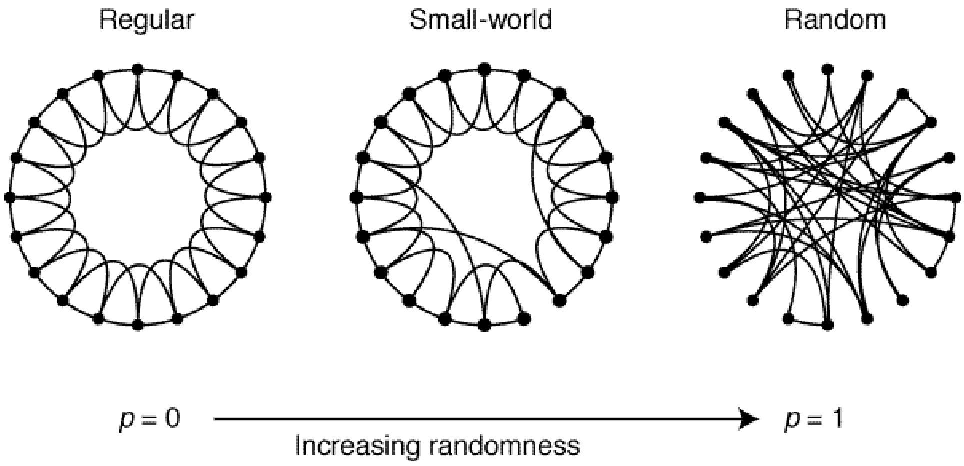


Figure 1.3: A small-world network ranges between the two extremes of a regular network and a random network (Source: Watts and Strogatz, 1998).

nodes and edges to represent the graph. This makes it a suitable tool for quantitative comparisons between networks. However, it also means that there is no gold standard for defining nodes and edges, which at the same time creates a weakness (Rubinov and Sporns, 2010).

A phenomenon of graph theory often associated with real-world systems is *small-worldness*. The phenomenon was first seen in social networks, in which the term "six degrees of separation" is used: the link between any two random strangers on earth is only six steps on average, because the two often share a mutual acquaintance (sometimes via intermediaries). In other words, there is a short path between cliques of a typical friendship circle (Reijneveld et al., 2007; Stam and Reijneveld, 2007).

Watts and Strogatz (1998) were the first to mathematically describe small-worldness (see Figure 1.3). The small-world network is characterized by a structure with a high amount of cliques (or *clustering)* and a short *path length* (the amount of steps between any two nodes in the network). As such, its structure lies in between the two extremes of a regular and a random network. The regular network shows high clustering, but also high path length; information transfer is slow, but robust. Starting from the regular network and considering that each edge has a chance p of being randomly rewired, the network becomes random when $p = 1$. The random network is characterized by much shorter path lengths, but with low clustering; information transfer is fast, but at the cost of low robustness. Therefore, if p is slightly increased and only few edges are rewired, the network remains high clustered but with a decreased path length; information transfer is fast and robust. This behavior was found in many systems, including both the human brain and the social network (Watts and Strogatz, 1998).

The human brain as a network

The neuronal network has an ingenious architecture that allows for rapid and cost-efficient information transfer. Efficiency on the one hand, requires a high level of interconnectedness and thus a high number of connections; if all elements would be connected to each other, communication would be the most efficient. However, the building and running of anatomical connections costs metabolic energy. The neuronal network therefore negotiates a trade-off between maximizing efficiency and minimizing costs (Bullmore and Sporns, 2012).

To achieve this structure, each neuron is connected to only a small fraction of around thousands of neighbors, the concept of which is shown in Figure 1.4. In the brain, spatially close neurons form (dynamical) assemblies with short-distance connections, thereby keeping energetic costs low. Typically, such local assemblies specialize for some aspects of perceptual or motor processing (e.g., color, depth, motion). The local assemblies are highly interactive and functionally coupled by means of unifying their activity (*synchronization*). In turn, long-distance connections link multiple specialized assemblies to establish global information processing. This allows for high efficiency of information transfer, although at high costs. As an analogy, one can imagine a full arena in which people close together can talk easily, and of which some need an expensive walkie talkie to communicate with the other side. As such, a single perceptual or cognitive function can involve many areas far apart in anatomical space, unifying their activity into a coherent whole (e.g., vision) (Varela et al., 2001; Bullmore and Sporns, 2012).

The connections within and between the assemblies are dynamic; that is, the *functional* network created by the flow of communicating neurons changes over time in the order of milliseconds to minutes. In other words: the functional network does not work like a pre-programmed machine merely looking for the most optimal cost-efficient information flow. Instead, it is flexible and highly prone to change. In turn, the communication flow is enabled by an underlying *structural* network of anatomical connections. It is comparable to cars (functional network) driving on roads (structural network); the cars can only use the available roads, but are still in control which roads to take. This road network changes less quickly, in the order of days to years. The way in which the neurons are placed inside the neuronal network, the network *topology*, is thought to enable brain characteristics, like small-worldness and hierarchy. Possibly, such properties make the brain a flexible system (Rubinov and Sporns, 2010; Stam and Reijneveld, 2007; Honey et al., 2007).

Brain network studies focus on patterns of simultaneously active brain regions. By approaching the brain and its corresponding information flow from a network perspective, the brain's structure and function can be examined more holistically; it allows for a better understanding of the interacting dynamic processes in the brain than it would by studying separate brain regions. Similarly, it offers new insights in brain disorders by pointing out possible aberrant network structures in migraine using graph theory (Allen et al., 2012).

The patient as a network

Many other systems can be studied from a graph theory perspective to examine the network's behaviour and assess the level of e.g. information flow. One such network is the social network. The rise of social network analysis started around 1950. At that time, individual and group behavior was sometimes inexplicable by considering only demographic groups (villages), kin groups or tribes (Berkman et al., 2000). It was noticed that the access to jobs, marriages, political activities and other behaviors traversed such groups. Social network models provided a way to understand the traversing connections and other properties of the network.

Hall & Wellman (1985) state that "social network analysis focuses on the characteristic patterns of ties (connections) between actors in a social system rather than on characteristics of the individual actors themselves and use these descriptions to study how these social structures constrain network members' behavior." Social network analysis focuses on the content which flows through the network, similar to the brain's functional network. An elaboration of this analogy is given in Chapter 2.

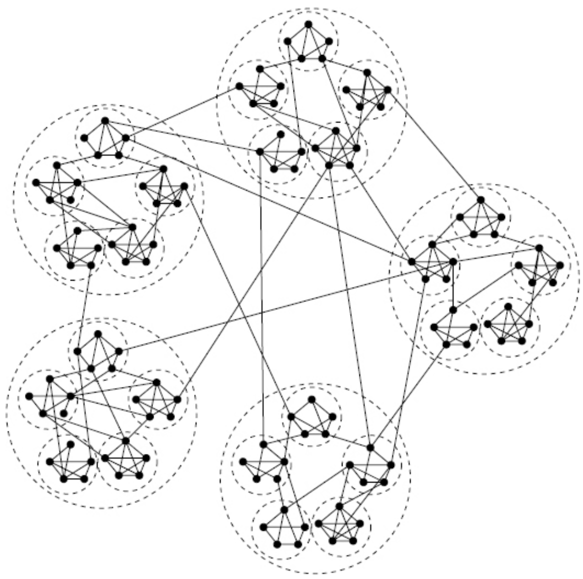


Figure 1.4: In the brain, short and long-distance connections ensure that the assemblies interconnect their activity, thereby forming a coherent whole (Source: Kaiser et al., 2007).

As every person is nested in a complex system of social connections, so is our health. That is, mechanisms working within the social network (e.g., social support or social engagement) influence our health behaviours, like smoking, disease spreading and even an individual's level of feeling responsible for his own physical and mental well being (Dhand et al., 2016). An example of social network analysis in health is given in a study by Dhand et al. (2016). They showed that people who arrived at the hospital later than 6 hours after an acute ischaemic stroke had small social networks with strong ties compared to those who arrived faster than 6 hours. In case of the late arrival, there possibly is an over-reliance on strong ties (who might downplay the symptoms) and a lack of weak ties (Dhand et al., 2016). Despite the rise of social network analysis, the patient has been viewed as a solitary individual for a long time in clinical and research settings.

1.3 Research Aim

Similar to the brain's complex network topology and its possible abnormalities in migraine, studying the patient's social network might provide insight into "abnormalities" influencing health behaviour. One of the ultimate goals in social network analysis is to apply interventions by adding nodes or rewiring existing ties that will influence or accelerate behavioral change. In the brain, medication can influence aberrant network structures in a similar fashion. Therefore, both projects were conducted using the same approach (by means of graph theory). The analogy between the two can lead to new insights on social interventions on the one hand and on brain interventions on the other hand, that might ultimately improve migraine management. Therefore, the aim of this research is as follows:

> **Research aim**
> The aim of this research is to gain insight in the applicability of approaching migraine patients as similar to the neuronal network, in order to explore the possibilities of intervening both to improve migraine management.

1.4 Research approach

The analogy between the neuronal network and the patient's social network is used to fill in the blind spots of both professions. Therefore, a comparative research approach was conducted. Differences and similarities between the two projects can be revealed in this way, which might increase our understanding of both types of networks.

1.5 Thesis outline

The main focus of the thesis is the analogy between the migraine neuronal network and the patient's personal social network. Therefore, the thesis is composed of four parts (see Figure 1.5). Part I (including the current chapter) is a general introduction to both research projects and the encompassing thesis aim. Chapter 1 explains the rationale, relevance and structure of the thesis and the conceptual motor to the analogy is given in Chapter 2. The following two parts are stand-alone studies, each with their own aim and research questions.

Part II contains the Mechanical Engineering research project on the migraine neuronal network. It consists of one chapter in the form of a scientific article. Within this research, the neuronal networks of migraine patients are compared to those of healthy controls.

Next, Part III, the Science Communication part of the thesis, comprises the research on the patient's personal social network. An introduction of this project can be found in Chapter 1, in which the research questions and research aim are given. After an explanation of the methods in Chapter 2, a literature study on patients' perceptions is conducted in Chapter 3. The resulting theoretical framework, on which the rest of the research is based, is given in Chapter 4, followed by a more elaborate explanation of the *headache-specific locus of control* in Chapter 5. Within this research, the social networks of patients with high internal headache-specific locus of control are compared to those with low headache-specific locus of control, similar to the brain research. The resulting social networks and a more elaborate explanation of the case study are presented in Chapter 6, followed by an extrapolation of the data on possible interventions in Chapter 7 and the conclusion and discussion in Chapter 8 and 9 respectively.

Finally, the synthesis of the two projects is discussed in Part IV. A reflection of the general research aim (as presented in Section 1.3) will be given, as well as an elaboration on what both fields of topic can learn from each other.

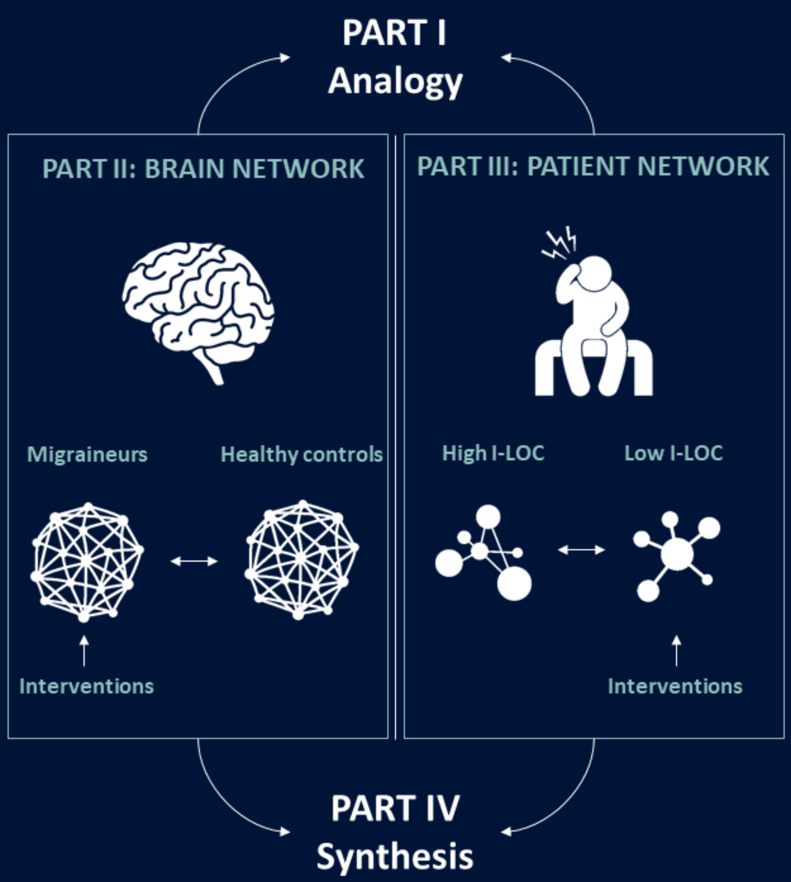


Figure 1.5: The thesis consists of four parts: an analogy (Part I), a research project on the brain network (Part II), a research project on the patient network (Part III) and a synthesis of both projects (Part IV).

2 Analogy

In this chapter, a general introduction of analogies is given in Section 2.1. Furthermore, the analogy between the brain and the patient is provided in Section 2.2, which forms the basis of the synthesis of the two research projects within this thesis.

2.1 What is an analogy?

A little boy asks his mother: "What does a bird use for a chair?" Occupied by this deep issue, he figures that the bird uses a tree to sit on. His mother adds that the bird could sit in its nest as well, which is also its house. The boy then thinks again and concludes: "The tree is not the bird's chair - it's the bird's backyard!" (based on a story by Holyoak and Thagard, 1999).

An analogy is a comparison between one thing and the other based on parallels or shared characteristics. Typically, the purpose of an analogy is to help us understand (the essence of) new concepts by drawing context from our past experiences and knowledge (Holyoak and Thagard, 1999). Similarly, the child in the story uses an analogy to try to understand the world of birds, based on familiar patterns he knows from his own life. He explores the connections between two completely different objects, to understand how an unfamiliar idea is similar to a familiar one.

Analogies are widely used as a model for explanation, and even as arguments for e.g persuasion or decision-making. Our brains are extremely suitable for the use of analogies, as they are wired to recognize patterns. When confronted with an unfamiliar situation, we immediately fit what we see to past experiences or interactions. Like the child, we often struggle to grasp novel and abstract ideas, because we can describe new information only in terms of what we already know. Accordingly, analogies are a practical way to sort new information and place it in context (Pollack, 2015).

The power and pitfalls of analogies

When used well and within the right context, analogies can be very powerful for several reasons. First of all, they resonate emotionally. In this way, emotions are triggered that override the rationale. Furthermore, they allow for the simplification of complex problems (Pollack, 2015). An example is the explanation of the layers of the earth by means of a peach: the earth's core, mantel and crust can be compared to a peach's pit, flesh and skin to portray the abstract (and to us invisible) inside of the earth.

Analogies can be powerful tools, but they can also be misleading when used in the wrong way. That is, the definition of an analogy (as described above) is like a rubber band: it can stretch a bit, but it will eventually reach a breaking point. As such, Rietberg (2017) states that "the analogy only makes sense when the subject of comparison is clear." By this, she means that an analogy should be made within certain boundaries to be the powerful tool it can be. As an example, she explains that the analogy "gecko feet are like Velcro straps" only gets a meaning when adding the subject of the analogy: sticking to walls. If considered as things to walk on, the analogy is insignificant (Rietberg, 2017). As such, the smaller the subject of comparison, the more powerful the analogy can be.

2.2 The analogy between the brain and the patient

In this section, the subject of comparison is given first. Then, the analogy between the brain and the patient is described based on a model of social network analysis.

The subject of comparison

The aim of this research is to gain insight into approaching the patient as a neuronal network. The brain and the patient are not seemingly comparable systems, hence the subject of comparison is on the abstract level of graph theory. Therefore, the subject of comparison is defined as *the network topology of the functional network*. That is, the cars driving on the roads will be compared for both projects, not the roads themselves. This subject provides the basis for explaining possible similar behavior or characteristics. As such, we need to consider the communication between the constituent elements of both systems. The social network model by Berkman et al. (2000) forms the backbone of this analogy and is introduced in the following section.

The social network model: backbone of the analogy

As stated in Section 1.2, mechanisms within the social network facilitate pathways through which health-related factors and disease patterns affect a person's health status, like smoking, treatment adherence or the *locus of control*. The three determinants involved, from small to large scale, are therefore: 1) the pathways of health-related factors, 2) the *psychosocial* mechanisms through which the pathways operate, and 3) the underlying structure of the social network that facilitates the working of the mechanisms (see Figure 2.1). Nested within the social network, the psychosocial mechanisms form a mediating formation between the health-related pathways and the social network structure. In turn, macroscale determinants influence the structure by social-structural conditions like culture, politics and economic depression (Berkman et al., 2000).

The psychosocial mechanisms are not mutually exclusive. As can be seen in Figure 2.1, the model by Berkman et al. (2000) shows that various types of support are (or can be) provided via the social network ties, and that not necessarily all ties are supportive. Some ties may provide only one type of support, while others influence the individual's health via several ways simultaneously. A distinction based on the

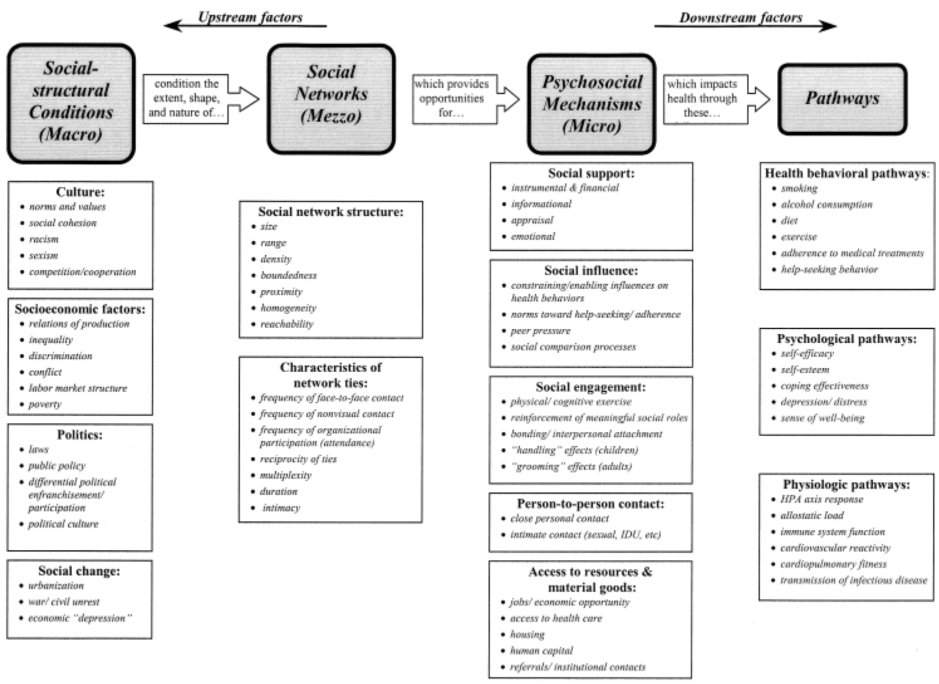


Figure 2.1: The social network model by Berkman et al. (2000).

type(s) of support an alter provides can unravel the various psychosocial mechanisms through which health-behaviors operate.

The analogy with the neuronal network

As stated in Section 1.2, the analogy between both systems can fill in blind spots, which are pathways of communication flow in the case of this research. The analogy will be made for the entire social network model as described by Berkman et al. (2000), but the focus of this research is on the level of communication flow (i.e., psychosocial mechanisms in case of social networks).

The analogy is shown in Figure 2.2 and will be explained from right to left. Starting on the right-hand side, the health-related factors in the social network are comparable to (aberrant) network behavior in the neuronal network. For example, migraine can be an outcome of such aberrant neuronal network behavior, and can be influenced by macroscale factors (medication) through the neuronal network.

Within the brain, the *anatomical* connections between neurons are made up by *axons*, the long thread-like part of the neuron responsible for sending information. This anatomical or *structural* network can be visualized by means of imaging data (Bullmore and Sporns, 2009). As explained in Section 1.2, the actual communication between the neurons, the temporal correlations between their signals due to the dynamic activity, forms the *functional* network. However, this network may not always coincide with the underlying anatomical infrastructure. As it is dynamic, the topology of the functional network constantly changes, depending on the task. Rest enables a different functional network than memory for example. As such, many functional networks exist in the brain (Rubinov and Sporns, 2010), comparable to the psychosocial mechanisms in the social network. These task-dependent functional networks are hereafter called *functional connectivity*.

Likewise, the social network *structure* is the anatomical construct through which "functional" psychosocial mechanisms work, like social support, social influence and access to resources (see Figure 2.2). The totality of psychosocial mechanisms is hereafter called the *social functional network* for reasons of convenience. The egocentric social network is therefore defined by the social network structure and the corresponding social functional network.
The neuronal network comprises both the structural as well as the brain functional network. The structural network strongly influences the functional dynamics in the brain, as the patterns of functional connectivity are a reflection of and are shaped by the underlying structural network (Stam and Reijneveld, 2007; Bullmore and Sporns, 2009; Honey et al., 2007; Sporns et al., 2012). There might be multiple functional networks active in the brain simultaneously, like there are multiple psychosocial mechanisms involved in the social network at the same time. The exact

dynamics between structure and function in the brain remains a poorly understood field of subject (Honey et al., 2007). The same holds for the dynamics between the social network and psychosocial mechanisms. Typically, research is done on the influence of social support on health behavior, but the influence of other psychosocial mechanisms is often not considered.

In this research, the focus lies on the functional networks, as was explained in the previous section. The brain functional connectivity is considered on the timescale of seconds, whereas the social functional network is mapped in terms of months. Functional connectivity (and likely the psychosocial mechanisms) also change over smaller and larger timescales due to factors like age and learning (Honey et al., 2007). However, that is beyond the scope of this thesis and will therefore not be further mentioned.

Lastly, the left-hand side of Figure 2.2 compares the macroscale social-structural conditions with macroscale brain conditions. Brain conditions that impact the neuronal network can be medication or hormonal factors.

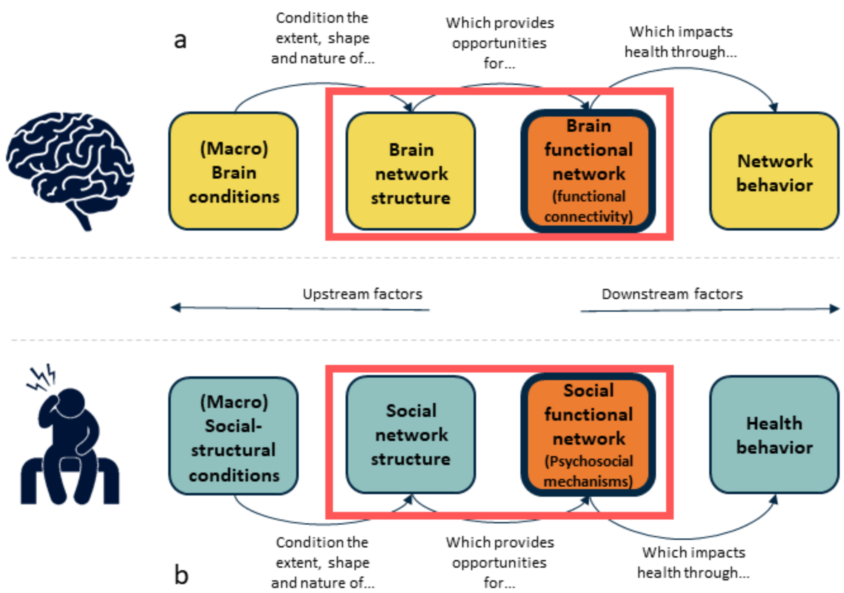
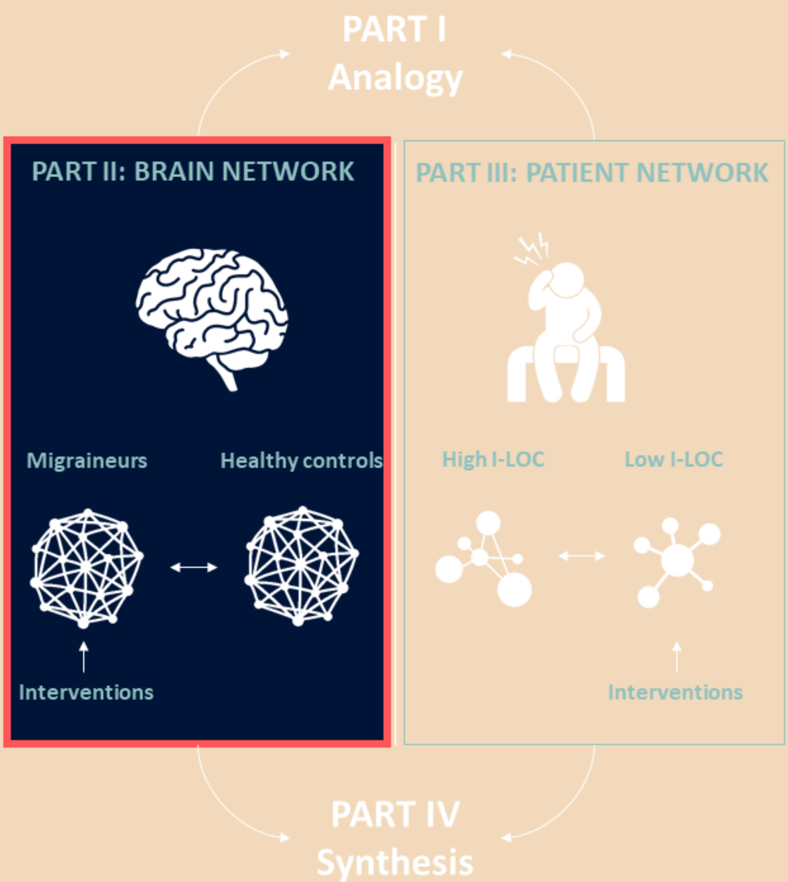


Figure 2.2: The analogy between the brain (a) and the patient (b), which is based on the social network model by Berkman et al. (2000). In both systems, the network structure and function comprise the network representation of the system (framed in red). The functional network is the subject of comparison in this research.


PART I
Analogy
PART II: BRAIN NETWORK
Migraineurs
Healthy controls
Interventions
PART III: PATIENT NETWORK
High I-LOC
Low I-LOC
Interventions
PART IV
Synthesis

PART II

THE BRAIN NETWORK

Mechanical engineering project

1 Scientific article

The second part of this thesis comprises the neuronal network research. To increase our understanding of the possibly aberrant neuronal network in migraine patients, we researched how the network topology of migraineurs deviates from those of healthy controls. In order to do so, this study focused on patterns of simultaneously active brain regions by means of network theory in terms of nodes (EEG channels) and edges (connections between the EEG channels).

This chapter was written in the form of a scientific article.

Graph analysis of resting state EEG functional networks in migraine

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***Abstract* - Migraine is associated with brain dysfunction, possibly due to disturbances in the interactions between distributed cortical regions. Detection of these disturbances in the topological organization of the brain's *functional network* would contribute to further understanding of migraine pathophysiology. Altered cortical responses to external stimulation of different modalities are observed in migraine patients, also between attacks (in the *interictal* state). However, it is yet unclear if abnormalities are detectable in the functional network at rest, i.e. without external stimulation. Here, we assessed abnormalities in migraine functional networks on a global and a local level, based on resting state electroencephalography (EEG) data and graph analysis. Scalp-wide (128-channel) eyes-closed EEG was recorded in 18 episodic migraine patients with and without aura and 15 healthy controls. We calculated functional connectivity based on coherence and phase-lag index, and performed graph analysis to characterize network topology. The minimum spanning tree, a subgraph with maximum functional connectivity, was used for comparison. No significant differences were found in network topology, nor in functional connectivity strength between groups. These results demonstrate that this type of graph analyses are not sensitive to any possible abnormalities in the interictal migraine functional network in resting state. Brain dysfunction in migraine might occur only on a local level, making EEG-based graph analysis a less suitable technique to uncover such abnormalities.**

1. INTRODUCTION

Migraine is a highly disabling brain disorder and affects approximately 15% of the global population (Global Burden of Disease Survey, 2010). Migraine attacks consist of severe, pulsating headache, typically accompanied by nausea and/or sensitivity to light, sound or smell. One-third of migraineurs experience neurological symptoms (usually visual) preceding the headache phase, known as *aura* (Goadsby, 2003). The recurrent nature of migraine suggests an underlying abnormality in the functioning of the brain. However, it is yet unknown what mechanisms lead to the pathogenesis of attacks (Moulton et al., 2011; Scheffer et al., 2013; Hougaard et al., 2015). A better understanding of these mechanisms is necessary to improve our understanding of migraine pathophysiology and thereby improve treatment.

Previous research found that migraine is associated with altered processing of sensory information when evoked by an external stimulation (e.g., visual or magnetic). Such abnormalities in information processing have been reported even between attacks, in the *interictal state*. This might be due to an extreme responsiveness of cortical neurons, or neuronal *hyperexcitability* (Aurora and Wilkinson, 2007; Moulton et al., 2011). However, it is yet unclear if abnormalities are detectable without external stimulation, i.e. in the *resting state*.

Resting state studies focus on the characterization of patterns of simultaneously active brain regions (Allen et al., 2012). The brain can be understood as a structurally and functionally integrated network: the structural network corresponds to anatomical connections between neurons, but electrical pulses of neuronal communication comprise the *functional network* (Bullmore and Sporns, 2009). The functional network might not always coincide with the underlying infrastructure of the structural network (Rubinov and Sporns, 2009). As an analogy, one can think of a road system: car drivers (functional network) are forced to drive the roads available (structural network), but can still decide which roads to take (Honey et al., 2007; Stam and Reijneveld, 2007). Traffic between brain regions continuously forms dynamic functional networks, even at rest (Eguíluz et al., 2005).

A smart spatial organization, or network *topology*, is important for proper functioning of the functional network. The brain constantly negotiates a trade-off between low metabolic costs by short connections and high topological efficiency by long connections. In this regard, neurons do not function as isolated units. Assemblies of spatially close neurons interconnect and specialize in certain aspects of functioning. By cooperating their activity, or *synchronizing*, the assemblies communicate and integrate their separate functions into a cognitive operation (Lopes da Silva, 2013; Varela et al., 2001). In other words, higher brain functions comprise a balance between local specialization and global integration of brain processes, mediated by a smart network topology. The functional network thus provides insight into functionally correlated (but spatially distant) brain regions (Bullmore and Sporns, 2009; Fingelkurts, Fingelkurts and Kähkönen, 2005).

Neurological disorders are directly associated with abnormal levels of synchronization, which shows in aberrant network topology (Bullmore and Sporns, 2009; Stam, 2014). Numerous neuroimaging studies showed aberrant resting state functional network topology compared to healthy controls in Alzheimer's disease (Brier et al., 2014), Parkinson's disease (Utianski et al., 2016), schizophrenia (Bullmore and Sporns, 2012) and epilepsy (Garcia-Ramos et al., 2016). Currently, it is not known if mechanisms leading to migraine pathogenesis might show in resting state functional network topology. Studying patterns of resting state activity in the migraine brain therefore provides us with meaningful information about potential abnormalities in the functional network.

Construction of the functional network topology requires three steps (see Figure 1). First, neuronal processes are recorded by a neuroimaging technique, in this case the electroencephalogram (EEG). EEG directly measures neuronal activity and has a high temporal resolution that can capture the fast changing functional network (Bullmore and Sporns, 2009). However, EEG is sensitive to volume conduction, when two electrodes measure activity form the same source (Van Diessen et al., 2015). Second, a tool to quantify synchronization from the recorded brain activity, is provided by *functional connectivity*. Functional connectivity estimates the temporal correlations between anatomically remote neurophysiological signals (in this case EEG time-series). Many methods to estimate functional connectivity have been proposed, each with their pro's and cons (Friston, 2011; David et al., 2004). Lastly, to characterize patterns of functional connectivity and thereby quantify the network topology, a mathematical tool is used: *graph analysis*.

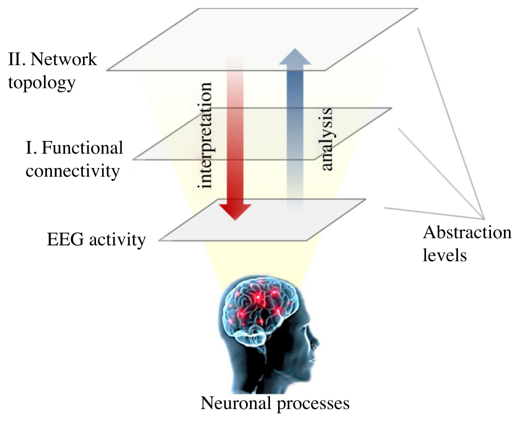


FIGURE 1: Abstraction levels of functional network analysis. New complementary information is found with every analysis step, which increases in abstraction compared to the original neuronal processes (upward arrow). However, an increasing abstraction level results in less intuitive interpretation of the original neuronal processes (downward arrow). Network topology cannot be directly linked to the underlying neuronal processes (image copied from De Vico Fallani et al., 2014).

A graph is an abstract, mathematical representation of a real-world complex network, consisting of nodes (the elements, in this case EEG channels) and edges (the connections between the elements). Edges have weights to represent the strength of connections. Together, nodes and edges form the spatial organization of the network (Bullmore and Sporns, 2012). The quantification of graph measures describing network topology allows for the characterization of efficiency and cost of information transfer in the network. Graph analysis can be applied on any complex network, as these networks typically show similar behavior and share certain organizational principles. Therefore, graph analysis provides quantitative comparison of network topologies in healthy brains and disordered brains (Bullmore and Sporns, 2009).

Although graph analysis of the complete network is helpful for understanding disorder mechanisms, it suffers from methodological issues which might bias comparison between different groups or conditions (Van Wijk et al., 2010). For example, graph measures are influenced by network size (i.e., the number of nodes) and network sparsity (i.e., percentage of edges present). Typically, network size and sparsity differ among individuals, making comparison inconvenient.

An alternative approach to represent brain networks is the *minimum spanning tree* (MST). The MST is a unique, acyclic subgraph of the complete graph, in which the sum of weights is minimized. The MST always has N nodes and $N-1$ edges, making direct comparison among networks possible and avoiding aforementioned issues (Stam et al., 2014; Tewarie et al., 2015). Furthermore, if the original graph possesses strong fluctuations in its edge weights, known as a *strong disorder limit*, most information transport flows over the MST (Van Mieghem and Van Langen, 2005). In terms of the road system, the MST in the strong disorder limit is comparable to a subnetwork of local roads interconnected by highways.

The goal of the current study was to examine the functional network topology in migraine patients using eyes-closed EEG resting state data. Analyses were performed only on alpha-band (8-13 Hz) data, as the alpha rhythm dominates in eyes-closed resting state EEG recordings (Van Diessen et al., 2015). Based on the assumption of hyperexcitability, it was hypothesized that the functional network is affected in migraine. The main objective was to investigate differences in functional network topology between migraine patients in the interictal state and healthy controls. This was done using MST measures on both a global level and a local node level. An intermediate cluster level was examined with sub-averages of functional connectivity in five predefined clusters of nodes. Furthermore, the influence of volume conduction was examined by using two different functional connectivity methods, one of which accounted for the effect of volume conduction.

2. METHODS

2.1. Participants

We included two groups of participants: 15 healthy controls (age 42.67 $\pm$ 19.32; 12 women) and 18 episodic[1] migraine patients in the interictal state (age 38.56 $\pm$ 11.50; 16 women). The sample characteristics of the migraine group can be found in Table 1. The inclusion criteria for migraine patients were based on the International Classification of Headache Disorders III guidelines. The study was approved by the Medical Ethics Committee of Leiden University Medical Center. All participants gave written informed consent prior to the experiment.

2.2. Protocol

EEG was recorded in the resting state. Participants lay on a bed with their head resting on a pillow, in a sound-attenuated and electrically shielded room. The participants were instructed to stay awake during the recording and think of nothing in particular. To avoid muscle and eye movement artefacts, participants were asked to lie still and concentrate their gaze to a designated point. The recording paradigm consisted of four blocks of 30 seconds eyes-open and 120 seconds eyes-closed, to prevent drowsiness. This resulted in 8 minutes of eyes-closed data per participant.

2.3. EEG recordings and preprocessing

EEG was recorded using a 128-channel cap (according to the 5/10 systems, by WaveGuard, ANT^{TM} Neuro with Ag/AgCl electrodes) with the left mastoid as reference. Channels M1 and M2 (see Appendix A) were not used during recording. All electrodes were prepared to have an impedance below 20 kΩ. Data were digitized at a sampling rate of 2048 Hz (Refa amplifier, TMSi, Oldenzaal, the Netherlands) and stored for offline analysis. Custom written scripts in MATLAB R2016b (The MathWorks, Inc.) were used for further processing and analyses of the EEG data.

[1]Episodic migraine is characterized by those with migraine who have 0 to 14 headache days per month (International Classification of Headache Disorders III)

TABLE 1: Sample characteristics of the migraine group (n=18).

	Mean (SD)
Age (years)	38.56 (11.50)
Migraine duration (years)	24.87 (12.82)
Number of attacks (p/month)	1.92 (0.71)
Migraine days (p/month)	3.25 (1.71)
Sex ratio (women:men)	8:1
Migraineurs with aura	6

Continuous EEG data were low pass filtered to prevent aliasing at 70 Hz using a zero-phase fifth-order Butterworth filter, and downsampled to 512 Hz. A 1 Hz high pass zero-phase fifth-order Butterworth filter was applied to remove slow drifts. To remove 50 Hz line noise, the data were band-pass filtered with a second-order infinite impulse response notch filter. The following 21 channels were excluded from further analyses, as scalp contact at these locations was suboptimal in most participants: Fp1, Fpz, Fp2, AF7, AF8, F7, F8, FT7, FT8, FT9, FT0, FTT9h, FTT10h, T7, T8, TP7, TP8, TPP9h, TPP10h, P9 and P10 (see Appendix A). Hence, 105 channels remained for further analysis.

The data were then divided into non-overlapping 4096 sample (8s) epochs. The epochs were visually inspected and 8 artefact-free epochs (a total of 64s) were selected using predefined criteria. These criteria were: 1) the first and last epochs in each of the four eyes-closed blocks are not selected to avoid transitions from closing/opening of the eyes; 2) epochs with obvious (muscle) artefacts are not selected; 3) epochs early in the recording are preferred to prevent the risk of drowsiness; 4) epochs with apparent alpha-band (8-13 Hz) activity are preferred; and 5) epochs without bad channels (i.e., low-quality or missing signals) are preferred to prevent loss of information. A second researcher evaluated the selected epochs, to improve reliability of epoch selection.

Before the selected epochs were extracted for further data analysis, the continuous EEG data were rereferenced to common average. The common average constituted all channels except bad channels. Lastly, bad channels were spherically interpolated by combining signals from neighboring electrodes. In two datasets, a total of six channels were interpolated: CP6 and P8 in one dataset and POO9h, CCP5h, CPP5h and CP2 in another dataset. Continuous EEG data were then filtered in the alpha-band (8-13 Hz) using high and low pass zero-phase fifth-order Butterworth filters. Finally, the selected epochs were extracted from the band-pass filtered data and used for construction of the functional network.

2.4. Data processing

Spectral power was calculated in the continuous EEG epochs of all participants included in the analysis using Fast Fourier Transform. Per epoch, power was averaged across the 105 EEG channels. The average group results can be seen in Figure 2. The power spectra confirmed that analysis of alpha band (8-13 Hz) activity was appropriate.

Per participant, the construction of the functional network was twofold (see Figure 3). First, functional connectivity was calculated per epoch between all possible pairs of 105 EEG channels. The eight resulting epoch-based matrices were averaged and represented in a single 105x105 matrix. Second, the minimum spanning tree was constructed based on the average functional connectivity matrix. This procedure was done for two different methods of functional connectivity.

I Functional connectivity analysis

Functional connectivity was estimated with two different methods: *spectral coherence* and *phase-lag index*. This was done to account for the effect of volume conduction on data analysis. Both methods are based on the phase difference between two signals. To obtain time-varying estimates of phase, a complex component of the signal is needed. Therefore, the complex signal was extracted from the band-pass filtered EEG time-series using the Hilbert transform (Cohen, 2014).

Spectral coherence
Spectral coherence is a measure of synchronization between two signals based on the consistency of their phase differences. Even though two signals may have different phases, coherence will be high if the phase difference between the signals remains constant. In other words, coherence estimates whether two signals can be related by a linear time-invariant transformation. Coherence is always real-valued between 0 and 1, with 0 indicating no relationship and 1 indicating a constant phase difference. High coherence between two EEG signals indicates a linear relationship, even though this does not imply that the underlying cortical dynamics are linear. Despite its fast and easy computation, coherence can detect only linear relationships between time-series (David et al. (2004), Van Diessen et al. (2015)). Coherence was calculated between all pairs of data channels using equation 1:

$$\gamma_{xy}^2 = \frac{|S_{xy}|^2}{S_{xx}S_{yy}} \tag{1}$$

in which S_{xy} is the cross-spectral density of signals x and y (here, time-series of different electrodes) and S_{xx} and S_{yy} are the corresponding auto-spectral densities. A more elaborate explanation of coherence can be found in Appendix B.

Phase-lag index
Like coherence, the phase-lag index (PLI) is based on the phase angle differences between two signals. However, the PLI accounts for volume conduction, when two electrodes measure activity from the same source. The signals of two volume-conducted electrodes will have phase-lags of either zero or π. Therefore, their phase angle differences will be distributed around zero or π radian on the imaginary axis of the complex plane. PLI values will be high if the phase angle differences are predominantly distributed on one side of the imaginary axis. In contrast, if half of the phase angle differences are positive and half are negative with respect to the imaginary axis, the phase-lag index will be zero (Stam, Nolte and Daffertshover, 2007; Cohen, 2014). PLI is calculated by equation 2:

$$PLI_{xy} = \left| n^{-1} \sum_{t=1}^{n} sgn(imag(S_{xy_t})) \right| \tag{2}$$

in which n is the total number of time points in the epoch and $sgn(imag(S_{xy_t}))$ indicates the sign of the imaginary part of the cross-spectral density at time point t.

Cluster analysis
Functional connectivity strength was calculated to assess differences between groups in two ways: first, by means of the connection strength of the whole FC matrix and second, by the connection strength in predefined clusters (frontal, central, left, right and occipital (see Figure 4))[2]. The connection strength in predefined clusters included sub-averages of all electrodes participating within those clusters. For example, the average connection strength of the central-occipital cluster is the average of functional connectivity

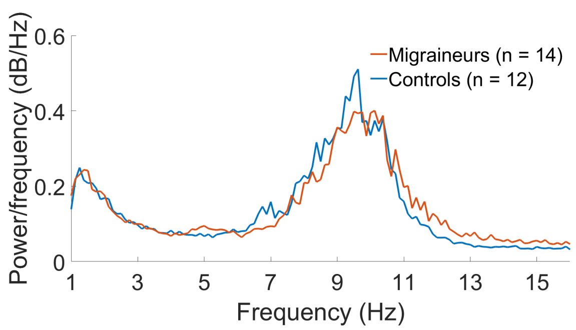


FIGURE 2: Power spectra averaged across 105 EEG scalp channels for the migraine and the control group.

[2]A bigger version of the 128-channel EEG layout can be found in Appendix A.

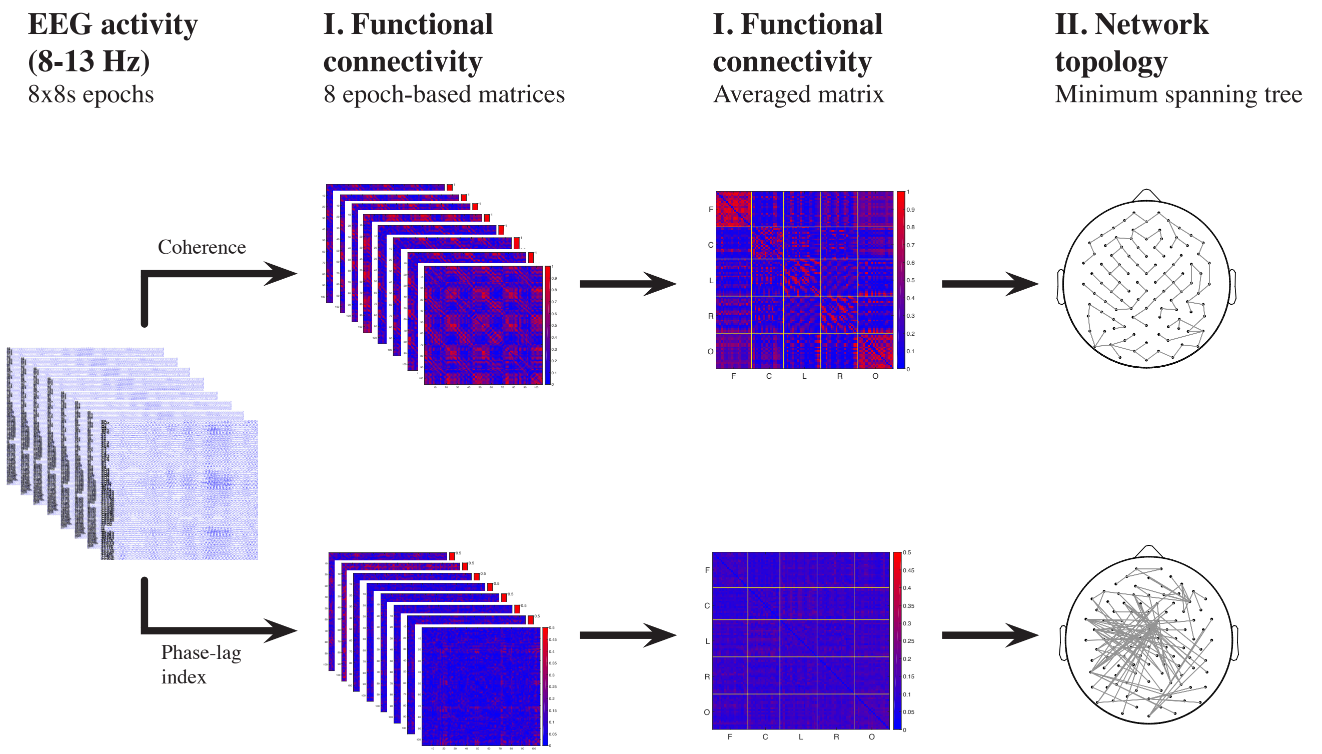


FIGURE 3: Data processing pipeline per participant. Based on 8 epochs (each of 4096 samples, or 8 seconds) of alpha-band data, the functional network was constructed. First, functional connectivity was calculated per epoch between all possible pairs of 105 EEG channels. The 8 resulting functional connectivity matrices were then averaged, out of which the minimum spanning tree was constructed. This procedure was done for two functional connectivity methods per participant.

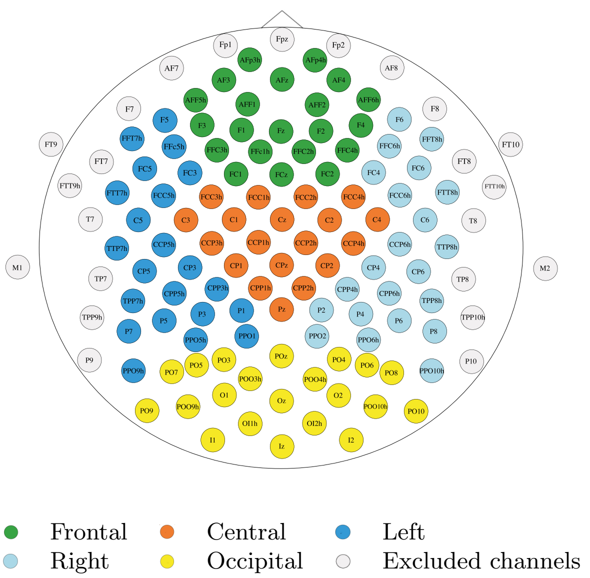


FIGURE 4: Layout of the 128-channel EEG cap. Colors indicate which channels (i.e., nodes) belong to which cluster. Gray channels were excluded from analyses, as scalp contact at these positions was suboptimal in most participants.

values of the 21 channels of the frontal cluster with the 19 channels of the central cluster.

II Minimum spanning tree analysis

The minimum spanning tree (MST) is a subgraph of the complete weighted graph (i.e., the functional connectivity matrix in graph form) that connects all nodes without forming loops, while minimizing the sum of edge weights. Nodes represent the EEG channels, while edge weights represent the connections between them. In the MST, the most important edges in the network are the ones represented by low weight. In the current study, however, the most important edges represent the strongest connections, i.e. the highest weights. For the computation of the MST, we therefore defined the edge weight as 1/(functional connectivity estimate) (Tewarie et al., 2015; Stam et al., 2014).

MST's were constructed with Kruskal's algorithm. The algorithm first arranges edge weights (in this case 1/(functional connectivity values)) in ascending order. The construction of the MST starts with the lowest link weight, after which the following lowest link weights are added until all nodes are connected. Once a link forms a cycle in the network, the link is discarded. This results in an acyclic subgraph in which all nodes N are connected by $m = N - 1$ links. It follows

TABLE 2: Summary of global and local minimum spanning tree measures.

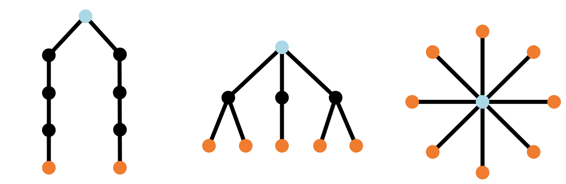
	Name	Explanation	Equation
N	Nodes	Number of nodes	
m	Links	Number of links	
k	Degree	Number of links per node	$k_i = \sum a_{ij}$, in which a_{ij} is the adjacency matrix
BC	Betweenness centrality	Fraction of paths that pass through a given node	$BC_i = \frac{1}{(N-1)(N-2)} \sum_{s \neq v \neq t} \frac{\sigma_{st}^{(v)}}{\sigma_{st}}$, in which σ_{st} is the number of shortest paths between node s and node t and $\sigma_{st}^{(v)}$ are the shortest paths between s and t that pass through node v
E	Eccentricity	Longest path of a given node	$E_i = (d_{ij})_{max}$, in which d_{ij} is the length of the path from node i to node j
L_f	Leaf fraction	Fraction of nodes L with only one link ($k = 1$)	$L_f = L/N$
D	Diameter	Longest of all paths (d) in the graph	$D = d/m$
T_h	Tree hierarchy	The trade-off between large scale integration and maximum betweenness centrality	$T_h = \frac{L}{2mBC_{max}}$
r	Degree correlation	Correlation between the degree of a node and the degrees its neighboring nodes (to which it is connected)	$r = \sum_{jk} \frac{jk(e_{jk} - q_j q_k)}{\sigma^2}$, in which $\sigma^2 = \sum_k k^2 q_k - [\sum_k k q_k]^2$ see Appendix C for more information
O	Overlap	The fraction of links that two MST's have in common	$O = \frac{MST_x \cap MST_y}{m}$

from the algorithm that two conditions must be met when constructing the MST: all nodes in the complete, weighted graph are connected and all edge weights are unique (Van Mieghem and Van Langen, 2005).

After construction of the MST, all edges were assigned an equal weight for the sake of proper comparison between groups. The resulting matrix is called the adjacency matrix. To quantify the topology of MST's, both global and local properties were examined. All measures are summarized in Table 2.

Local MST measures

Local MST measures indicate node importance within the network topology and are calculated for each node separately. In Figure 5, three examples of tree topologies with equal number of nodes are given. Three local MST metrics were examined in this study: degree (k), betweenness centrality (BC) and eccentricity (E). The degree of a node is the number of links connecting to that node. The path-like tree in Figure 5, consists of two nodes with degree one, and seven nodes with degree two. The star-like topology on the other hand, has one highly connected node (degree eight) and eight *leaf nodes* (nodes with $k = 1$). The betweenness centrality is the fraction of paths a given node participates in, between any two nodes in the network. The central node in the star-like topology in Figure 5, for example, participates in every path between any pair of its neighboring leaf nodes and therefore has a BC of one. The nodes with the highest BC carry the highest load. Finally, eccentricity is defined as the longest path of a given node. The blue nodes in Figure 5, have eccentricities of four (path-like tree), two (hierarchical tree) and one (star-like tree). The lower the eccentricity, the more central the node is (Tewarie et al., 2015; Stam et al., 2014). Here, eccentricity is normalized by the amount of links m and degree by the amount of nodes N. Local measures were characterized by means of critical nodes (maximum degree, maximum betweenness centrality and minimum eccentricity).



(a) Path-like (b) Hierarchical (c) Star-like

FIGURE 5: Examples of minimum spanning tree topologies. Blue nodes are the most central nodes, orange nodes are leafs (degree one). The path-like tree (a) and the star-like tree (c) represent two extreme shapes. The hierarchical tree (b) is situated in between those extremes.

Global MST measures

Global measures of MST topology provide information on the large scale integration of the network. Four global MST properties were examined in this study: leaf fraction (L_f), diameter (D), tree hierarchy (T_h) and degree correlation (R). The leaf fraction is the fraction of leafs (L) in the network. The number of leafs has a lower bound of 2 and an upper bound of $N - 1$. The

diameter of the network is the longest path between any two nodes in the tree. Diameter is related to leaf fraction by $d = m - L + 2$
in which m is the total number of links and L is the number of leaf nodes.

Figure 5 implies that the star-like topology results in efficient network communication; that is, all pairs of nodes are either one or two links apart. High global efficiency therefore requires a small diameter (i.e., many leaf nodes). A star-like topology, however, also is highly vulnerable due to high BC of the central node. Failure of this node will disrupt all communication in the network. A balance between diameter reduction and overload prevention (high BC comes with high load), captures an optimal configuration. This trade-off is reflected by tree hierarchy in equation 3:

$$T_h = \frac{L}{2mBC_{max}} \tag{3}$$

in which L is the number of leaf nodes, m is the total number of links and BC_{max} is the maximum betweenness centrality. The denominator is multiplied by 2 to assure that T_h ranges between 0 and 1. In the case of a path (i.e., $L = 2$ and m approaches infinity), $T_h = 0$ and in case of a star (i.e., $L = m$), $T_h = 0.5$ (Tewarie et al., 2015; Stam et al., 2014).

Degree correlation indicates whether the degree of a node is correlated with the degrees of its neighboring nodes. A positive degree correlation indicates that nodes prefer to connect to other nodes with the same or similar degrees. The tree is then called assortative (Stam and Van Straaten, 2012; Bullmore and Sporns, 2009; Newman, 2002). Finally, overlap is the fraction of links that two MST's have in common. Here, the overlap between all MST's of the migraine group compared to the backbone MST of the control group (based on the mean functional connectivity matrix of that group) was calculated, and vice versa.

Strong disorder limit
The MST is the critical backbone of the complete, weighted graph only under the condition of a *strong disorder limit*. If the link weights in the complete graph show strong variations, then the sum of weights (by which the MST is constructed) will be dominated by a single weight. The link weights then possess a strong disorder limit. If this condition holds, then most information flow goes over very few backbone links: the MST (Van Mieghem and Van Langen, 2005).

The weight distribution (F_w) of the complete graph can be described by the polynomial distribution in equation 4:

$$F_w(x) = \begin{cases} x^\alpha & \text{if } 0 \le x \le 1 \\ 1 & \text{if } x > 1 \end{cases} \tag{4}$$

in which x represents the weights (in our case either coherence or PLI values) and α is called the *extreme value index*. A strong disorder limit occurs when $\alpha \to 0$. A decreasing α corresponds to an increasing probability that shortest paths of the complete graph coincide with the MST (Tewarie et al., 2014).

For regular graphs[3], there is a critical $\alpha_c > 0$ for which $\alpha < \alpha_c$ indicates the critical backbone of the complete network (i.e., $\alpha \to 0$). According to Van Mieghem and Van Langen (2005), $\alpha_c = O(m^{-2})$, in which m are the number of links in the network. We will use the same criterion as a threshold for the strong disorder limit in this study. Therefore, with $m = 104$, $\alpha_c \approx 0.0001$.

From the complete graph (i.e., the functional connectivity matrix), for every participant separately, we ranked the weights of all matrix elements in descending order and estimated α from this distribution, using a power function $f(x) = ax^\alpha + b$.

2.5. Statistics

Global and local differences in network topology, as well as cluster-level differences in functional connectivity strength between migraineurs and controls were assessed using Mann-Whitney U-tests. None of the data were normally distributed or met the assumption of homogeneity of variance. Therefore, a nonparametric test was chosen for all measures. A value of $p < 0.05$ was considered significant.

3. RESULTS

Data from seven participants (four migraineurs and three controls) were excluded from analysis; one participant experienced migraine within three days after recording and was therefore not in the interictal state; three data sets were unusable due to recording issues (a broken ground electrode, a high noise level and problems with data storing); and eyes closed data in two participants were contaminated by regular artefacts (eye blinking and heartbeats).

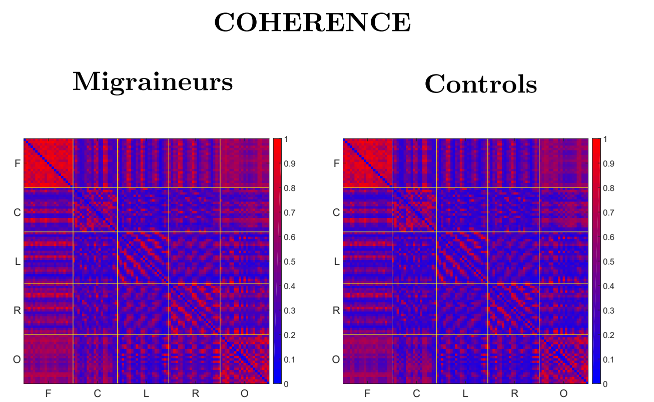
Functional connectivity
Connectivity strength was calculated in two ways. First, the mean strength of all 105 channels was calculated for every participant and compared between migraineurs and controls. Second, sub-averages in five predefined clusters (frontal, central, left, right and occipital) were calculated within and between clusters for every participant and compared between groups. This was done for both functional connectivity methods (coherence and PLI). Typical functional connectivity matrices, based on the mean functional connectivity per group, can be seen in Figure 6a and Figure 6c. The results of the Mann-Whitney U-tests for assessing differences between groups are presented Table 3. No significant differences were found in mean connectivity strength (including all channels) for both functional

[3]Regular graphs are graphs in which each node has the same degree

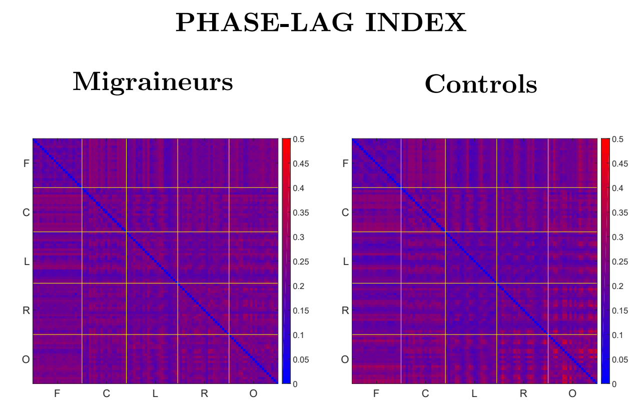
TABLE 3: Functional connectivity (sub-)averages based on coherence and phase-lag index in the alpha band (8-13 Hz). No significant differences were found between migraineurs and controls ($p<0.05$). Number of channels per cluster: Frontal (n=21), Central (n=19), Left (n=22), Right (n=22), Occipital (n=21).

	COHERENCE			PHASE-LAG INDEX		
Cluster	Migraineurs Mean (SD)	Controls Mean (SD)	p-value	Migraineurs Mean (SD)	Controls Mean (SD)	p-value
All	0.42 (0.11)	0.36 (0.07)	0.16	0.22 (0.10)	0.21 (0.09)	0.86
Frontal - Frontal	0.80 (0.11)	0.76 (0.12)	0.34	0.18 (0.06)	0.17 (0.08)	0.52
Frontal - Central	0.40 (0.12)	0.37 (0.15)	0.59	0.25 (0.12)	0.23 (0.13)	0.77
Frontal - Left	0.41 (0.13)	0.36 (0.12)	0.46	0.22 (0.09)	0.19 (0.10)	0.42
Frontal - Right	0.48 (0.16)	0.39 (0.11)	0.14	0.21 (0.09)	0.20 (0.07)	1.00
Frontal - Occipital	0.57 (0.15)	0.51 (0.13)	0.32	0.23 (0.11)	0.23 (0.10)	0.91
Central - Central	0.43 (0.07)	0.46 (0.09)	0.49	0.21 (0.09)	0.20 (0.09)	0.82
Central - Left	0.30 (0.07)	0.28 (0.08)	0.46	0.21 (0.09)	0.20 (0.10)	0.60
Central - Right	0.33 (0.11)	0.29 (0.08)	0.27	0.23 (0.11)	0.21 (0.08)	0.91
Central - Occipital	0.42 (0.12)	0.41 (0.11)	0.66	0.23 (0.11)	0.22 (0.10)	0.73
Left - Left	0.38 (0.05)	0.36 (0.05)	0.14	0.21 (0.10)	0.17 (0.09)	0.38
Left - Right	0.34 (0.08)	0.29 (0.07)	0.13	0.21 (0.10)	0.18 (0.07)	0.69
Left - Occipital	0.36 (0.10)	0.32 (0.10)	0.19	0.22 (0.10)	0.21 (0.10)	0.82
Right - Right	0.44 (0.11)	0.37 (0.05)	0.05	0.22 (0.10)	0.20 (0.07)	0.82
Right - Occipital	0.41 (0.16)	0.32 (0.10)	0.13	0.23 (0.11)	0.22 (0.08)	0.91
Occipital - Occipital	0.54 (0.12)	0.50 (0.09)	0.40	0.22 (0.11)	0.23 (0.09)	0.45

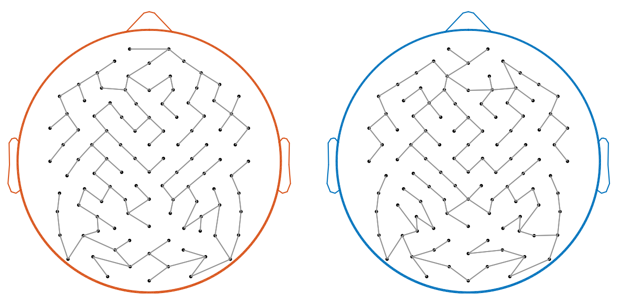
Note: SD= standard deviation



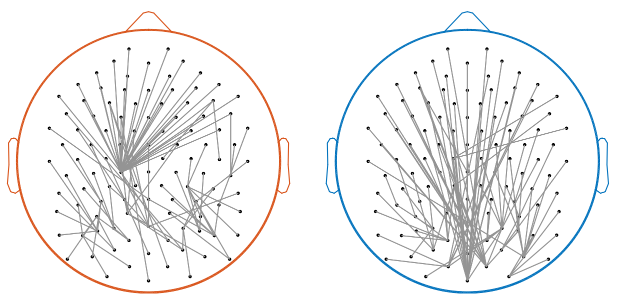
(a) Mean functional connectivity matrices based on coherence for migraineurs (left) and controls (right). Clusters are indicated by yellow lines: F = frontal, C = central, L = left, R = right, O = occipital.



(c) Mean functional connectivity matrices based on phase-lag index for migraineurs (left) and controls (right). Clusters are indicated by yellow lines: F = frontal, C = central, L = left, R = right, O = occipital.



(b) Minimum spanning trees based on the mean coherence matrix for migraineurs (left) and controls (right).



(d) Minimum spanning trees based on the mean phase-lag index matrix for migraineurs (left) and controls (right).

FIGURE 6: Functional connectivity matrices based on the mean functional connectivity per group for coherence (a) and phase-lag index (c). The corresponding minimum spanning trees are shown for coherence (b) and phase-lag index (d).

connectivity methods. Furthermore, no significant differences were found within or between clusters between groups for both connectivity methods. The group effect of the right within-cluster in coherence just fell short of significance (p = 0.05). However, after Bonferroni correction to correct for multiple comparisons ($p < \frac{0.05}{15}$), the group effect of the right within-cluster in coherence was far from significant.

MST measures
To quantify the functional network, measures of the minimum spanning tree (MST) were calculated on both a global and a local network level for every participant. Typical MST's, based on the mean functional connectivity matrices per group, can be seen in Figure 6b and Figure 6d. Global MST measures yielded no significant differences between groups for both functional connectivity methods (see Table 4). Local MST measures were calculated per node and mean distributions per group are visualized in Figure 7. No significant differences were found in the distributions of the local MST measures between groups for both functional connectivity methods. Furthermore, no significant differences were found in maximum degree, maximum betweenness centrality and minimum eccentricity between groups for both functional connectivity methods (see Table 4). The collection of critical nodes per group are shown in Figure 8. Minimum spanning trees including critical nodes per participant are shown in Appendix D. The amount of overlap was similar in both groups (see Table 4). Overlapping links within groups are shown in Appendix E.

Strong disorder limit
The MST forms the critical backbone of the complete graph only if the weight distribution possesses a strong disorder limit. For each participant, we estimated the extreme value index α in its weight distribution. The results can be seen in Figure 9. For all participants, the weight distributions had a value of α between 0.12 and 1.61. Therefore, none of the weight distributions possess strong disorder limit ($\alpha_c \approx 0.0001$).

4. DISCUSSION

The present study examined the topological organization of brain networks in episodic migraine patients and healthy controls by applying minimum spanning tree (MST) analysis to eyes closed resting state EEG data. This was done based on two different functional connectivity methods to account for the effect of volume conduction. For both functional connectivity methods, no significant differences were found in the MST; neither on a global level, nor on a local level. Furthermore, no significant differences were found in functional connectivity strength. In contrast with the hypothesis, the results indicate that the interictal resting state functional networks (RSFN) of migraine patients and healthy controls are not different.

Clinical interpretation
Our finding is in accordance with the only similar graph-based resting state study in migraine patients by Wu et al. (2016). With eyes-closed magnetoencephalography (MEG) data, they investigated the complete graphs of migraineurs (with and without aura) and healthy controls. Wu et al. (2016) found no significant differences in topological organization, nor in functional connectivity strength based on coherence between groups in the alpha band (8-12 Hz). This study supports the idea that the interictal migraine functional network might not function abnormally in the resting state.

However, multiple findings argue in favor of permanent abnormalities in the migraine RSFN. Firstly, studies based on resting state functional magnetic resonance imaging (rs-fMRI) found increased connectivity in specific brain areas in the RSFN of migraineurs compared to healthy controls, especially in pain-processing areas (Sprenger and Magon, 2013; Maneiro, Boshyan and Hadjikhani, 2011). The advantage of fMRI over EEG and MEG is a high spatial resolution, in the order of millimeters. In EEG and MEG, only activity in the upper layer of the cortex is recorded. Abnormalities in the migraine RSFN might be highly localized and not detectable with EEG- or MEG-based graph analysis. Possibly, brain dysfunction is attributed to the level of neuronal assemblies and not to abnormal network connectivity.

Furthermore, interictal migraine network topology might be comparable to that of epilepsy. Migraine and epilepsy follow the same sequence in attacks (defined by phases before (preictal), during (ictal) and after (postictal) attacks) and are believed to have pathophysiological overlap (Nye and Thadani, 2015). In some patients, the disorders occur comorbidly and are linked genetically. Like migraine, epilepsy originates from electrical disturbances in the brain and attacks are unforeseen and unprovoked. Accordingly, many epilepsy graph-based resting state studies found abnormal network topology in the interictal state compared to the ictal state and/or healthy controls (Ponten et al., 2007; Van Dellen et al., 2009; Garcia-Ramos et al., 2016). The interictal epilepsy network might be organized in such a way that it facilitates an increased tendency to synchronize. This advocates that the interictal migraine functional network might be abnormal in the resting state too.

It is currently not known if functional connectivity and topological organization are abnormal in the preictal, ictal or postictal migraine states. Future neuroimaging studies should investigate whether migraine patients show abnormal interictal network topology when compared to other states. Furthermore, the interictal RSFN might differ between migraineurs with and without aura (Hougaard et al., 2015). Future research

TABLE 4: Minimum spanning tree measures in the alpha band (8-13 Hz). No significant differences were found between migraineurs and controls (p<0.05).

	COHERENCE			**PHASE-LAG INDEX**		
MST measure	**Migraineurs Mean (SD)**	**Controls Mean (SD)**	**p-value**	**Migraineurs Mean (SD)**	**Controls Mean (SD)**	**p-value**
Leaf fraction	0.32 (0.05)	0.31 (0.04)	0.86	0.73 (0.09)	0.71 (0.08)	0.62
Diameter	0.35 (0.05)	0.32 (0.07)	0.22	0.13 (0.04)	0.12 (0.04)	0.66
Tree hierarchy	0.52 (0.08)	0.52 (0.07)	0.95	1.00 (0.14)	0.95 (0.12)	0.45
Degree correlation	-0.23 (0.10)	-0.18 (0.09)	0.32	-0.43 (0.11)	-0.38 (0.11)	0.52
Max. degree	4.08 (0.29)	4.57 (1.50)	0.61	22.79 (8.08)	21.08 (8.20)	0.62
Max. BC	0.31 (0.03)	0.30 (0.02)	0.80	0.37 (0.03)	0.37 (0.03)	1.00
Min. eccentricity	0.17 (0.03)	0.16 (0.03)	0.23	0.07 (0.02)	0.07 (0.02)	0.94
Overlap	0.59 (0.08)	0.60 (0.05)	0.84	0.04 (0.03)	0.04 (0.03)	0.53

Note: SD = Standard deviation

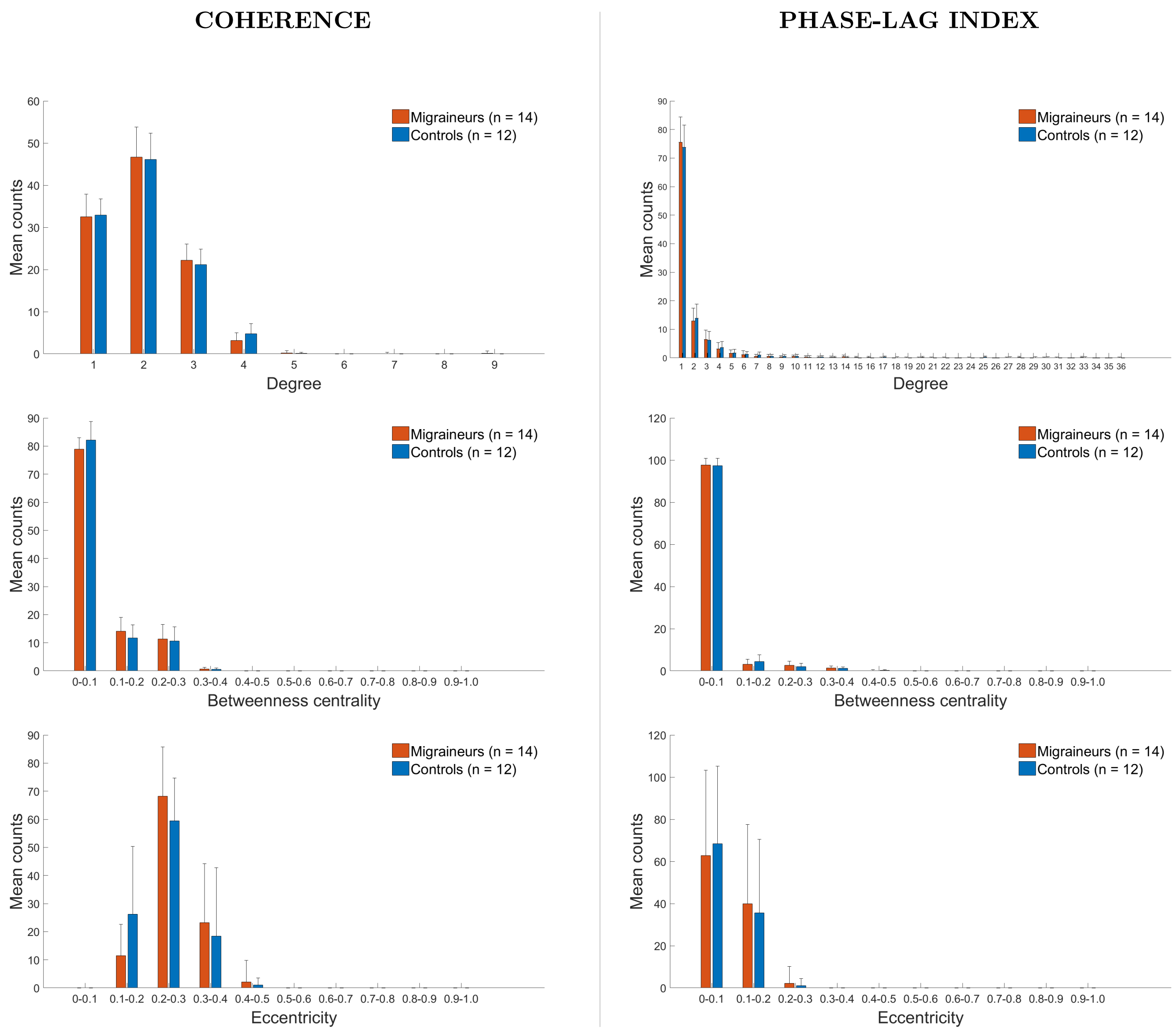


FIGURE 7: Distributions of local minimum spanning tree measures based on coherence (left side) and phase-lag index (right side). All distributions show the mean and standard deviation of migraineurs (orange) and controls (blue).

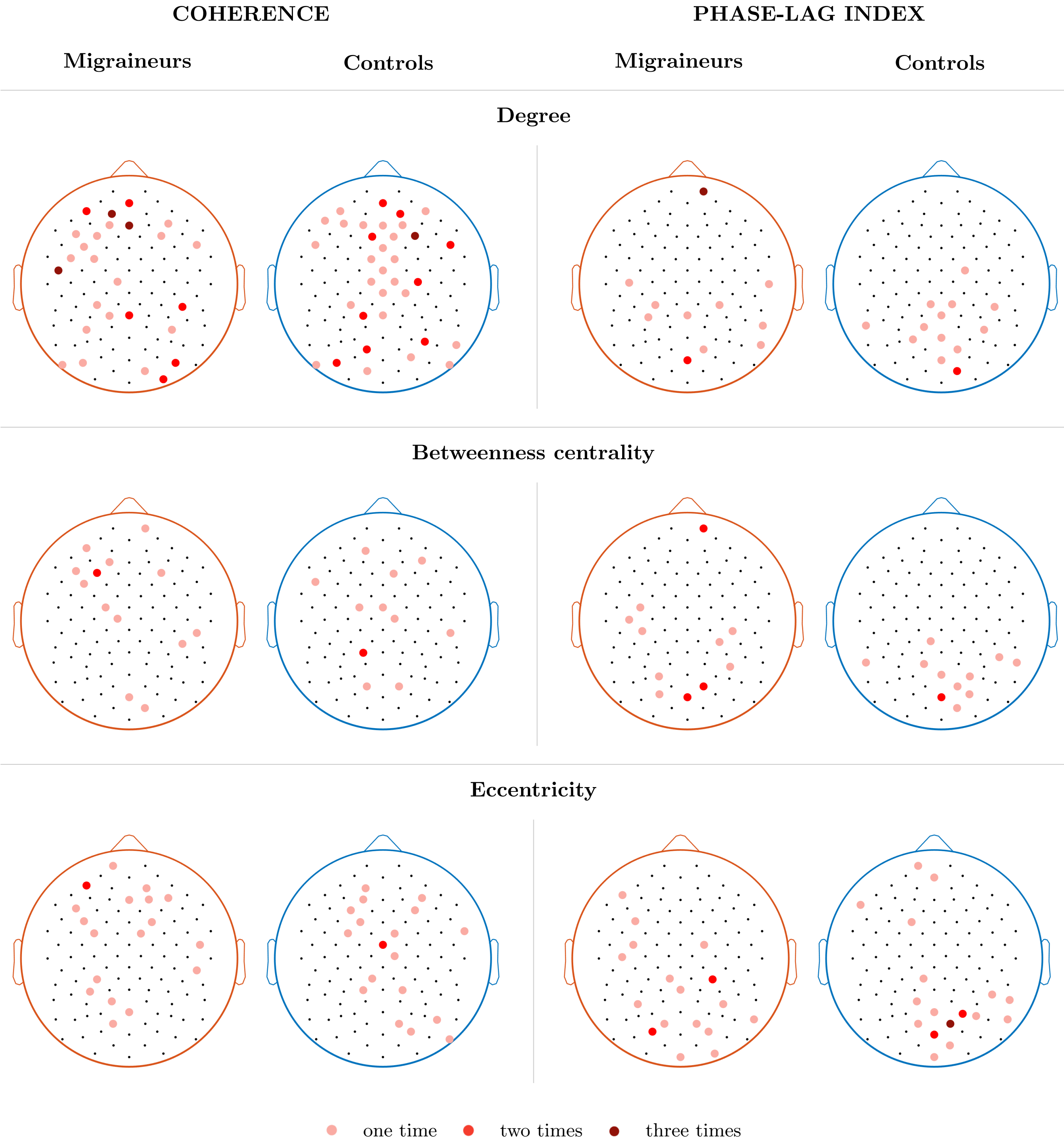


FIGURE 8: Totality of critical nodes based on coherence (left side) and phase-lag index (right side) in migraineurs (orange) and controls (blue). The colors of the dots indicate the counts of a critical node, if the particular node appeared in more than one participant.

should elucidate the effect of aura on the RSFN. Lastly, a combination of fMRI (with high spatial resolution) and EEG (with high temporal resolution) recordings might give complementary information and therewith provide more accurate results.

Data interpretation

The functional connectivity measure is of major influence on the shape of the MST. Both coherence and PLI detect coupling in EEG time series, but with different sensitivity profiles; coherence is able to detect only linear coupling, while PLI detects weak and nonlinear coupling (David et al., 2004), and accounts for volume conduction (Stam, Nolte and Daffertshover, 2007). However, in epilepsy, measures affected by volume conduction better discriminate between the preictal and ictal state (Christodoulakis et al., 2014). Choice of functional connectivity measure therefore depends on the research objective.

Comparison between the topological organizations of the coherence-based MST and the PLI-based MST clearly reveals the effect of volume conduction (see Figure 6). In the coherence-based MST, network topology was dominated by local connections between neighboring channels. Such local connections were not present in the PLI-based MST, which was dominated by long distance connections. Functional connectivity for neighboring channels might strongly be influenced by volume conduction in coherence-based MST's. This might also explain the higher amount of overlapping links in coherence compared to PLI.

Based on the constant trade-off between metabolic costs and topological efficiency due to functional segregation and functional integration in the human brain, the MST is expected to show star-like as well as path-like characteristics, like a hierarchical tree (Tewarie et al., 2014). Coherence-based MST's showed a hierarchical tree with path-like branches, while MST's based on phase-lag index showed a hierarchical tree with typical star-like characteristics. PLI-based MST's were characterized by some high-degree nodes and many leaf nodes (k=1), typical for star-like trees. The degree distribution in coherence showed a peak at $k = 2$, which is typical for a tree with a filamentary structure, or longer "branches" (Lovelace Rainbolt and Schmitt, 2017). T_h in PLI was close to 1 for both groups, suggesting an optimal combination of short distances and prevention of overload of any node.

Critical nodes were assessed to visualize local MST measures. Most critical nodes were expected in the occipital cortex, as alpha-band activity predominantly originates from here during wakeful relaxation with eyes-closed (Van Diessen et al., 2015; Liu et al., 2015). In coherence-based MST's, critical nodes were scattered throughout the EEG electrodes in both groups, possibly due to the effect of volume conduction (see Figure 8). Contrarily, in PLI-based MST's, most critical nodes originated from the occipital/central part in the control group. In the migraine group, PLI-based critical nodes were more scattered. Considering the fact that the migraine RSFN might show abnormalities only on a local level, the location of critical nodes should be investigated more thoroughly in future MST analyses.

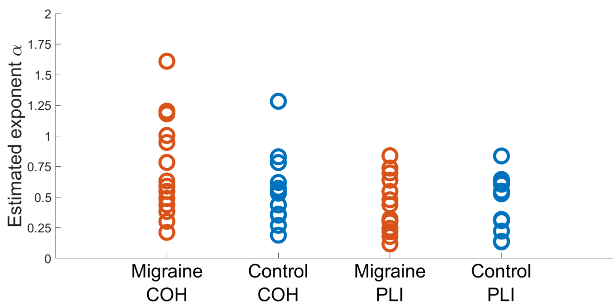


FIGURE 9: Estimated exponent alpha. Link weights of the complete network possess a strong disorder limit if $\alpha < 0.0001$. In this case, alpha ranges between 0.12 and 1.61 for both groups based on coherence (COH) and phase-lag index (PLI).

Influence of the strong disorder limit

MST topology, and thereby MST measures, depend only on the ranking of link weights of the complete graph and not on the absolute values or distribution of those weights. The MST is robust only if link weights possess strong variations; otherwise, slight changes in link weight could result in substantially different MST topology (Stam et al., 2014). Merely a comparison of MST measures between groups, might therefore not be conclusive. The distribution of link weights, and especially the strong disorder limit, should be investigated too. Only if the weights of the complete network possess a strong disorder limit, the minimum spanning tree is the critical backbone of the complete weighted network (Van Mieghem and Van Langen, 2005). None of the networks in the current study possessed a strong disorder limit ($0.12 \leq \alpha \leq 1.61$). Therefore, none of the MST's in this study dominated the information flow of the original network. For the comparison of brain networks, the distribution of link weights might be more important than network topology itself; the latter only matters if the MST truly reflects the complete graph.

Most of the minimum spanning trees in the current study possess a *weak disorder limit*; the link weights contribute equally to the sum of weights by which the minimum spanning tree is created (Havlin et al., 2005). Information flow in these networks is spread out over more paths than just the MST, leading to a more balanced overall network load (Van Mieghem and Van Langen, 2005). Since $\alpha_c = O(m^{-2})$, a lower m (number of links) will result in a higher α_c. MST analyses might therefore better reflect underlying activity with 32- or 64-channel EEG.

Methodological issues

In general, many methodological choices are required in EEG-based graph analyses, which may have great influence on results. The choice of reference electrode, artefact handling and filtering, the number and length of epochs and the choice of frequency band can all affect network topology. Furthermore, there is no gold standard in defining nodes and edges. These methodological issues make comparison among studies difficult (Van Diessen et al., 2015).

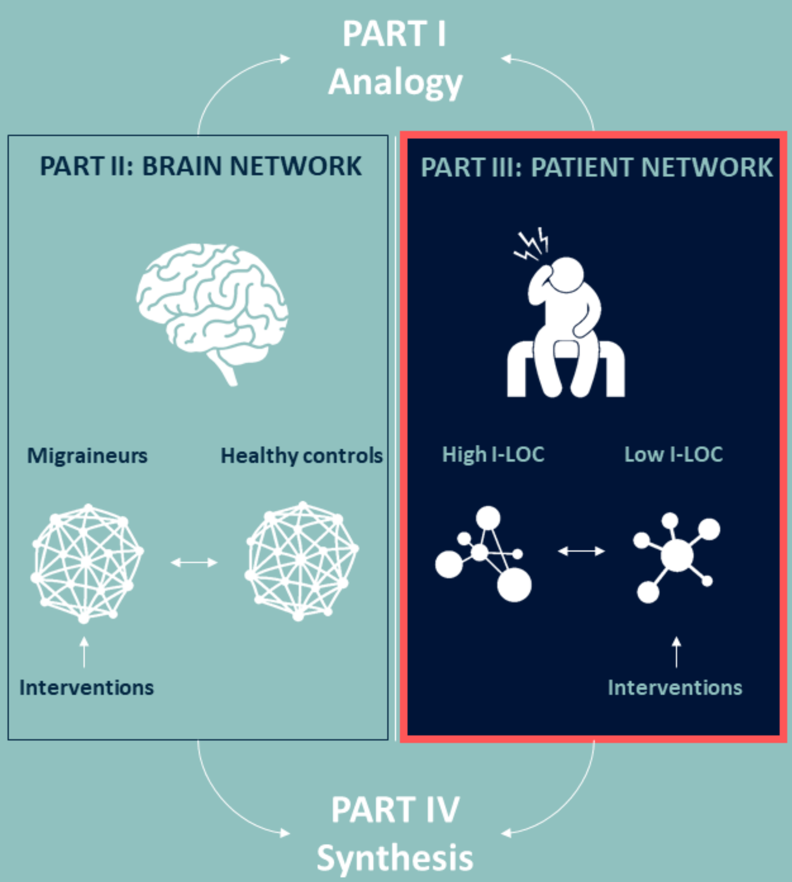
The present study showed advantages compared to other neuroimaging-based migraine studies. Resting state recordings are simple and not harmful to participants, while stimulation studies have a complex design (Diaz et al., 2013; Meisel et al., 2015) and might trigger migraine attacks. Furthermore, the MST is barely affected by epoch length and shows similar results even for very short epochs (Fraschini et al., 2016). The use of MST's makes proper comparison among complex networks possible (Stam et al., 2014).

However, the current study had some methodological issues. The time signals in epochs were assumed to be stationary, while the brain continuously changes configuration on multiple time scales, even in the order of seconds (Bullmore and Sporns, 2012; Honey et al., 2007). Smith et al., 2017 proposed a method for both coherence and phase-lag index to handle dynamic connectivity. Furthermore, the resting state comprises multiple levels of cognition (Diaz et al., 2013; Van Diessen et al., 2015) and it was not verifiable if all participants were in the same state. This might have biased the results. Lastly, graph analysis increases the abstraction level of information and interpretation of MST results cannot be directly related to neuronal dysfunction. Cluster analysis (without the use of predefined clusters) of functional connectivity patterns might give more intuitive results compared to the original neuronal processes. A method for data clustering in MST's can be found in Yu et al. (2015).

5. CONCLUSION

The EEG-based resting state functional network of interictal migraine patients does not show any abnormalities on a global, intermediate or local network level compared to healthy controls. Possibly, abnormalities in resting state are highly localized at the level of individual neurons or neuronal assemblies and do not show on network level. The spatial resolution in EEG might be too low to detect such subtle abnormalities. Even though resting state EEG studies are easy to compute and participants do not experience the resting state as harmful, external stimulation might be necessary to assess differences between the functional networks of migraineurs and controls.

Furthermore, the minimum spanning tree offers an unbiased method for comparison between groups. The effect of volume conduction can clearly be seen in MST topology. However, high density EEG recordings increase the threshold by which the MST is considered the critical backbone of the complete graph. Therefore, a trade-off between spatial resolution of the neuroimaging technique and the resulting number of links in the MST should be accounted for in future MST studies.


PART I
Analogy
PART II: BRAIN NETWORK
Migraineurs
Healthy controls
Interventions
PART III: PATIENT NETWORK
High I-LOC
Low I-LOC
Interventions
PART IV
Synthesis

PART III

THE PATIENT NETWORK

Science communication project

1 Introduction and problem description

In this part of the thesis, the patient's social network is analyzed. As stated in Part I (Section 1.1), the gap between patient and physician might be detrimental to good migraine outcome. This gap and the associated importance of self-management is explained further in the current chapter. Starting with an introduction to migraine management in Section 1.1, this chapter continues with an elaboration on the research context and problem description in Section 1.2 and the research aim and questions in Section 1.3.

1.1 Introduction to migraine management

Migraine is a highly disabling and unpredictable condition that everyone experiences differently. Some migraineurs suffer severe attacks and require complete bed rest, while others suffice with just painkillers. Migraineurs experience stress (relief) as the trigger in some cases, while in other cases the attacks are said to be provoked by certain foods, the weather or flickering lights. The severity of migraines and their related triggers can even differ within an individual; migraine attacks are sometimes initiated by these triggers, and sometimes they are not. The exact biological mechanisms contributing to the development of an attack are still unknown, as are the mechanisms that weaken and stop an attack (Burstein, Noseda and Borsook, 2015).

One thing is certain: migraine is more than a headache. It is a complex neurological disorder that affects multiple areas in the brain (Burstein, Noseda and Borsook, 2015). As such, many studies have focused on biological factors influencing the development of attacks and the working of associated medication. Despite the resulting progress in pharmaceutical treatment, some researchers, however, are doubtful about the use of medication only. According to Nicholson et al. (2007), "biological factors alone fail to account for all aspects of headache and disability" in migraine.

Some researchers therefore argue that proper migraine management should involve more than just medication. Lifestyle adjustments, like regular eating and sleeping patterns or a reduced level of stress, might be necessary in migraine management too. In fact, several of such *nonpharmaceutical* treatments have shown to be as effective as medication (Rains et al., 2006a; Rains et al., 2006b; Grazzi et al., 2002; Seng and Holroyd, 2010).

An important part of successfully dealing with migraine constitutes *self-management*. Unlike some conditions, migraine occurs mostly in the absence of health care professionals. Individuals suffering from migraine are therefore largely responsible for their own care. Inevitably, patients are forced to make decisions about their treatment every day, or to self-manage their condition (Peters et al., 2005). Dawn Buse expressed the importance of self-management for successful migraine treatment outcomes with the following quote:

> "A physician can prescribe medications for a treatment plan, a psychologist can teach relaxation techniques or a physical therapist can teach stretching exercises, but the success of these practices depends on implementation by the patient."
>
> **Neurologist Dawn Buse**

Patient-physician communication and information sharing

As stated in Chapter 1 of Part I, effective patient-physician communication is key to good migraine outcome. Furthermore, better compliance to the treatment regimen has been linked to a more personal relationship with the physician, more frequent communication and longer encounters (Rains et al., 2006a). However, physicians are restricted by the limited available time for consultation and other patient appointments. Good patient-physician communication typically has to be established in a time frame of (tens of) minutes. Within this time, headache diagnosis depends on the patient's information supply, which is prone to recall bias due to its episodic nature; patients might only remember the worst migraine cases, unintentionally exaggerate the duration of an attack or forget how often they take medication. Therefore, headache diaries are generally used (Rains et al., 2006a; Patwardhan et al., 2007; Nappi et al., 2006).

The headache diary enables a proper recording of migraine attacks and headache days. Typically, the patient needs to fill out the diary every day for the course of one or two months. The characteristics of attacks are often recorded as well, which can be helpful to the physician in the diagnosis and treatment (Nappi et al., 2006).

Collaborative care

Patients are their own principal caregivers in migraine. As such, care should be a collaboration between patient and physician, in which the physician's expertise (about migraine) is equally important as the patient's expertise about his own life. In theory, this collaborative care could harmonize the ideas and perspectives of the patient and the physician. A vast amount of literature therefore states that patients should be actively involved in their own migraine management, both through decision-making during encounters as well as in their self-management behavior. This will not only encourage collaborative care and thereby create a common goal, but is also necessary for proper self-management (Bodenheimer et al., 2002; Peters et al., 2007).

However, collaborative care requires that the patient *accepts responsibility* to properly self-manage his/her migraine (Bodenheimer et al., 2002). Not every patient is necessarily feeling responsible, let alone wants to become an expert in migraine management. Therefore, "good" patient-physician communication might not necessarily require encouragement of active involvement, as prescribed by literature. Other ways of communication, perhaps via the alters in the patient's social network, might be more effective to achieve good migraine outcome.

1.2 Problem description

This research project was carried out at the Headache Outpatients Department (HOD) at Leiden University Medical Center (LUMC). The HOD performs research and offers specialist care to people suffering from migraine or other severe types of headache. Prior to the appointment, migraine patients are requested to keep track of a headache diary. A pilot study by the HOD showed that none of the five participants fully completed this diary. The reason for this might be that patient expectations do not match those from the HOD; that is, patients might not expect to keep a diary when seeking help. The HOD fears that patients might not use the headache diary on a daily basis when applied in practice. As such, the expectation differences can lead to a gap between patient and physician, which, in turn, influences treatment compliance and migraine outcomes.

1.3 Research aim and questions

The starting point of this project therefore was: what do migraine patients want? The aim of this project is to point out interventions in the patient's social network (e.g., by adding nodes or rewiring existing ties) to accelerate behavioural change, in this case behaviour related to the internal headache-specific locus of control. The reason for the headache-specific locus of control will be elaborated on in the literature study (Chapters 3, 4 and 5). Ultimately, the interventions could close the gap between patient and physician. The research aim resulted in the following research questions:

Main question:

How can patient perceptions on migraine treatment be managed through the patient's social network in order to harmonize the mutual expectations between patient and physician?

Sub-questions:

1. What are the perceptions of migraine patients on treatment?
2. What (social) mechanisms contribute to those perceptions?
3. To what extent can the headache-specific locus of control be linked with the egocentric social network architecture?
4. What interventions in the patient's social network would contribute to increase the internal headache-specific locus of control?

1.4 Research methodology

This research project was conducted in the form of a case study. First, a literature study was conducted to assess the perceptions of patients towards migraine management. The resulting theoretical framework provided insight into the rationale of the behaviour of migraine patients. Second, the social networks of migraine patients at the HOD were mapped by means of surveys. The methods are explained in the following chapter.

2 Methods

In this chapter, the methods used to answer the research questions are explained. The first and second sub-questions were addressed with a literature study and the corresponding theoretical framework respectively, which is elaborated on in Section 2.1. The literature study formed the basis on which the case study could build. The case study was used to answer the third and fourth sub-questions. The way in which the case study data was collected is explained in Section 2.2 and the analysis is described in Section 2.3. A summary of what method was used for which sub-question and where it can be found in this part of the thesis, is given in Section 2.4.

2.1 Literature study

The starting point of the literature study was defined by the question: what do migraine patients want? As this question is rather broad, it was first refined to: what do migraine patients want *from their physician*? As such, the very starting point of this research was a paper by Lipton and Stewart (1999) entitled: "Acute Migraine Therapy: Do Doctors Understand What Patients With Migraine Want From Therapy?" From there on, similar studies were found that formed the basis of the literature study, using the following search query in either Google Scholar of PubMed:

```
    ( migraine OR headache )
AND ( patient perceptions OR patient expectations )
AND ( management OR treatment )
```

Literature was also found by relevant references, or by searching in Google Scholar for the same researcher or research group.

The resulting entirety of patients' perceptions and expectations was incoherent, as all studies treated slightly different topics. For example, the items referred to ranged from consultation at the general practitioner to the use of preventive medication and from side effects to behavioral treatment. To bring some consistency, the four areas of migraine management strategies as defined by Peters et al. (2005) were adopted. The four categories are: *medication*, *consultation*, *general management* and *social support*. Based on each of those categories, literature was sought in a more specific manner, i.e. using each of the four category terms in addition to the above search query.

The literature study on patients' perceptions can be found in Chapter 3 and specifically answers the first research question. The results vary widely, which might relate to the fact that no one study approached similar groups of migraineurs or discussed similar topics of perceptions and preferences. Therefore, no unambiguous conclusions could be drawn from the literature study to answer the question that was initially started with. Yet, it became clear that, indeed, everyone experiences the same condition differently. Therefore, an explanation of the origin of these differences was sought in the mechanisms underlying patient perceptions. The result was a theoretical framework, which provided a basis for the next step in this research.

Theoretical framework

Three recurring factors arose from the literature on patients' perceptions:

1. Migraine is an individual disorder, which should be approached with an individualized treatment plan
2. Satisfaction with treatment derives from expectations
3. Self-efficacy is important in migraine management

However, none of the literature was clear on the rationale behind any of these three factors. Only one paper clarified the first factor by stating that "the experience and expression of migraine, like all chronic illnesses, is a complex interaction among biological, psychological and social variables, and their interactions play significant roles in the experience and outcome of the condition." (Rathier et al., 2013). This led to the *biopsychosocial model of health* as a starting point for the theoretical framework. To better understand why migraine is experienced differently among individuals, theories were sought on 1) the biopsychosocial model of health, 2) how the relationship between satisfaction and expectation is established and 3) why self-efficacy (and later: locus of control) is especially important to migraineurs. The three search queries consisted of:

1. `( biopsychosocial model )`

2. `( perceptions OR expectations OR treatment outcome ) AND ( satisfaction ) AND ( migraine OR headache )`

3. `( self-efficacy OR locus of control ) AND ( management OR treatment ) AND ( migraine OR headache )`

Finally, the resulting theories based on the three factors were linked into a framework, which can be found in Chapter 4. The theoretical framework answers the second sub-question of this research project. Based on the framework, the *locus of control* was chosen as the topic of further investigation, as that was the most central and pivoting issue.

2.2 Data collection

After converging from the wide variety of patients' perceptions to the locus of control in the literature study, a case study was performed to map the social networks of migraine patients. The case study consisted of two questionnaires and a survey, for which all participants signed an informed consent.

Locus of control questionnaire

The locus of control (LoC) in migraine patients was measured with a self-report questionnaire, specifically designed for the headache version of locus of control. This *headache-specific* locus of control questionnaire (HSLC) is widely applied in headache research. Willekens et al. (2018) recently translated and validated the questionnaire in Dutch. The reason to use the Dutch version of the HSLC (HSLC-DV) was convenience to the researcher as well as the participants, since the language of the questionnaire was the mother tongue of all.

The HSLC-DV can be found in Appendix F. It consists of 33 items with a Likert response scale ranging from 1 (strongly disagree) to 5 (strongly agree). The questionnaire examines three subscales, namely internal LoC (how responisble do I hold myself for getting migraine attacks), medical professional LoC (how responsible do I consider the medical professional to be for my migraine attacks) and chance LoC (to what extent are my migraine attacks a matter of fate), by 11 questions each. Therefore, the score per subscale ranges from 11 to 55; the higher the score, the higher the measured trait by that subscale (Willekens et al., 2018).

The HSLC-DV was provided online, and patients received an e-mail with the corresponding link upon arrival at LUMC. For those without a mobile phone, a paper version was provided.

Patient attributes questionnaire

The second stage of the case study involved a questionnaire on patient characteristics (see Appendix G). The patient was asked for his/her sex and age, whether he/she suffered from migraine with or without aura and how many migraine and headache days were experienced per month. Furthermore, to test whether patients indeed are inclined to neglect filling out the diary, they were asked if they had *directly* completed the two obligatory online questionnaires prior to the appointment (immediately after receiving an invitation from LUMC).

Additionally, the questionnaire contained questions on migraine management strategies. Four types of strategies were given, being: consultation, medication, general management and social support. Each of the four types consisted of multiple examples. The patient identified which strategies applied or had applied to him/her by ticking the boxes corresponding to those examples. The management strategies were asked in order to "plant a seed" in the patient's head; as the next step of the case study involved a survey on the social network, the patient might think about certain alters more easily, like the general practitioner or a headache patients association.

Social network survey

The last step of the case study comprised a survey in which the social network was inquired. This study used the *egocentric* approach to map the social networks of migraine patients. Egocentric networks describe the relationships between a focal person, the "ego" (the migraine patient), and a set of individuals, the alters, surrounding the ego. A survey is the standard instrument to generate data for personal social networks. Typically, it consists of three elements: first a name generator to identify the alters in the network, second a name inter-relater to uncover the pattern and strength of connections between all the nodes, and third a name interpreter to bring about data on individual alter characteristics. The last step might unravel possible social influences acting on the ego (Dhand et al., 2016).

The name generator consisted of one question, which was adapted from the validated General Social Survey, a population-based annual survey in the USA. The question asked was: "Who has been important to you in dealing with your migraine in the last six months?" One of the challenges in social network data collection is to define the boundaries of the network. Therefore, the patients were asked to name all alters who have been important to them within the last *six months* concerning their migraine management. Three colors of sticky notes represented three levels of importance: slightly important, moderately important and highly important. The colors were later translated to node weights of 1 (slightly important alters), 2 (moderately important alters) and 3 (highly important alters). Participants were instructed to write down one name per sticky note and use as many sticky notes (and as many colors) as they required.

Participants were asked to make a distinction between an "emotional" side and an "otherwise" side, by sticking each of the notes on the corresponding side of a poster; alters who mainly provided emotional support were put on the "emotional" side, and all other alters were placed on the "otherwise" side. Some alters, who provided multiple kinds of support, were placed in the middle. The distinction between emotional support and other kinds of support was made, because internal locus of control is associated with emotional migraine-related quality of life (i.e., anxiety and other emotional burden) (Grinberg and Seng, 2017). The amount of emotional support was therefore seen as a point of special interest.

Then, the name inter-relater was carried out. All connections between ego and alter or alter and alter who would *recognize* each other on the street were colored orange and all connections of those who knew each other well (i.e., better than only recognition) were colored red. These colors were later translated to tie weights of 1 (orange) and 2 (red). Lastly, patients were asked to indicate whom of the alters suffered from migraine or another severe type of headache disorder as well (name interpreter). Other alter characteristics were not asked in this study, to constrain the survey length.

Participants were not asked about the nature of their relationships (i.e., the psychosocial mechanisms) for two reasons. First, it is highly impractical to ask participants about the type of support they receive. Descriptions of all possible types within the psychosocial mechanisms should then be interpreted in the same way by all participants, while they might find it troublesome to name and categorize the support that is received from alters. Second, it possibly is perceived as disturbing to share such personal information.

2.3 Data analysis

The egocentric social networks were visualized and, subsequently, measures of graph theory were calculated. Furthermore, the participants were clustered according to their headache-specific locus of control profile (as will be explained in Chapter 5). The social network measures of those with high internal headache-specific locus of control were compared to those with low internal headache-specific locus of control by means of statistical analysis. Lastly, the data was extrapolated to investigate possible interventions in the social network. All these steps will be explained in detail in this section.

Table 2.1: Social network measures

	Network measure	Explanation	Equation
N	Size	Total number of nodes excluding the ego	
L	Ties	Total number of observed ties	
D	Density	The extent to which alters are interconnected	$D = \frac{2L}{N(N-1)}$
ni	Observed node importance	Total weight of all nodes excluding the ego	
I	Node importance	Ratio between maximum node importance and observed node importance	$I = \frac{3N}{ni}$
	Average tie strength	Average of the strength of all ties in the network	
HP	Health professionals	Number of contacts categorized as health professional	
F	Family	Number of contacts categorized as family	
C	Community	Number of contacts categorized as community	
O	Others	Number of contacts categorized as other	
B	Functional diversity	Measure of diversity of the network	$B = 1 - \sum {P_i}^2$

Social network measures

Measures of graph theory for social network analysis used in the current research were based on measures found in literature (Dhand et al., 2016; Hemmati and Chung 2014; Levula et al., 2013). The most common measures of graph theory were captured, like size, density and functional diversity. Density relates to the ratio of all possible ties that are actually present in the network. As such, density indicates if the alters in the network are highly interconnected or not. The node importance reveals if the ego generally considers the alters as being important for migraine management. Many slightly important (i.e., low weight) alters discloses a large network that might not easily impact the ego. The average tie strength indicates if the ego knows his/her alter generally well or not. Lastly, functional diversity is a measure that indicates how diverse a network is in terms of different categories of alters (i.e., health professionals, family, members of a community (friends, colleagues) and others). If the ego has connections to all such types of alters, the functional diversity is considered high. The diversity index as defined by Blau (1977) was used, in which P_i is the percentage of the *i*th category. Multiple measures were derived in Microsoft Excel 2016. The measures are summarized in Table 2.1

Cluster analysis

To obtain the clusters of headache-specific locus of control profiles, the subscores (i.e., internal, medical professional and chance locus of control) of the HSLC-DV were classified by K-means clustering. The goal of the algorithm is to divide *n* observations into *k* clusters. The observations are formed by the three subscores of each participant, represented as points in 3D space (i.e., one point in space per participant). The K-means algorithm works iteratively by assigning each data point to *k* randomly chosen cluster centers (*k* should be predefined). The shortest distance between the points and one of the cluster centers then determines the clustering. In this way, data points are clustered based on feature similarity, in which the clusters represent the locus of control profiles.

The K-means clustering was started with $k = 8$, as Wallston and Wallston (1982) described eight possible locus of control profiles (see Chapter 5). The HSLOC-DV subscale averages per cluster were then compared to the subscale averages of the entire sample to differentiate between high and low levels of subscales. The subscale was labelled "low" if the cluster average was lower than the sample average and "high" if the cluster average was higher than the sample average. This resulted in three scores per cluster, for example: low internal locus of control, high medical professional locus of control and low chance locus of control (i.e., the "pure powerful others" profile). However, some profiles occurred twice or three times in the $k = 8$ clustering. Therefore, *k* was adjusted until no double profiles occurred.

Statistical analysis

Initially, participants with high internal HS-LoC would be compared to participants with low internal HS-LoC, based on the locus of control profiles. However, group sizes were too small (6 and 9 participants respectively) to make a proper comparison. Therefore, network measures of the whole sample were compared to each of the three HS-LoC subscales (i.e., internal, medical professional and chance), to investigate possible links. Since we are interested in correlations, the Pearson's correlation coefficient was chosen as statistical test for all graph measures. A value of $p < 0.05$ was considered significant.

Extrapolation of data

Interventions in the egocentric social network would be revealed by adding nodes or rewiring existing ties, based on the network differences between those with high internal HS-LoC and those with low internal HS-LoC. However, since no dichotomized groups (i.e., high vs. low HS-LoC) were defined, the data was extrapolated to discover possible interventions in the egocentric social network. This extrapolation consisted of three steps. First, differences between profiles with high internal HS-LoC and profiles with low internal HS-LoC were analyzed on face value to discover a direction of possible interventions. Second, literature on treatment strategies other than medication was sought and third, these treatment strategies were viewed in light of the egocentric social networks in the current research.

2.4 Methods outline

Each of the upcoming chapters (with the exception of Chapter 5) was used to answer one of the four sub-questions. The corresponding methods can be found in Table 2.2.

Table 2.2: Methods used, with the corresponding chapter number and research question. RSQ = research sub-question, CH = chapter.

RSQ	Method (corresponding section)	CH
1	Literature study (patients' perceptions)	3
2	Literature study (theoretical framework)	4
3	Case study (cluster analysis, social network measures and statistical analysis)	6
4	Case study (extrapolation of data)	7

3 Patients' perceptions on migraine treatment

Chapter 3 presents the literature study of this research project, in which patients' perceptions are identified. First, broad treatment expectations, together with a holistic view of possible migraine management strategies are presented in Section 3.1. Then, perceptions based on each of the four self-management strategies are described in Sections 3.2 to 3.5.

3.1 Broad treatment expectations

In general, migraine patients have high global expectations of treatment at the first visit to a headache clinic. A study by Kelman (2006) showed that nearly all of the 1750 migraine patients interviewed during their first visit expected reduced frequency, reduced severity and an improved quality of life after treatment (see Figure 3.1). The results indicate that migraine patients feel optimistic about treatment at their first encounter with specialists.

Migraine management was divided into four groups of strategies, based on Peters et al. (2005): medication & pharmaceutical treatment, consultation, general management & non-pharmaceutical treatment and social support. A summary of these strategies can be found in Figure 3.2.

3.2 Medication and pharmaceutical treatment

Utilization

The vast majority of migraineurs (80-99%) relies on at least one type of *acute* medication to treat symptoms during an attack (Diamond et al., 2007; Peters et al., 2005; Gallagher and Kunkel, 2002; Dowson and Jagger, 1999). Acute medication includes over-the-counter (OTC) medication and prescription medication. Contrarily, *preventive* medication is used in 5-48% of cases, depending on the study population (e.g., patients in a clinical trial or general population) and the severity of migraine (Dowson and Jagger, 1999; Peters et al., 2005). Preventive medication can be prescription or homeopathic remedies and vitamins/minerals. Despite the high level of medication use, many migraineurs (64-75%), irrespective of study population, are not completely satisfied with their treatment medication (Lipton and Stewart, 1999; Davies et al., 2000; Dowson and Jagger, 1999; Brandes, 2002).

Needs and expectations

Patient satisfaction with medication mainly revolves around the expectations of the patient. In a survey among a general population in the United States, 688 migraineurs were asked to rate attributes of acute migraine treatment on the level of importance (rated from "Not at all important" to "Very important"). Complete pain relief was rated as "important" or "very important" by 87% of migraineurs, followed by no recurrence of pain (86%) and rapid onset of pain relief (83%), no side effects (79%), relief of associated symptoms (76%) and the route of administration (56%) (Lipton and Stewart, 1999).

A similar study in the USA by Gallagher and Kunkel (2002) showed akin results. Most migraineurs (77%) considered complete relief of pain as an important attribute of acute migraine medication, although only 34% ranked this attribute as the most important out of seven (Gallagher and Kunkel, 2002). Likewise, Brandes (2002) found that 39% of clinically diagnosed migraine patients in France, Ger-

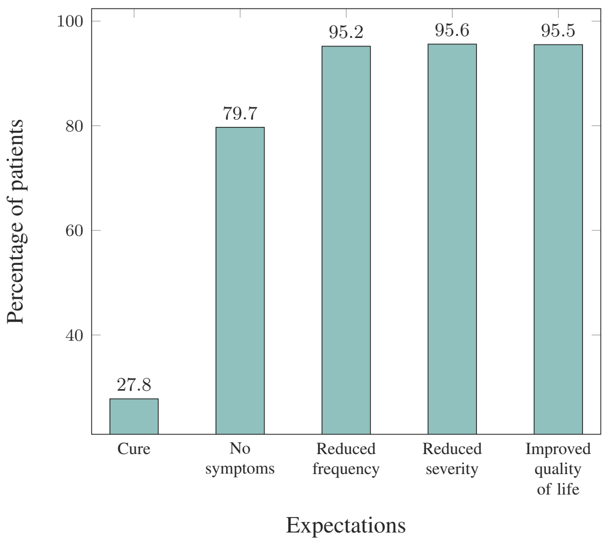


Figure 3.1: Broad treatment expectations of migraine patients at the first visit of a headache clinic. Source: Kelman (2006).

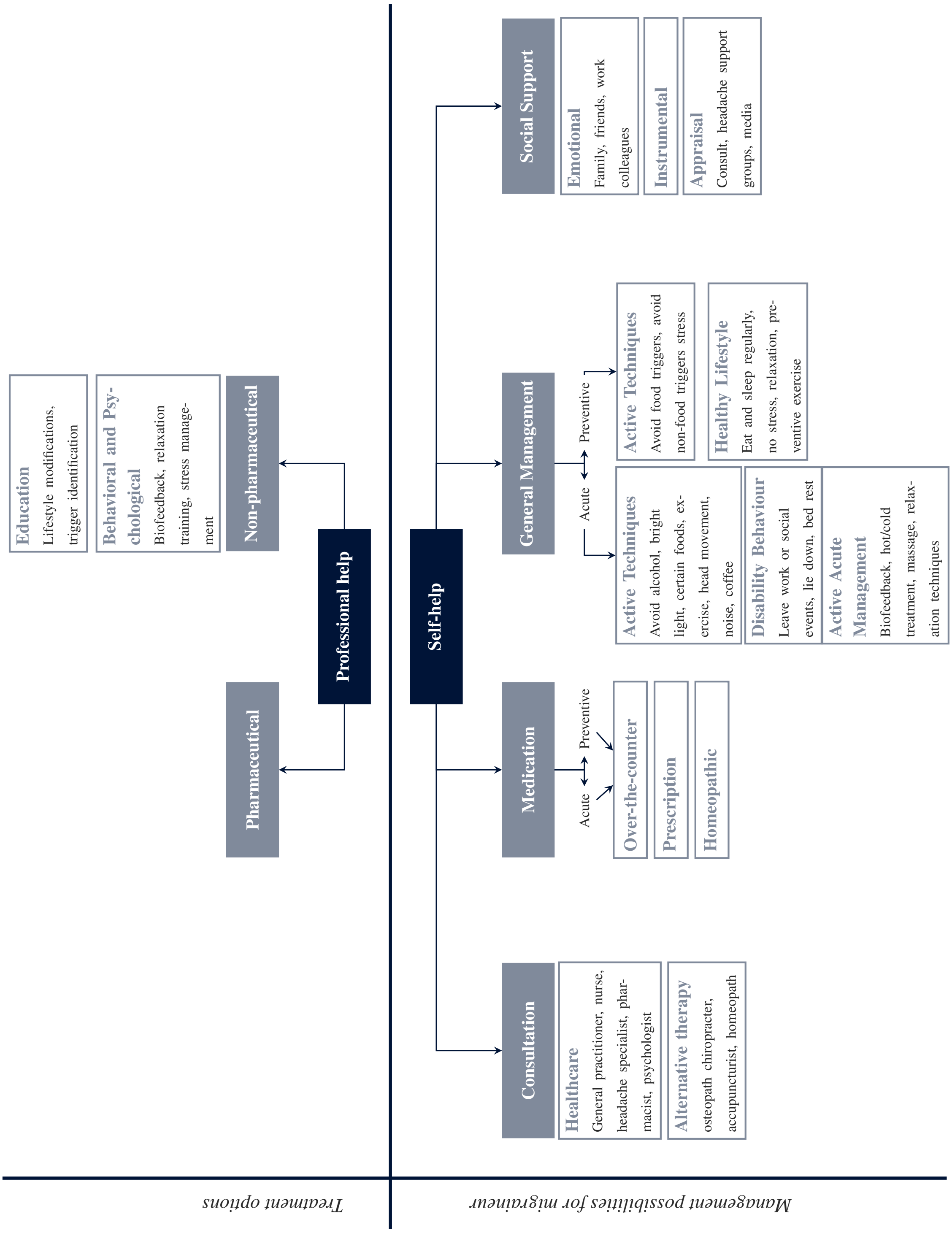


Figure 3.2: A holistic view on the possible management strategies for migraineurs, based on the division by Peters et al. (2005).

many, Italy, the UK and the USA considered high efficacy as the most important attribute, followed by rapid pain relief (33%).

An international, clinic-based study among 250 patients from Brazil and the USA showed similar results for preventive medication. The participants were asked to rate preventive treatment attributes in order of importance (from 1 to 7). The majority of patients (72%) rated efficacy (i.e., headache elimination) as the most important or second most important attribute of preventive medication, followed by speed of onset (12%) and absence of side effects (6%) (Peres et al., 2007).

All previous mentioned studies used predefined lists of attributes to discover the needs and expectations of migraineurs. Smelt et al. (2014) researched patient expectations among 300 migraineurs in the Netherlands, without predefining possible attributes. Instead, the researchers created a list of attributes based on the patients' opinions. The answer to the open question "what would you wish the effect of a new medicine would be?", was most frequently answered by "the elimination of headache" (18%) and "no adverse effects" (15%). The researchers, however, excluded all items not focusing on the direct effect of migraine on the patient (e.g., "not too expensive") in the final outcome. The five most important attributes according to the participants were:

1 Take away the headache 82%

2 Prevent the attack from carrying through 68%

3 Make sure no other attack follows within a few hours or within a day 56%

4 Let me function properly again 56%

5 Clear my head 38%

In order to review if the self-conceived answers of the participants would match the current (predefined) ideas of patient expectations in earlier literature, the participants additionally ranked existing outcome measures normally used in clinical trials. Again, many attributes were considered important. Decrease of headache (pain relief) and time of effect (rapid onset) were ranked highest, followed by no recurrence.

All studies show similar results, although a proper comparison is difficult. First of all, scores are influenced by personal preferences of participants. For example, in the study of Gallagher and Kunkel (2002), the 11% of participants who rated "no side effects" as the most important attribute were slightly older and reported milder headaches compared to the rest of the study population. Furthermore, Lipton and Stewart (1999) only indicated the use of a Likert-scale from "Not at all important" to "Very important", without noticing the exact scale. The same holds for the study of Gallagher and Kunkel (2002). Brandes (2002) used the same method as Smelt et al. (2014) by giving an average assessment score, but without the amount of migraineurs actually experiencing the symptom. Such differences should be taken into account when comparing research outcomes.

In general, migraineurs consider a wide range of attributes as important in acute medication use. Still, it can be concluded from the above findings that medication that relieves all pain with rapid onset will most likely meet the needs of migraineurs.

Dissatisfaction

Several approaches have been used to study patient (dis)satisfaction of acute and preventive medication. One such method is to study satisfaction based on the outcomes, or endpoints, in clinical trials, in which the level of pain, the speed of onset, the headache recurrence rate and side effects are measured (Davies et al., 2000). The use of predefined endpoints make clinical trials scientifically robust and constitute a major part of the evidence for the efficacy of treatment. Based on patient expectations, the International Headache Society created guidelines for controlled trials of migraine medication. As a primary outcome, the IHS recommends to measure the percentage of participants who are completely free of pain at two hours after taking medication (pain free at 2h). Kramer et al. (1998) found that participants were pain free at 2h in approximately 30% of attacks, left with mild pain in 31% of attacks and continued having moderate to severe pain in 39% of attacks. All attacks in this study were moderate to severe at the beginning of treatment. Other studies found comparable results with similar medication (Goadsby et al., 2008).

Davies et al. (2000) found that the majority of migraineurs who were pain free at 2h are very satisfied with their treatment in terms of level of pain, functional ability, associated symptoms and the speed of onset. However, participants were completely satisfied in only 27% of migraine attacks. Apparently, most of the satisfied participants who are pain free at 2h are still (slightly) unsatisfied about some attribute of their migraine treatment. Furthermore, participants experienced complete pain relief at 2h in only 30.3% of cases, meaning that in a little less than 70% of attacks residual pain after two hours was experienced. (Davies et al., 2000).

Residual pain seems to be a reason for dissatisfaction among migraineurs. Inadequate pain relief was also mentioned as a reason for dissatisfaction by 84% of participants in a qualitative study by Lipton and Stewart (1999). Among the 688 migraineurs, 71% was unsatisfied to some extent. Most participants (87%) were unsatisfied, because the medication took too long to relieve the pain. Furthermore, the inconsistent working of medication (84%) was an important issue to migraineurs, as well as headache recurrence (71%). Too many side effects were a reason for dissatisfaction for less migraineurs (35%) (Lipton and Stewart, 1999).

Two explanations for dissatisfaction

Two (related) explanations for dissatisfaction can be found:

1. Patients are afraid of side effects

2. "Rapid" onset means 30-60 minutes according to migraineurs

Medication intake is often postponed or avoided, because migraineurs are afraid of side effects, fear that the effectiveness of medication will decrease when taken too frequently or do not want to be dependent on medication (Peters et al., 2004; Foley et al., 2005). These concerns can delay or avoid the timing of medication intake, while early intake (i.e., when the headache is still mild) has been associated with improved outcomes of migraine treatment (Gallagher and Kunkel, 2002; Goadsby et al., 2008). Approximately one-third (37%) of migraineurs delays and almost one-half (44%) avoids their prescription medication (Gallagher and Kunkel, 2002). According to Gallagher and Kunkel (2002), "the impact of delaying or avoiding the use of prescription medication was: more intense pain, the need to lie down, extended duration of the headache, the need to cancel social activities, suboptimal performance at school or work and absence from work."

If medication is taken in time (i.e., within 1 hour of onset of the migraine attack), then it is more likely to meet the patients' expectations. Goadsby et al. (2008) found that the "act-when-mild" (AwM) paradigm ensures a significantly increased amount of patients with a pain free status at 2h compared with late medication intake. Significantly less AwM-patients had headache recurrence within 24h and the average duration of migraine attacks was significantly lower (Goadsby et al., 2008). Furthermore, the AwM-patients achieved the pain free status significantly faster (1.5h) than patients taking medication after pain had become moderate to severe (2.1h).

According to migraineurs, the time to satisfactory relieve migraine pain is less than 30 minutes according to 71% and less than 60 minutes according to 21% of the 688 participants in the survey by Lipton and Stewart (1999). Another study (Dahlof, 1999) confirmed these findings, stating that 30 minutes to pain relief was considered rapid by 84% of participants, 60 minutes by 16% and no participant considered more than 60 minutes as rapid.

3.3 Consultations

Utilization

Healthcare utilization rates for migraine vary greatly per country, per migraine type and per study sample. In the US and UK, many migraineurs from a population-based sample (68-75%) have consulted a healthcare professional regarding their disorder at least once in their lifetime, including alternative therapists (Dowson and Jagger, 1999; Lipton and Stewart, 1999). This number is slightly higher for members of a lay headache organization (78%) (Peters et al., 2005). Of all health professionals, the general practitioner is consulted most often (67-79%), followed by the pharmacist (18-31%) and the neurologist (10-23%), depending on the type of migraine. Lastly, consultation rates are even higher for migraineurs on prescription medication; 75% visits the GP frequently and 27% consults the neurologist at least once (Gallagher and Kunkel, 2002).

On the contrary, healthcare utilization for migraine is poor in (the rest of) Europe. A recent study conducted in 10 western-European countries discovered that only 21-40% of the general population consulted a healthcare professional (medical or non-medical) regarding their migraine. The number of migraineurs not consulting any professional is highest in the Netherlands (80%) and lowest in Spain (60%). Merely 10-18% of the population visits the GP and 3-15% seek advice from a specialist. Again, those numbers are higher for members of a lay headache organization (consulting: 56-59% of which GP: 13-30%, specialist: 22-34% and non-medical: 4-11%, depending on the country) (Katsarava et al., 2018).

Attitudes

As shown in Section 3.2, migraineurs are often not entirely satisfied with their pharmaceutical treatment. As such, many migraineurs try multiple types of medication. Still, 67-75% of those who have ever tried a certain drug continue taking it, even if that drug is not considered as the best therapy (Dowson and Jagger, 1999). The reason for continuing (partly) ineffective treatment might be found in the reliance of patients on the advice of the GP or pharmacist. Accordingly, “Doctor recommended the medication” was considered as an important attribute for taking medication (Gallagher and Kunkel, 2002).

Expectations

In general, migraine patients consider consultations with their GP as a means to obtaining prescription medication or advise on over-the-counter medication (Peters et al., 2004). However, most patients would also like to discuss migraine-related issues, such as the impact of migraine, the uncovering of triggers or the search for a cure (Peters et al., 2004; Cottrell et al., 2002). A survey among 688 migraineurs revealed six items of importance to migraine patients regarding consultation with their GP (Lipton and Stewart (1999). These items and the respective percentage of patients considering them important are:

1 The willingness to answer questions 86%

2 Education about the causes of migraine 72%

3 Teaching how to treat attacks 72%

4 Teaching how to avoid attacks 69%

5 Medical expertise in diagnosis and treatment 69%

6 Being understanding and compassionate 61%

Although the above items apply for GP consultation, it is likely that migraineurs want the same from other medical professionals. In fact, expectations, but not satisfaction, are even higher for specialist consultations (Peters et al., 2004).

3.4 General management and non-pharmaceutical treatment

Utilization

Even though migraineurs believe that migraine management mainly revolves around pharmaceutical treatment and healthcare consultations (Peters et al., 2004), most of them use additional acute or preventive management strategies (Peters et al., 2005). These include avoidance techniques (e.g., avoiding bright light), disability behaviours (e.g., bed rest), active strategies (e.g., biofeedback) and a healthy lifestyle (see Figure 3.2).

Some strategies are generally used, while others seem particularly relevant to the individual migraineur. For example, some migraineurs report that digging fingers into the neck or banging the head off walls is helpful, while others avoid head movements as much as possible. According to Peters et al. (2005), both disability behaviour and a preventive healthy lifestyle are widely adopted management strategies (see Figure 3.3). The majority of migraineurs (93%) lie down and/or slow down during an attack (Peters et al., 2005). Likewise, Brandes (2002) found that more than half of migraineurs (62%) supplement their prescription medication with bed rest. Acute avoidance techniques are generally used often as well, while the amount of migraineurs using preventive avoidance strategies is slightly lower. Active strategies are less likely to be implemented by migraineurs (Peters et al., 2005; Leiper, Elliot and Hannaford, 2006).

Expectations of non-pharmaceutical strategies

Non-pharmacological treatments are not typically considered as a standard part of treatment. However, both Peters et al. (2004) and Leiper, Elliot and Hannaford (2006) point out that the participants in their studies generally express interest in such therapies (e.g., homeopathy or reflexology) and most current users are positive.

Morgan et al. (2016) researched patient experiences and satisfaction with behavioral treatment based on pretreatment expectations. Prior to the treatment, 60% of participants indicated to take part because of treatment "fatigue"; they wanted to try an alternative after a long history of treatment approaches that were insufficient, or side effects that were not well tolerated. The desire of alternative treatment approaches did not depend on migraine frequency. However, 35% of participants were skeptic about the link between behavioral treatment and migraine management (Morgan et al., 2016). After treatment, 90% of participants felt they had benefit from the treatment to at least some extent, even the ones who were skeptic at first. Relaxation techniques were mostly reported as beneficial, particularly to reduce the onset of migraine.

3.5 Social support

Research on experiences and needs considering social support for migraine management are scarce. Social support is the least used management strategy of the four according to Peters et al. (2005). Most approaches of social support were used at least once by 30% of their study sample. These approaches were the use of media (internet, magazines, newspapers), going to family and friends and patient support by other headache patients and support groups. Social support can be important to migraineurs in order to "give and receive support and understanding and to exchange information and gain insights into other management strategies," (Peters et al., 2004).

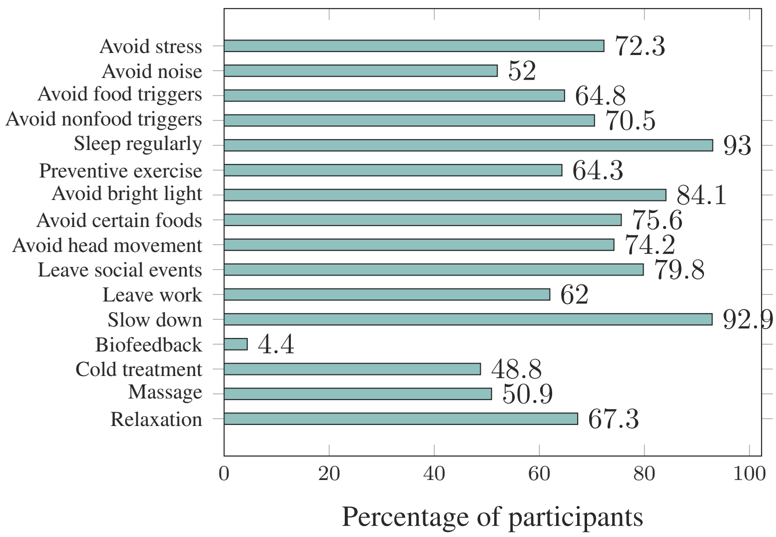


Figure 3.3: The general use of avoidance techniques, disability behaviors, active strategies and healthy lifestyle among members of a lay migraine patient organization (Peters et al., 2005)

Social support has been linked to health outcomes and behaviors. As such, it influences treatment adherence as well. Lack of support and poor family communication have been associated with bad adherence rates. (Rains et a., 2006b).

4 Theoretical framework

In this chapter, an explanation for the wide variety in patient perceptions is presented, which answers to the second sub-question in this research. As such, the theoretical framework is introduced first in Section 4.1, in which theories and theoretical models are connected. Each theory is then presented in a separate subsection, being the biopsychosocial model of health, a theoretical model of expectations, theory on patient-physician communication and theories on psychological mechanisms and behavior.

4.1 Theoretical framework

The theoretical framework can be found in Figure 4.1. As can be seen, there are two entries into the framework: pharmaceutical treatment and non-pharmaceutical treatment. The combination of pharmaceutical and non-pharmaceutical treatments was demonstrated to be highly effective (Seng and Holroyd, 2010). Yet, as explained in Chapter 3, the standard approach today to migraine treatment is pharmaceutical, and most migraineurs are not entirely satisfied with their migraine medication. Other forms of professional help are sometimes used, like non-pharmaceutical treatment, but migraineurs are generally skeptical and reluctant to such approaches. At the end of this section, we will argue why medication is the prevailing approach to treatment and why migraineurs are reluctant about alternatives (non-pharmaceutical treatment) based on the theoretical framework.

The framework starts with the biopsychosocial model of health (subfigure 4.1 a).

The biopsychosocial model of health

Migraine comes along with headache. One way to explain such pain is by the *biomedical model*, in which the perspective is purely biological. As such, pain is characterized by "a direct transmission of impulses from the periphery to structures

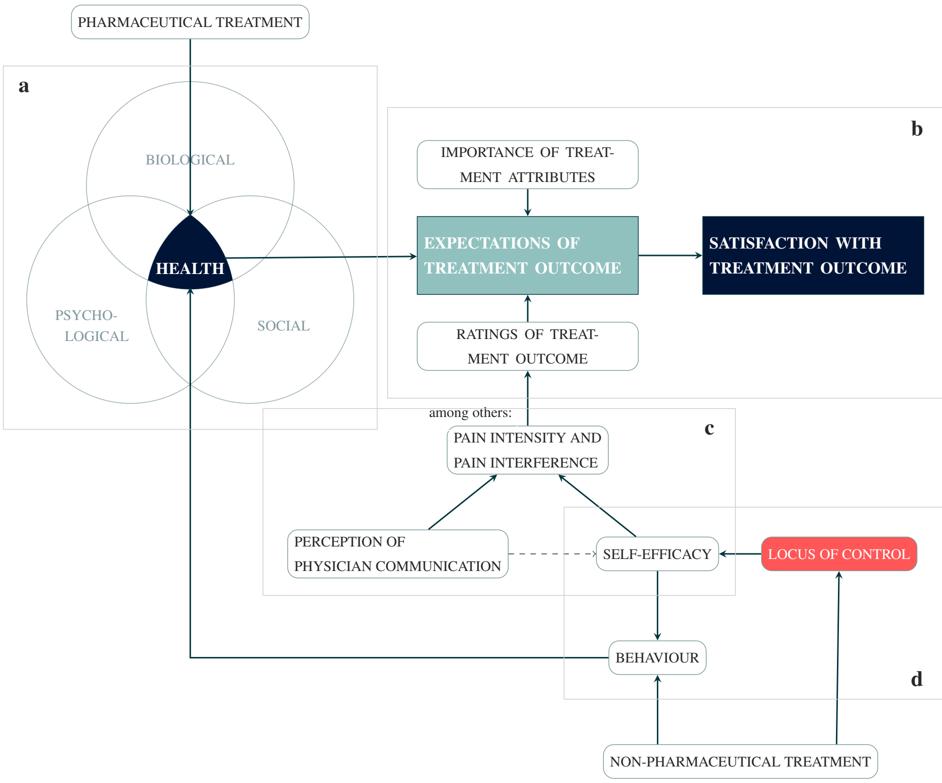


Figure 4.1: The theoretical framework consists of four theoretical models or theories that have some overlap. The framework consists of the biopsychosocial model (a), a theoretical gap model of expectations (b), the influence of patient-physician communication on physical pain experiences (c) and theories on psychological mechanisms and behavior (d). The locus of control is considered as to have a pivotal role in migraine self-management and was chosen as the topic of further research.

within the central nervous system" (Turk and Flor, 1999). Hence, pain can (in theory) be relieved by interrupting this transmission with medication. However, two arguments oppose the biomedical model of health.

First, the biomedical model cannot explain the failure of medication to consistently relieve pain (Andrasik, Flor and Turk, 2005). Second, according to Merskey (1986) pain is "unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an *emotional experience*". It is debatable whether pain is always experienced as unpleasant, but there is no doubt that pain goes hand-in-hand with anxiety, depression and/or anger (Andrasik, Flor and Turk, 2005). As such, psychological treatments have demonstrated to be effective for migraine outcome as well (Seng and Holroyd, 2010). Other factors, like social support, have also shown to improve medication adherence and thereby health outcomes, as was explained in Section 3.5. The biomedical model therefore fails to explain certain aspects of the development, course and consequences of migraine.

An alternative viewpoint is the more heuristic *biopsychosocial model*, in which health is characterized as arising from a complex interplay between biological, social and psychological factors. Examples of such factors are genetics, prior learning history, psychological status and cultural context, and patients' perceptions can be understood as emerging from their complex interactions (Andrasik, Flor and Turk, 2005).

In light of the biopsychosocial model, health in migraine is not just influenced by biological factors. Instead, the state of health is mediated by biological, psychological and social factors. This state of health drives the patient to have certain *expectations* concerning treatment.

A gap model of expectations

Chapter 3 provided an elaborate description of patient expectations on different aspects of migraine management. Stimson and Webb (1975) showed that pretreatment expectations have a strong relationship with perceptions of the benefits of care and patient satisfaction (Stimson and Webb, 1975). Subfigure 4.1b therefore shows the relationship between expectations and satisfaction. Based on models of consumer satisfaction, the best prediction of patient satisfaction is by measuring the difference between pretreatment expectations and the perceived performance of the treatment. Treatment satisfaction will therefore improve when the gap between expectation and performance is reduced. The perceived performance of the treatment is indicated by "ratings of treatment outcome". Additionally, the underlying patient preferences may be represented by a measure of "importance of various treatment attributes" (pain relief, speed of relief, side effects etc.). As such, patient preferences are an important source of the patient's expectations (Patrick et al., 2003).

Two measures of treatment performance are pain intensity and pain interference (Antonaci et al., 2008), see Subfigure 4.1c. Pain interference indicates the effect of pain on the patient's quality of life. The following subsection therefore takes these two ratings of treatment outcome as a starting point.

Patient-physician communication and pain experience

As explained in Chapter 1 of Part I, the mechanisms through which patient-physician communication reduces pain are still not known. Street et al. (2009) state that "while talk itself can be therapeutic (e.g., by lessening the patient's anxiety of providing comfort), more often patient-physician communication influences health outcome via a more mediated route." Factors like trust, mutual understanding and *self-efficacy* are among the pathways that might influence health outcomes as well (Street et al., 2009).

Still, patient-physician communication has a direct impact on the quality of care and achievement of successful treatment (Peters et al., 2004; Leroux et al., 2017; Cottrell et al., 2002). As such, Patwardhan et al. (2007) performed a systematic review on the impact of patient understanding and physician communication on migraine management. They accumulated indirect evidence, resulting in the following associations (Patwardhan et al., 2007):

- "Improved patient-provider communication results in greater satisfaction with individual medical encounters;
- Over time, improved patient-provider communication results in increased patient knowledge and empowerment;
- Improved patient knowledge and outcome results in improved patient self-management;
- And improved patient self-management results in improved satisfaction with medical care and improved clinical outcomes".

The findings by Patwardhan et al. (2007) imply that patient-physician communication should be improved for better clinical outcomes, as is also depicted in Subfigure 4.1c.

Furthermore, self-efficacy is thought to be an outcome of patient-physician communication and as such plays intermediary role in health outcomes. Self-efficacy is "the confidence in one's ability to use behavioral skills to prevent and manage recurrent headaches" (Seng and Holroyd, 2010). This and another psychological mechanisms (the *locus of control*) influencing health behavior are elaborated on in the following subsection.

Psychological mechanisms and behaviour

Based on social psychology, two types of beliefs that influence self-management behavior (e.g., diet or self-imposed work pressure) are self-efficacy and the locus of control (see Subfigure 4.1d). The locus of control are the "beliefs about the factors that influence the onset and course of headache attacks," (French et al., 2000). Self-efficacy beliefs, however, are located closer to the actual execution of self-management behavior (Seng and Holroyd, 2010), which is why a direct link exists in Subfigure 4.1d.

High levels of self-efficacy have been associated with increased pain tolerance, increased levels of physical activity and enhanced adaptation to pain problems (French et al., 2000, Ruben et al., 2017). The locus of control has been linked to coping with chronic pain as well, as will be explained in the following chapter. Typically, non-pharmaceutical treatment is directed to change the locus of control beliefs (Seng and Holroyd, 2010).

Locus of control and self-efficacy are most probably related, as the confidence to execute behavior (self-efficacy) must require the believe that the factors influencing migraine are within the patient's control (locus of control). However, this relationship is not necessarily reciprocal; a patient can believe that he is in control over the factors influencing attacks, but completely lack confidence in the ability to act upon it (French et al., 2000; Seng and Holroyd, 2010).

The locus of control plays a pivotal role in the theoretical framework as depicted in Figure 4.1. It affects self-efficacy, which in turn influences health-related behavior and the way in which pain is perceived, both of which influence satisfaction with treatment outcome indirectly. Therefore, the locus of control was chosen as the topic for further research.

Pharmaceutical and non-pharmaceutical treatment

Pharmaceutical treatment has a direct impact on biological factors of the patient's state of health. The state of health, in turn, forms the basis of treatment expectations, which has shown to have a strong relationship with treatment satisfaction. The link between medication and treatment satisfaction is therefore rather direct. Non-pharmaceutical treatments, however, have a much more indirect impact on treatment satisfaction, as they focus on behavioral changes, which in turn affect health. Satisfaction with treatment therefore takes more time. Or, as Andrasik et al. (2009) state: "behavioral treatments rarely provide the quick relief that can occur with medication." This might explain why migraineurs are reluctant to non-pharmaceutical treatments; they do not provide the quick pain relief that is typically an important attribute of treatment.

5 Headache-specific locus of control

The locus of control was chosen as the topic of further investigation for this research, as it is related to the impact of headache and is thought to be central to the success of migraine management. Although commonly mentioned in literature as being an important aspect, few studies have researched the influence of locus of control on migraine management. This chapter will elaborate on the *headache-specific* locus of control (HS-LoC). The headache-specific locus of control is introduced in Section 5.1, after which different profiles of locus of control are explained in Section 5.2.

5.1 Introduction to the headache-specific LOC

Literature on self-management of chronic disease posits that changing disease-specific self-efficacy and locus of control is a central goal in self-management interventions for chronic disease. The theoretical framework presented in Chapter 4 supported this statement. As stated before, the locus of control is the belief one has about factors influencing the onset and course of headache attacks. It is about the feeling of responsibility and, as such, can be divided into three subscales: internal, medical professional and chance locus of control.

Internal locus of control refers to the responsibility one feels for controlling his/her own migraine attacks. Medical professional locus of control indicate the extent to which patients hold the medical professional responsible for resolving the migraine attacks. Lastly, chance locus of control reveals the extent to which the patient considers his/her attacks as a matter of fate (Wallston and Wallston, 1982).
The LoC subscales have been associated with health outcomes in a wide range of studies. Concerning *health LoC* (which is on a somewhat more general level than headache-specific LoC), a higher internal LoC has been linked to better adjustment of the disorder, more adaptive coping, less pain and disability and a higher likelihood to returning to work (Cano-Garcia et al., 2013; Nicholson et al., 2007). Individuals with high chance LoC are typically fatalistic and use maladaptive cop-

ing strategies. Furthermore, high chance and high medical professional LoC are usually associated with the interference of pain in daily life, decreased physical activity and abuse of medication.

5.2 LoC profiles

Despite the aforementioned study results, the role of each of the subscales in chronic pain is not consistent throughout literature (Cano-Garcia et al., 2013). Consequently, the separate interpretations of internal, medical professional and chance LoC for disease management have been criticized. Wallston and Wallston (1982) proposed eight possible locus of control profiles, based on high or low scores on each of the three subscales (see Table 5.1). Instead of the interpretation of each separate subscale, a profile of locus of control is made based on a combination of the three. Ultimately, such profiles provide better information on how to incorporate the locus of control in therapeutic interventions.

Only a handful of studies on health behavior have used the profiles as proposed by Wallston and Wallston (1982) to explore LoC patterns. These studies looked at cancer patients (Frick et al., 2007), university students (Rock et al., 1987), women (Raja et al., 1994), adolescents (Ozolins et al., 2003) and chronic pain patients (Buckelew et al., 1990; Cano-Garcia et al., 2013). A distinction can be made between high and low values of each subscale by using *cluster analysis*. Therefore, it is possible that not every profile appears in the study sample. Of all profile-studies, the number of clusters found ranged from three to eight. The method for cluster analysis can be found in Chapter 2. One might expect that headache-specific locus of control would be correlated with education or sex. However, Willekens et al. (2018) found no statistical significant difference between men and women or low versus high education. However, medical professional HS-LoC was higher in those who participated in treatment compared to those who did not. Higher chance HS-LoC was linked with a more headache days and headache duration. Interestingly, those who moderately exercised showed lower internal HS-LoC compared to those who did not sport at all.

The characteristics of all profiles, resulting from the above mentioned literature, are described here. Care should be taken when interpreting the findings of these studies; they are not always consistent. As such, the participants in the current research might have different characteristics than the ones described in this section.

Pure internal

The pure internal profile shows a high level of internal locus of control and low levels of powerful others and chance locus of control. This profile has been associated with active disease coping styles and a better general state of health. However, chronic pain patients in the pure internal group have also been found to self-blame

Table 5.1: Locus of control profiles, adopted from Wallston and Wallston (1982).

Type	Description	I-LOC	P-LOC	C-LOC	Comment
I	Pure internal	+	-	-	"...depends on me"
II	Pure powerful others	-	+	-	"...depends on others"
III	Pure chance	-	-	+	"...depends on chance"
IV	Double external	-	+	+	"...does not depend on me"
V	Believer in control	+	+	-	"...depends partly on me and partly on others"
VI	Type VI-LOC	+	-	+	"...depends partly on me and partly on chance"
VII	Yeasayer	+	+	+	"...depends on all three factors"
VIII	Naysayer	-	-	-	"...does not depend on any of the three factors"

(Buckelew et al., 1990). Other studies found that the pure internal profile was related to high educational and socioeconomic levels and a better general state of health. Furthermore, this profile was associated with the best adjustment to pain of all the patterns (Cano-Garcia et al., 2013).

Pure powerful others

Pure powerful others have also demonstrated to adjust well to pain. Individuals in the pure powerful others profile generally have active coping styles and a better state of health compared to the other profiles (Cano-Garcia et al., 2013). However, this profile has also been associated with worry (Rock et al., 1987).

Pure chance

Not much is known about the pure chance profile, except for a worse state of health (Cano-Garcia et al., 2013).

Double external

The double external profile has been linked to depressive coping styles by Frick et al. (2007). No other information was found on this profile.

Believer in control

According to Wallston and Wallston (1982) the believer in control is the most adaptive of all profiles. However, Cano-Garcia et al. (2013) found that the believer in control has worse adaptation to pain than the pure internal and pure powerful others profiles. Individuals in the believer in control group do not consider luck or fate as the underlying element of their disease. Instead, they believe that their health is controllable, either by themselves or by someone else. This profile has been associated with active search for treatment in patients with chronic pain (Buckelew et al., 1990; Raja et al., 1994). An association with active pain coping styles was found as well. According to Wallston and Wallston (1982): "This constellation of beliefs could be particularly beneficial to a person who has to cope with a chronic illness, where much of the responsibility for successfully treating the condition lies with the patient carrying out the treatment regimen prescribed by the physician."

Type VI-LOC

According to Wallston and Wallston (1982), this profile is "probably non-existent, extremely rare or conceptually difficult to understand." This profile was only found in one of the profile studies, in which it was associated with poor general state of health (Ozolins and Stenstrom, 2003).

Yeasayer

The yeasayer profile is similar to the believer in control profile, except for the additional high level of chance LoC. Like the believer in control, the yeasayer has an active coping style (Cano-Garcia et al., 2013). In some of the other studies, the yeasayer profile was associated with the worst general state of health (Cano-Garcia et al., 2013) and low educational and socioeconomic levels (Raja et al., 1994). Yet, according to Wallston and Wallston (1982), the yeasayer might be better off than the believer in control. If a patient knows that chance plays a role in getting migraine, he might better understand and accept the attacks when his own efforts or those of a professional lead to no result. However, according to Cano-Garcia et al. (2013), this profile is highly maladaptive.

Naysayer

This profile was shown in many of the profile studies of health locus of control, but it was not associated with any outcome.

6 Case study

This chapter outlines the case study and answers the sub-question: to what extent can the headache-specific locus of control be linked with the egocentric social network? A description of the case is given in Section 6.1, followed by the results in Section 6.2.

6.1 The case

Patient journey

Individuals with severe headaches are referred to the HOD, mostly by the general practitioner. From that point on, the HOD will take action to help the headache patient to the best of their ability. The first step is to uncover the type of headache (e.g., migraine or cluster headache) in order to designate the patient to the right physician. Accordingly, the patient is invited by the HOD to fill out online questionnaires (see Figure 6.1) on which a screening of the type of headache is based. The online questionnaires are a prerequisite for making the hospital appointment. If the disorder is screened as migraine, the patient is additionally asked to keep track of an online headache diary for 28 days (prior to the appointment). The goal of the diary is to acquire a better picture of medication (over)use and the frequency, duration and severity of migraine attacks. This additional information will help the physician to provide more specific advice to the patient.

Actors at the HOD

The actors who are involved in the HOD and their roles are:

- Secretaries; plan the appointment (after questionnaires are filled out). They are the first point of contact for patients.
- Headache nurses; provide support to patients by means of information, a treatment plan to detox from medication overuse or by involvement in the

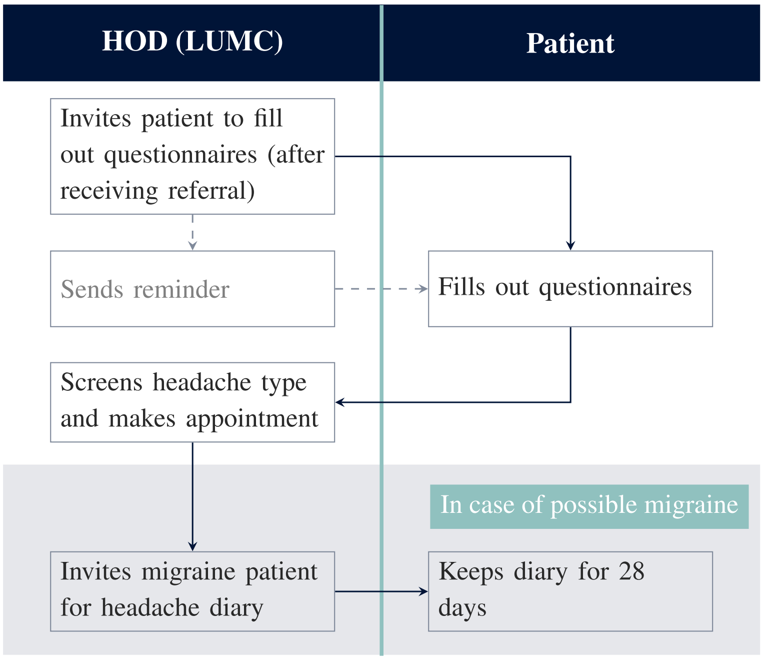


Figure 6.1: The patient journey from the moment of referral to the day of the appointment.

patient's progress. Furthermore, patients are invited to contact the headache nurse in case of any questions.

- A team of physicians (neurologists, trainee neurologists and physician researchers); offer specialist care and advice to patients either face-to-face or by telephone.

Participants

Fifteen migraine patients under HOD treatment participated in the current research. The sample characteristics can be found in Table 6.1. The aim was to include 30 to 40 participants, but this number was halved for several reasons. Some of the eligible migraine patients did not want to participate in the study. Furthermore, some physicians forgot to refer the patients to the researcher after their appointment. Data could be collected only one day a week and, due to limited research time, the data collection took place within three weeks.

6.2 Results

The participants were questioned about their headache-specific locus of control and personal social network. Based on the HS-LoC subscales (internal, medical professional and chance), the patients were grouped in HS-LoC profiles. Due to

Table 6.1: Sample characteristics of the participants. SD = standard deviation.

	Mean (SD)
Age (years)	42.8 (8.6)
Migraine duration (years)	18.1 (14.6)
Number of attacks (p/month)	6.1 (3.6)
Headache days (p/month)	9.4 (6.6)
Sex ratio (women:men)	13:2

the low amount of data, the resulting profiles were not dichotomized (high vs. low internal headache-specific locus of control) and tested for group differences in terms of various social network measures. Therefore, social network measures of the entire sample were compared to each of the HS-LoC subscales instead to test for possible correlations between locus of control and the social network.

Cluster analysis

Cluster analysis of the HS-LoC subscales (internal, medical professional and chance) yielded four profiles in this study: the *pure powerful others*, the *yeasayer*, the *believer in control* and the *pure chance*. Table 6.2 shows the descriptive statistics for the entire sample as well as for the four profiles.

The deviation of group means from the sample means are presented in Figure 6.2. Participants with the *pure powerful others* profile are characterized by the lowest internal HS-LoC (compared to the sample average) of all profiles, with higher medical professional HS-LoC and lower chance HS-LoC than average. The *believer in control profile* shows the highest internal HS-LoC, with comparable medical professional HS-LoC as the pure powerful others group. Internal HS-LoC is high compared to the sample average in the *yeasayer* group as well, with near average medical professional HS-LoC and higher chance HS-LoC. The *pure chance* profile shows slightly higher chance HS-LoC compared to the average, but lower internal and medical professional HS-LoC.

Table 6.2: Mean, standard deviations and number of subjects for each headache-specific locus of control subscale per profile.

HS-LoC subscale	**Internal** $M \pm SD$	**Med. prof.** $M \pm SD$	**Chance** $M \pm SD$	Number
Entire sample	30.8 ± 13.1	28.8 ± 5.7	34.0 ± 5.1	15
Pure powerful others	17.3 ± 5.7	32.0 ± 1.5	31.0 ± 1.7	3
Yeasayer	42.3 ± 4.4	29.0 ± 5.6	38.7 ± 4.9	3
Believer in control	47.7 ± 3.5	33.0 ± 3.5	29.0 ± 2.6	3
Pure chance	23.3 ± 5.2	25.0 ± 5.7	34.0 ± 4.6	6

Network measures and statistical analysis

Correlations between each HS-LoC subscale (internal, medical professional and chance) and various network characteristics were calculated using Pearson's correlation coefficient. The network characteristics were "size", "density", "node importance", "average tie strength", "functional diversity", "number of contacts categorized as health professional", "number of contacts categorized as family", "number of contacts categorized as community" and "number of contacts categorized as other" (see Section 2.3).

The descriptive statistics for the social network characteristics are shown in Table 6.3. No statistically significant correlations were found between the internal, medical professional or chance HS-LoC and network size, density, average tie strength or functional diversity. Node importance revealed a positive correlation with the internal HS-LoC (r=0.52, p <0.05), but not with medical professional or chance HS-LoC. The correlation is significant even whilst controlling for network size (r=0.535, p <0.05), which suggests that network size has little influence on the relationship between internal HS-LoC and node importance.

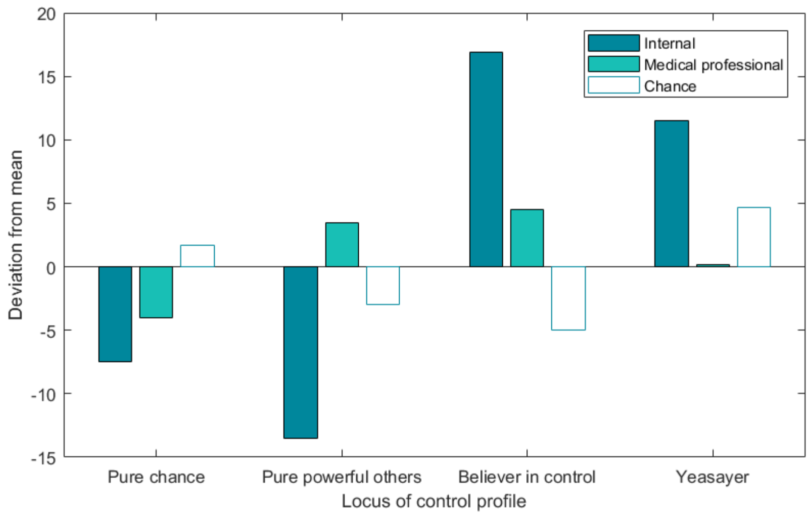


Figure 6.2: The deviation of internal, medical professional and chance scores from the mean of each subscale for the four headache-specific locus of control profiles.

Table 6.3: Descriptive statistics of the social network measures

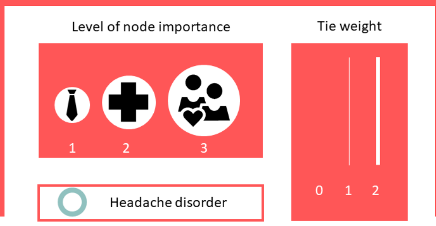
Network measure	M ± SD	Min	Max
Size	3.8 ± 3.2	0	11
Density	0.4 ± 0.4	0	1
Node importance	0.7 ± 0.2	0	1
Average tie strength	1.6 ± 0.5	0	2
Functional diversity	0.4 ± 0.2	0	0.8
Health professionals	0.5 ± 0.5	0	1
Family	2.0 ± 1.6	0	6
Community	1.2 ± 1.9	0	7
Other	0.13 ± 0.35	0	1

The social networks

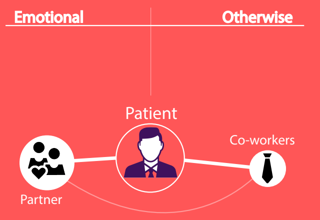
The egocentric social networks are visualized in the following pages. As explained in Section 6.2, the participants are divided into four clusters that represent the locus of control profiles. The interpretation of the social network is as follows: the center of the network is the patient (ego). The ego was asked who he/she regarded as important (over the course of the last six months) for the ego's migraine management. These alters are depicted by icons of various sizes. The size of the icon represents the level of importance of that alter to the patient. Furthermore, the tie weights are represented by the thickness of the tie and represent if the ego knows the alter rather well or not. The networks are divided into an "emotional" side and an "otherwise" side, to distinct between alters providing emotional support and any other form of support. An elaborate analysis of the interpretation of the networks is provided in the following chapter.

6.3 Summary

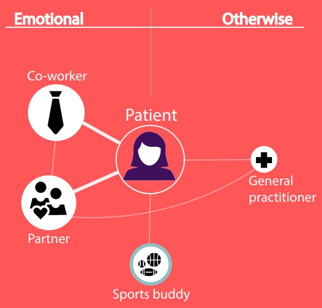
The extent to which the headache-specific locus of control can be linked to the egocentric social network measures was examined in this chapter. The research included fifteen participants, which led to four profiles of locus of control. Initially, the participants would be dichotomized in high versus low internal HS-LoC, but the sample size was too small to do so. In order to discover if a link exists at all between the HS-LoC and the social network architecture, each of the three HS-Loc subscales (internal, medical professional and chance) was compared to the network measures instead. No significant correlations were found between any of the social network measures and internal, medical professional or chance locus of control, except for a positive correlation between node importance and internal locus of control.



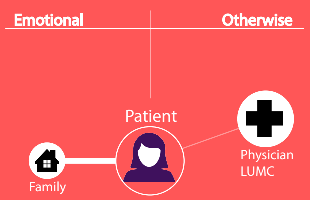
PURE CHANCE



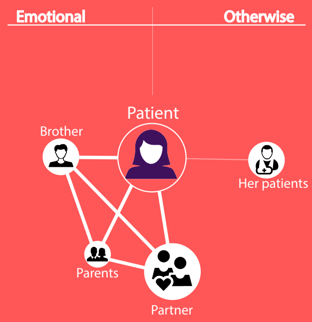
Participant 1	
Internal	31
Medical professional	15
Chance	35



Participant 2	
Internal	19
Medical professional	21
Chance	40

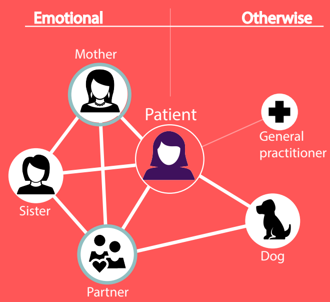


Participant 3	
Internal	25
Medical professional	26
Chance	35



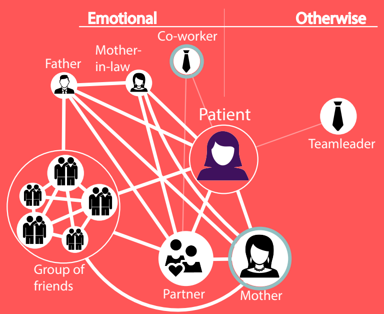
Participant 4

Internal	24
Medical professional	27
Chance	30



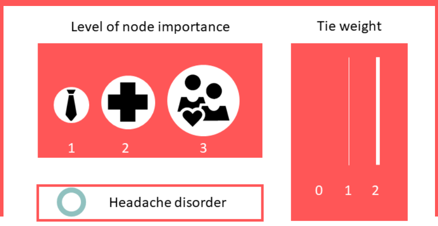
Participant 5

Internal	25
Medical professional	30
Chance	32

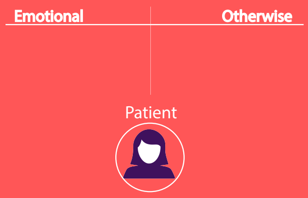


Participant 6

Internal	16
Medical professional	29
Chance	42

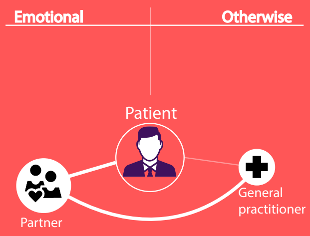


PURE POWERFUL OTHERS



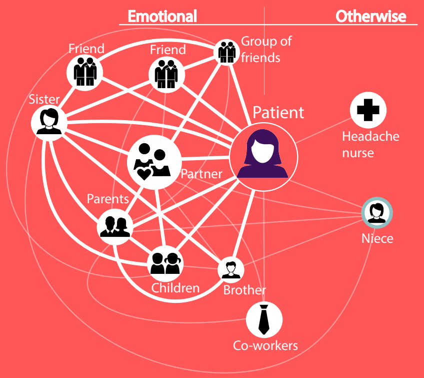
Participant 7

Internal	11
Medical professional	31
Chance	30



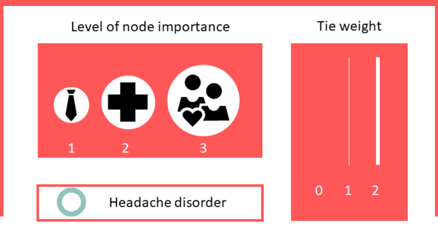
Participant 8

Internal	22
Medical professional	34
Chance	30

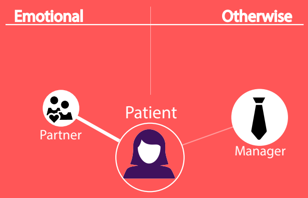


Participant 9

Internal	19
Medical professional	32
Chance	33

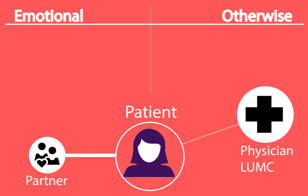


BELIEVER IN CONTROL



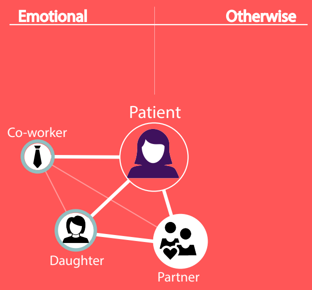
Participant 10

Internal	44
Medical professional	37
Chance	30



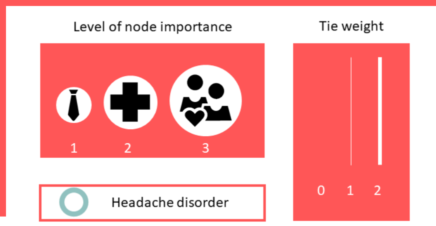
Participant 11

Internal	51
Medical professional	33
Chance	31

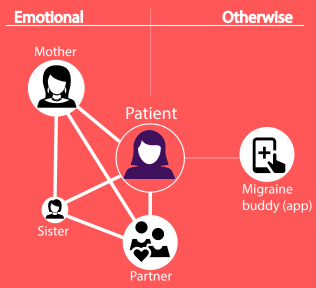


Participant 12

Internal	48
Medical professional	30
Chance	26

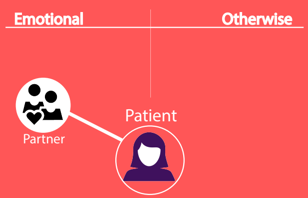


YEASAYER



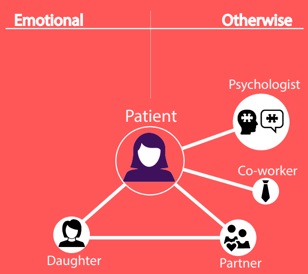
Participant 13

Internal	47
Medical professional	35
Chance	42



Participant 14

Internal	41
Medical professional	24
Chance	41



Participant 15

Internal	39
Medical professional	28
Chance	33

7 Extrapolation of the data

Due to the small sample size, the group was not dichotomized in high versus low internal headache-specific locus of control (based on the HS-LoC profiles). Consequently, no statements can be made on interventions by means of alterations in the social network architecture (i.e., by adding or removing nodes and/or edges). Therefore, an extrapolation of the data was performed *on face value* to investigate other possible interventions on the social network. This was done using literature, a peer-group review and an expert's opinion. The resulting interventions are presented in this chapter.

Starting with an analysis on the differences in the social networks of those with high versus low internal HS-LoC profiles in Section 7.1, some challenges were identified and addressed. The possible interventions to increase the internal HS-LoC are presented in Section 7.2.

7.1 High vs. low internal HS-LoC profiles

As can be seen in Table 5.1, profiles with high internal HS-LoC are the "believer in control" and the "yeasayer". Contrarily, the "pure chance" and "pure powerful others" have low internal HS-LoC. Notable differences were sought between those two groups: the high internal (HI) HS-LoC (believer in control and yeasayer) versus the low internal (LI) HS-LoC (pure chance and pure powerful others).

First of all, the networks of the HI group are seemingly smaller than the networks of the LI group. As can be seen in Section 6.2, the HI networks range in size between 1 and 4, whilst the LI participants have 0 to 11 alters in the networks. Clearly the range is much larger in the LI group than it is in the HI group, and the statement does not hold for all participants in the LI group. However, the size of the HI networks is consistently small, whereas those in the LI group are not. The fact that individuals with low internal HS-LoC seek responsibility externally rather than internally (see Section 5.2) argues in favor of large networks. In this line of reasoning, it suggests that the HI participants cope better by themselves as they need less support from within the social network, or they might know better what kind of support they need.

Subsequently, the emphasis is much more on the "emotional" side in the LI group than it is in the HI group. That is, the number of actors and the level of importance are both greater on the "emotional" side of the network in LI. The only exception is participant 14. Due to her low medical professional score, she floats in between profiles. In the cluster analysis, this participant ended up in the yeasayer group, whereas she would be a Type VI-LOC in earlier stages of the cluster analysis. This finding suggests that the LI participants have a greater need not only of support, but specifically of *emotional* support from the social network than the HI participants.

Furthermore, the partner is on the "emotional side" in most of the LI networks (not for participants 3, 4 and 7), whilst having the highest level of importance. In the HI group, the partner does not always play this role. Either the partner is on the emotional side, but not so important (participants 10 and 11), or he/she is important for other kinds of support than emotionally (12, 13, 15). Again, participant 14 is an exception. Issues for which the partner was considered important, other than emotional support, were: taking over care of the household and/or children, or helping with migraine medication shots.

Challenges

The greatest challenge is to shift those in the LI groups towards one of the HI groups, as higher internal HS-LoC is generally desirable for optimal migraine outcome (see Chapter 5). Furthermore, participant 7 creates a complicated challenge: how to reach someone with interventions who has no one in the social network? Similarly: how to deal with patients with "unreachable" alters, like a dog? Patients with different locus of control profiles create a difference in approach to the health care professionals. If the patient's social network is known, then possibly this network can be involved to support the treatment approach.

7.2 Possible interventions in the social network

In literature, it is often stated that physicians should "involve patients in their own care, to maximize compliance. Physicians should discuss the rationale for a particular treatment, when and how to use it and what adverse events are likely," (Bodenheimer et al., 2002). However, reality is not as black and white as is suggested in this advice. Individuals with migraine experience the same disorder differently, hence their management strategies also differ (as was explained in Chapter 3). Patients with an over-reliance on the medical professional, may not benefit from the above approach. Likewise, patients with a low internal locus of control and/or low level of self-efficacy, might not be ready yet to comply to the treatment plan and believe that they can make a difference themselves. Therefore, we argue that interventions can benefit every individual patient, as long as they match with the patient's HS-LoC profile.

What can be derived from the above findings on high vs. low HS-LoC, is that the interventions in the social network might focus on emphasizing the "otherwise" side, in order to increase the internal locus of control. Additionally, as LI participants cope with migraine more externally than internally, the intervention might best be done via an alter within the social network.

A two-fold approach was used to discover possible interventions in the social network. First, existing management strategies were derived from literature. Second, these strategies were reviewed as possible interventions in the social network.

Interventions based on literature

Non-pharmaceutical treatment is increasingly seen as equally effective as pharmaceutical treatment (Rains et al., 2006a; Rains et al., 2006b; Grazzi et al., 2002; Seng and Holroyd, 2010). Therefore, more and more research on interventions based on non-pharmaceutical treatments are performed. Such research is presented here, reviewed in light of the social network.

Three types of interventions were found in literature, being:

1. Minimal contact behavioral therapy
2. Self-management education, performed:
    - at home by either lay trainers, experienced migraine patients or a headache nurse
    - at a headache school
    - using online resources (both passive and active)
3. Informatics to share information among patient, family, friends and health professionals

1. Minimal contact behavioral interventions
Behavioral interventions are a broad concept, which consists (among others) of relaxation training, cognitive behavioral therapy (a technique used to modify negative thoughts about the self and the world) or biofeedback (a technique to control body functions, like heart rate). In the study by Cousins et al. (2015), such behavioral interventions were delivered over 5 weeks in 3 individual face to face sessions, complemented with 2 phone calls to address the progress. Participants

were required to practice relaxation techniques for 15 minutes a day using a CD. Morgan et al. (2016) examined the patients' experiences on the interventions by qualitative methods.

The majority of patients who used behavioral interventions experienced benefits from the therapy. Therefore, the participation and continuation of such therapies is linked with feelings of personal gain (Morgan et al., 2016). As such, this type of intervention might be particularly effective for patients with either the "yeasayer" or the "believer in control" profile; they are active in their coping style and might well respect the provider's homework due to the responsibility they hold both in medical professionals as well as in themselves to resolve migraine. The "pure powerful others" group could benefit from this kind of intervention as well, although there is a risk that these patients drop out of the sessions or fail to do the homework assignments (as the internal HS-LoC is low).

2. Self-management education

Leroux et al. (2017) used a trained headache nurse for self-management education. Together with the headache nurse, the participant evaluated nine headache management themes concerning lifestyle and medication use, and indicated which of the themes he/she considered relevant to the migraine situation. As Leroux et al. (2017) state: "The nurse used a motivational approach aimed to enhance patients' motivation to improve health behaviors and to move patients to action." Participants were required to keep a headache diary, which the nurse summarized and discussed with the participants during face-to-face sessions and phone calls. Furthermore, the patient's goals and action plan were discussed.

Due to the active and motivating approach of the headache nurse, this intervention could be appropriate for those with low internal and high medical professional headache-specific locus of control: the "pure powerful others" profile. Both the "yeasayer" and the "believer in control" could benefit from this type of intervention as well due to their high medical professional HS-LoC.

Self-management education may also be provided via online resources. According to Koivunen et al. (2008), patients are not always satisfied with face-to-face patient education, due to high provider workload, poor communication skills or an information overload in to short of a time. Therefore, they argue that online patient education can be used to assist (rather than replace) the patient-physician relationship. Online education programs allow patients to self-educate at their own convenience and can increase social support as well (Win et al., 2016). According to Bromberg et al. (2012), online interventions that provide educational and self-management resources increase the level of self-efficacy. Marcus and Bohwmick (2013) state that "participants utilizing primarily online resources can become more empowered to manage health problems." As such, (passive) online patient education (i.e., by means of a website) can be effective for all profiles.

3. Informatics to share information
Sharing of information enables patients to exert control over their own care. According to Snyder et al. (2011), "low quality information is shared frequently among patients" by means of unmoderated discussion platforms. Informatics give the patient an opportunity to provide their physician with information, but also to share this information with others (family, friends or other patients). That is, physicians are much better suited to judge migraine management information quality, and patients can feel more empowered. The idea of using informatics (e.g., personal health records) by patient and physician, is to direct both to high-quality information and to share this information with each other. The result is that migraine management might be more tailored on the needs and preferences of patient and family.

The sharing of information might be particularly suitable for those who have large social networks. Furthermore, as the approach requires an active attitude to search for and share information, this type of intervention might be particularly effective for those with active coping styles, like the believer in control, the yeasayer and the pure powerful others profiles.

Interventions based on the theoretical framework

As was explained in Section 4.1, cognitive variables, like self-efficacy and the locus of control, influence whether the patient engages in behaviors that decrease the likelihood of getting migraine attacks. In turn, non-pharmaceutical treatments can increase the internal locus of control. Two factors within the social network have been demonstrated to influence health behavior, and as such these factors might be a suitable way to perform the intervention. The first is a proper patient-physician relationship (see Section 4.1). Greater treatment compliance has been associated with increased duration of the encounter, more frequent communication and a more personal relationship with the health care provider. Second, social support by family has been associated with treatment compliance and better health outcomes as well, as was explained in Section 3.5.

With the above two concepts in mind, it might be interesting to see *who* can perform the previously stated interventions by considering the ego's type of HS-LoC profile and his/her alters in the social network. Four examples are considered here, one for each HS-LoC profile.

Participant 11 (Believer in control)
Participant 11 explained that the LUMC physician was especially important to her for several reasons. First, the physician provided her with the right medication. Second, the physician was able to explain how migraines develop in the brain and third, the physician gave clear answers to questions on what the patient could do to

avoid attacks. Furthermore, the ego's partner was important, because he/she would comfort the ego in times of migraine attacks. Participant 11 came across as confident about her migraine, which reflects in her score of 51/55 on internal HS-LoC.

Considering the types of support the ego received from the physician and the high level of internal HS-LoC, this participant might not benefit a lot from an intervention that requires the intense involvement of a healthcare professional. Furthermore, as the partner does not play a major role in the ego's migraine management (hence sharing of information is not particularly suitable), an intervention that could be effective is self-management education by online resources.

Participant 7 (Pure powerful others)
The participant did not name any alters in her social network. Therefore, she might particularly benefit from health behavior interventions. The intervention that can be effective to this participant is self-management education by online resources. As the internal HS-LoC is the lowest possible, an active coping style is not expected. As such, the risk of aborting minimal contact behavioral therapy is high. Self-education with the help of a headache nurse might move the participant to action. However, due to the extremely low HS-LoC, this participant might not be open to change her health behavior. Therefore, a motivational approach towards self-management education by online resources might be most effective.

Participant 2 (Pure chance)
Participant 2 is situated within the "pure chance" group and both the co-worker as well as the partner are very important to the ego on an emotional level. The sports buddy provided information on certain types of medication and general management methods, as the sports buddy was a migraineur him/herself. The general practitioner was considered important, because he/she diagnosed the disorder and referred the ego to the HOD.

Little is known about the typical behavior related to the pure chance profile. Based on the level of importance of the alters in the social network, this participant could benefit from sharing information. Furthermore, the GP would be suitable to perform an intervention, as he is already situated within the social network.

Participant 13 (Yeasayer)
Participant 13 generally considers the alters in her network as highly important. Furthermore, she uses a migraine tracking app. The sharing of information by informatics could therefore be an effective method to perform interventions.

8 Conclusion

In this chapter, the conclusions of the research are drawn. First, the research sub-questions are answered in Section 8.1, which forms the basis for the conclusion of the main question in Section 8.2.

8.1 Research sub-questions

What are the perceptions of migraine patients on treatment?

Patients' perceptions on migraine management vary widely. Some migraineurs are fatalistic and do not seek help from health care providers, others show an active attitude towards coping with their disorder. The broad expectation of patients towards treatment generally includes reduced frequency, reduced severity and improved quality of life. Migraine management can be divided into professional help and self-help, the latter of which was subdivided into four domains: medication (and pharmaceutical treatment on the side of professional help), consultation, general management (and non-pharmaceutical treatment on the side of professional help) and social support.

Medication and pharmaceutical treatment
Considering medication, a wide range of attributes is considered important by migraineurs. Still, it can be concluded that medication that relieves all pain with rapid onset will most likely meet the needs of migraineurs. This conclusion is supported by the two most common reasons for dissatisfaction with migraine medication: 1) patients are afraid of side effects. The fear of side effects means that patients take their medication too late, so that it does not work properly and does not relieve all pain. And 2) what the patient considers as rapid does not correspond to what clinical research considers as rapid.

Consultation
The use of healthcare specifically for migraine varies greatly per country, per migraine type and per study sample. Physician advice is taken seriously, as many migraineurs continue taking drugs that are not considered the best therapy merely because the physician advised them. The most important attribute of consultation is the willingness of physicians to answer questions, followed by education on the causes, treatment and avoidance of migraine attacks, medical expertise and being understanding and compassionate.

General management strategies and non-pharmaceutical treatment
Commonly used general management strategies are disability behavior during attacks (i.e., lying or slowing down) and a preventive healthy lifestyle. However, migraineurs believe that migraine management mainly revolves around pharmaceutical treatment and healthcare consultations. Most migraineurs are unaware of non-pharmaceutical approaches (like homeopathy or reflexology) and many are skeptic. Yet those who use it are positive about the working of such therapies.

Social support
Lastly, social support is not often used as a migraine management strategy. No literature was found on the perceptions of migaineurs on social support, other than that it was considered important.

What (social) mechanisms contribute to patients' perceptions?

The variety of patient perceptions found in literature can be explained by the theoretical framework given in Chapter 4. Four models or theories were elaborated in the framework, being the biopsychosocial model of health, the gap model of expectation, the impact of patient-physician communication on health outcomes and the influence of psychological mechanisms on health behavior.

The biopsychosocial model of health explains health from the interplay between biological, psychological and social factors. In turn, the state of health, including the frequency, severity and duration of migraine, determines the expectations of the patient with regard to treatment. These expectations form the basis of treatment satisfaction and are influenced firstly by what treatment attributes the patient considers important and secondly by the actual rating of the treatment. As such, treatment satisfaction will improve when the gap between expectation and actual performance is reduced. Two of the ratings of treatment performance are pain intensity and pain interference (the consequences of pain on the patient's life). Both are influenced by two aspects, namely patient perceptions of physician communication and the patient's level of self-efficacy. The latter has a close link with the locus of control, hence the *headache-specific* locus of control was chosen as the core of driving patient perceptions in migraine management.

Table 8.1: A summary of the suitability of possible interventions in the egocentric social network based on the headache-specific locus of control profiles. HS-LoC = headache-specific locus of control, PC = pure chance, PPO = pure powerful others, BiC = believer in control and YS = yeasayer. ++ probably highly effective, + probably effective, - probably not effective, N/A No answer

	HS-LoC profiles			
Intervention	**PC**	**PPO**	**BiC**	**YS**
Minimal contact behavioral therapy	N/A	-	++	++
Self-management education by headache nurse	N/A	++	+	+
Self-management education by online resources	+	+	+	+
Sharing of information	N/A	+	+	+

To what extent can the headache-specific locus of control be linked with the egocentric social network architecture?

The current study found four locus of control profiles based on fifteen participants. The locus of control profiles incorporate the combination of the three locus of control subscales: internal, medical professional and chance locus of control. One statistically significant positive correlation was found between node importance and the internal headache-specific locus of control. The node importance indicated the ratio of important nodes in the network. No significant results were found for other network measures of graph theory and internal, medical professional or chance headache-specific locus of control. As such, the social network and the headache-specific locus of control are linked on the level of node importance and internal locus of control only.

What interventions in the patient's social network would contribute to increase the internal headache-specific locus of control?

Three types of interventions were found in literature: 1) minimal contact behavioral therapy, 2) self-management education, and 3) the sharing of information. These interventions were not originally carried out to increase the internal headache-specific locus of control. Therefore, the social networks of four participants (each with a different headache-specific locus of control profile) were reflected on to hypothesize which intervention would suit best. It can be concluded that the type of intervention might be highly dependent on the patient's headache-specific locus of control profile. Hence, not every intervention is suitable for every patient. Table 8.1 gives an overview of interventions that might be suitable for each of the headache-specific locus of control profiles.

8.2 Research main question

The main question of this research project was: how can patient perceptions on migraine treatment be managed through the patient's social network in order to harmonize the mutual expectations between patient and physician?

The answer to the main research question is a summation of the four sub-questions. The headache-specific locus of control is the pathway that can be managed through the patient's social network in order to control treatment expectations and perhaps even other perceptions. The node importance in the network topology demonstrated to play a significant role for the internal headache-specific locus of control. Therefore, interventions within the egocentric social network should focus either on increasing the importance of nodes or on adding important nodes to the network, both possibly by HS-LoC profile specific interventions.

9 Discussion

This chapter outlines the discussion with regard to the patient network project. First, limitations and other points of discussion of this particular research are covered in Section 9.1, from back to front. That is, the possible interventions, case study methods and results, and literature study are reviewed. The general applicability of network theory for social networks is then discussed in Section 9.2. Finally, recommendations for future research are given in Section 9.3. After looking back from interventions to literature, network theory as a way of thinking will be critically reflected on in Part IV.

9.1 Discussion of the current research project

The present study examined a possibility to close the gap between patient and physician by reflecting on the link between the migraine patient's network architecture and the headache-specific locus of control, which was derived from a literature study on patients' perceptions. A significant positive correlation was found between node importance and the internal locus of control, although this result is disputed due to the small sample size. Differences between those with high and those with low internal locus of control were found on face value, which formed the basis of possible interventions in the social network.

Interventions

In Section 1.3 we wrote that "one of the ultimate goals in social network analysis is to apply interventions by adding nodes or rewiring existing ties that will influence or accelerate behavioral change, similar to the neuronal network." In other words, we want to be able to use simulation as a tool to study information flow in a social network. Knowing the network's behavior can provide a basis for interventions, by comparing the network architecture with the architecture and working of known models (such as the small-world network). As such, rewiring only a couple of ties can already have major effects, as was explained in Section 1.2. Optimization of information flow in simulations is therefore mainly about rewiring connections (Dekker, 2007), which seems sensible given the fact that the network is then retained most (i.e., adding nodes might change the complete structure of the network). The current interventions given in Chapter 7 were all geared towards adding nodes; the rewiring of existing ties seemed futile in the small networks. An interesting issue therefore, is to understand how big the egocentric network should be in order to rewire ties and thereby provide ground for a simulation study.

No literature was found on rewiring ties in egocentric social networks. According to Uzzi et al. (2007), "most prior work on social networks was at the egocentric level, whereas small-world research is principally on the sociocentric level of analysis of the structure and functioning of the entire network." As such, Uzzi et al. (2007) imply that small-worldness is a matter of degree. This, in turn, suggests that the network characteristic of small-worldness exists due to the "sum of the parts". Therefore, we might state that the egocentric social network cannot be simulated in order to rewire ties, as the real-world social network characteristics (as given by Dekker (2007)) only occur on the macro-level of sociocentric networks. For egocentric social networks, it therefore is not a question of how big the network should be for simulation, but rather if we can simulate at all.

Case study methods and results

The interventions are supposed to increase the internal headache-specific locus of control of those with low values. A distinction between "high" and "low" values was therefore made based on locus of control profiles (as introduced by Wallston and Wallston (1982)). However, results showed very weak profiles; strong profiles would occur when the differences between the profile's average and the entire sample average are high. This is not the case for the current study. As can be seen in Figure 6.2, the chance LoC is only 2 points higher than the sample average in the "pure chance" group. Similarly, the "yeasayer" group shows barely increased medical professional LoC. This finding only holds for the chance and medical professional subscales; the internal LoC is distinctive in all profiles, which results in two clear groups: one with high and one with low internal HS-LoC.

Yet a division of groups and the associated interventions based on a personal trait (like the locus of control) might be inconclusive in itself for two reasons. Firstly, the locus of control might change over time and secondly, the headache-specific locus of control during a migraine attack might differ greatly from the headache-specific locus of control outside of attacks. We have treated the locus of control as a stable trait. Ryan and Gleason (2014) however, assert that the locus of control is both a stable trait as well as a state variable, i.e. with a variation on a daily basis on the "within-person" level. They argue that the locus of control consists of stable as well as malleable components and that the latter "may recover quickly if negative circumstances do not continue." (Ryan and Gleason, 2014). A more elaborate investigation on the (in)stability of the locus of control and its daily variation might be necessary for future studies on headache or migraine research.

As such, the generalizability of the current study is a point of discussion as well. Both the locus of control as well as the social network might vary on a daily basis. Furtermore, the current results suggest that there is no direct relationship between the headache-specific locus of control and the social network, but it is unclear if similar results will be found in other countries. Cultural differences play a role in migraine management (as was explained in Section 3.2). The macro-scale social-cultural conditions which influence the social network vary per country and it is unknown how this affects the locus of control (see Figure 2.1). And lastly, practical issues, like the accessibility to care, are not the same everywhere (Morgan et al., 2016).

Although the small sample size did not allow us to divide the sample into two groups, a statistically significant positive correlation was found between node importance and the internal headache-specific locus of control. This suggests that the more highly important nodes the network contains relatively, the higher the patient's internal headache-specific locus of control is. The causality of the relation is however unclear. Furthermore, the result loses its significance once the outliers (participants with either 0 or 11 alters) are removed. More research into the relationship between the two should reveal whether there is indeed a correlation.

Finally, the data collection method of the social network yielded inconsistent and ambiguous results. Participant 3 names the "family" as important, whereas participant 6 mentions her partner, mother, sister, brother and children separately. Obviously, this has a huge impact on network structure and measures of graph theory. Despite the clear instruction to write down one name per sticky note, participants sometimes did not do so. Furthermore, the networks were not validated; the alters were not asked about their relationship with the ego, as this was not feasible in the current study. By validating the ego's network and eventually expanding it with (part of) the networks of the alters, we might be able to reveal additional alters that work as catalysts and with whom the ego does not necessarily share a relationship. This can increase our understanding of the influence of the social network on the headache-specific locus of control.

Literature study

In Chapter 3 we stated that patients are searching for emotional support in healthcare professionals. However, none of the participants in the current study named a healthcare professional on the emotional level. What was found in literature therefor does not entirely coincide with our results.

9.2 Applicability of network theory for social networks

Although little data was gathered, the results from the current research suggest that there is no direct link between the social network architecture (in which the mediating role of psychosocial mechanisms was *not* taken into account) and the headache-specific locus of control. Given the social network model by Berkman (see Figure 2.1), we therefore state that the analysis of the social network based on graph theory is not comprehensive, as is substantiated in the following section.

The deficiency of egocentric social networks

The visualization of the social networks in Section 6.2 already show that the link is not apparent. For example, participant 3 and participant 11 have very similar egocentric networks, but both show two completely opposite locus of control profiles: participant 11 is a "believer in control", while participant 3 is situated in the "pure chance" group. Similarly, the social networks of participant 4 and participant 13 look very much alike. In both networks, the partner is considered very important on an emotional level as well as on other levels of support. Both have two alters on the "emotional" side (of which one alter of minor importance) and one alter on the "otherwise" side. Yet, participant 13 is a "yeasayer" and participant 4 is in the "pure chance" group. There may be several possible explanations for this anomaly.

Firstly, the nature of relationships within the egocentric social network was not taken into account in this research. That is, the patient was not asked about the psychosocial mechanisms, or the type of social interaction with those he/she considered important. Such a distinction on the type of social interaction could unravel the pathways through which the headache-specific locus of control operates within the social network (hence it might reveal more specifically what kinds of interventions could increase the internal locus of control). However, the distinction was not taken into account for practical reasons and because the psychosocial mechanisms were not considered important for the social network architecture (see Section 2.2).

However, based on the above examples, the nature of the relationship (i.e., via what psychosocial mechanisms the HS-LoC affects health) might nonetheless be an important aspect that cannot be ignored. Yet research using a similar approach as the current one do not take the nature of relationships into account either. Typically, such research map the network architecture to reveal influential people or patterns that impact health behavior, based on the fact that social isolation is harmful. For example, Dhand et al. (2016) state that "patients who are at risk of poor outcomes are typically surrounded by a small number of close-knit alters." They therefore assume that "neurologists might be able to identify patients who are at risk of poor outcome," merely by evaluating the network architecture. However, similar to the brain's functional network, the psychosocial mechanisms might play an important *functional* role that could explain different HS-LoC profiles with similar network architectures.

Secondly, alters might act as catalysts to the individual, without the individual being aware of it. In that case, the actual egocentric social network is larger than the perception of the individual. The ego might not know that he/she receives social support from a person via one of the alters in the network. The effect of the catalyst, then, is that a different pathway is opened through which the health-related factors influence the ego. An example is the influence that patients have on e.g. a headache nurse, which the headache-nurse might in turn exert on the ego.

Lastly, it is possible that the headache-specific locus of control simply does not fit into the model of Berkman et al. (2000). In other words, there might be no correlation whatsoever between the social network topology and the headache-specific locus of control. This argument is however contradicted by the relationship between social support and locus of control demonstrated by Garcia et al. (2002).

Whether or not the role of the psychosocial mechanisms matter, the alters unconsciously work as catalysts or there might be no link at all between the social network and the headache-specific locus of control, there still are deficiencies in the model by Berkman et al. (2000). For example, it does not take into account that we have a certain bias to connect better with one person over the other; trust, attractiveness and differing perspectives are not considered. The same holds for differing motives; the connection one feels for the other is not necessarily reciprocal, because other, non-supportive motives might play a role in relationships as well. These are all intangible characteristics, properties that are generally hard to capture.

Another dimension of the social network model

As such, there might be an underlying layer within the social network influencing individual tie characteristics. Concerning trust, Lewis and Weigert (1985) state that "trust must be conceived as a property of collective units, not of isolated individuals. Being a collective attribute, trust is applicable to the relations among people rather than to their psychological states taken individually." Similarly, attractiveness and other such characteristics might be collective attributes as well. The model by Berkman et al. (2000) could therefore be extended with another dimension, to take account for the intangible characteristics. This concept is visualized in Figure 9.1.

Social network analysis therefore flattens out what cannot be flattened. Even if the network architecture and the associated psychosocial mechanisms are known, there are still underlying layers of personal traits, characteristics and preferences that might affect the pathways of locus of control.

Network analysis by graph theory is widely used to solve complex social issues. Yet we have to take into account that it flattens something that cannot be flattened. Especially in the case of egocentric networks, for which typical social network characteristics do not necessarily apply, it is hard to base the interventions on simulations of the network architecture. A good alternative is to add nodes by means of qualitative interventions, as described in Chapter 7. However, we have to be careful with these as well: the locus of control is variable from day to day. Graph theory might therefore not be a convenient instrument to approach such complex concepts as social networks.

9.3 Recommendations

Future research on social network analysis should take the nature of relationships (i.e., the psychosocial mechanisms) into account as well. This will provide a somewhat more detailed image of the social network. Furthermore, short as well as long term variations in locus of control should be considered in future research, as the headache-specific locus of control might not be a stable trait.

The link that was found between node importance and internal headache-specific locus of control warrants further investigation. However, the method of data collection should be critically reconsidered next time, as many limitations were found.

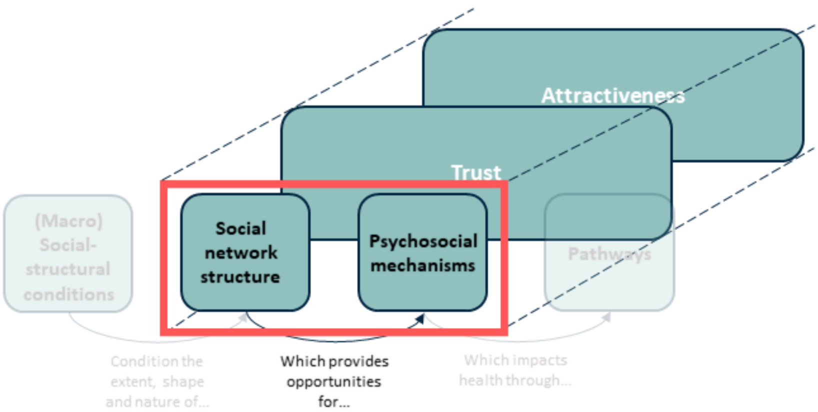
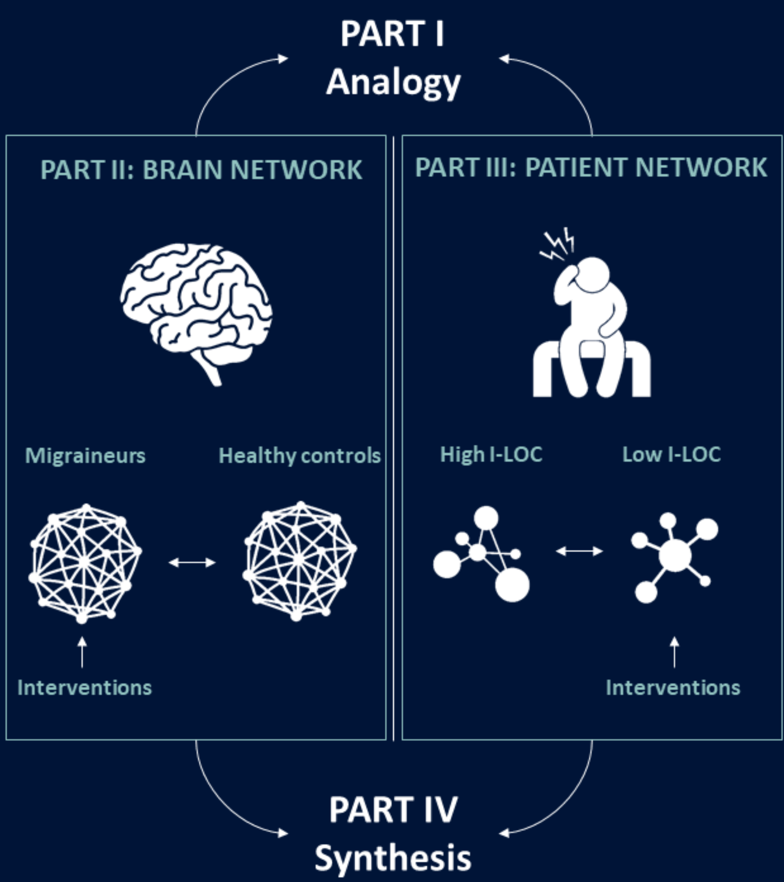


Figure 9.1: Possibly, the social network knows underlying layers that are hard to capture, like trust and attractiveness.

For example, the instructions on the name generator were not clear enough in the current study and can be improved by correcting the participant as soon as a "collective" name is written (e.g., family). The locus of control profiles of alters can be recorded as well to provide a better view of the influence of alters on the ego.

Lastly, research on decision making among migraineurs based on the headache-specific locus of control might reveal more insight into what interventions to perform (possibly within the social network).


PART I
Analogy
PART II: BRAIN NETWORK
Migraineurs
Healthy controls
Interventions
PART III: PATIENT NETWORK
High I-LOC
Low I-LOC
Interventions
PART IV
Synthesis

PART IV

SYNTHESIS

1 Synthesis

Two projects were carried out in this research: one investigating potentially deviating brain activity in the migraine brain and one studying the personal network of the migraine patient. Both projects were approached as networks, for which graph theory was used. In this chapter, the two projects are synthesized. To do so, the analogy as explained in Chapter 2 (Part I) is used, to discover what both fields of expertise can learn from each other.
The two projects are compared in light of the topology of the functional networks (the subject of comparison) in Section 1.1, after which Section 1.2 covers the potential next steps in both fields of expertise. The chapter is closed with some concluding remarks in Section 1.3, with a short interpretation of the new insights on thinking in network terms.

1.1 Comparison of the projects

The comparison is done in three ways: based on the working of the systems themselves, on the method of data collection and on the interventions. We start where we closed the discussion in the previous chapter, i.e. with the underlying layer of intangible network characteristics. The findings of the comparison are summarized in Table 1.1.

The systems

Network analysis by means of graph theory applied on social networks has too little resolution to be accurately modeled, as was argued in Section 9.2 (Part III). The social network model by Berkman et al. (2000), which was used as a basis for our analogy, seems inconclusive. That is, the model is "flat", such that the working of the network can in theory be predicted. If we know the network structure, tie characteristics and what interaction concerns which psychosocial mechanism, it would be possible to fully simulate the social network. However, the model does not explain large-scale social network characteristics such as trust or attractiveness. An additional dimension was therefore proposed to account for these "intangible" network characteristics. This dimension was viewed as an underlying layer of the entire system, i.e. the structural and functional network collectively. Here, we argue that those characteristics are properties of *self-organization* of the system, based on the concept of self-organization of brain activity.

Self-organization is defined by a fully autonomous process in which structure and function of a system are spontaneously created, without the interference of an external agent. Self-organization is thought to be a propertie of the neuronal network. As explained in Chapter 1 of Part I, local neuronal assemblies interact with other assemblies to establish coherent function. This is an autonomous and spontaneous process; nothing directs the assemblies to create such a functional network. In other words: neuronal assemblies seem to have a certain preference for their integration with other assemblies. Self-organization is reflected in the neuronal network by *assortativity*, which means that high-degree nodes (nodes with many connections) prefer to connect with other high-degree nodes (Stam and Reijneveld, 2007; Rubinov and Sporns, 2010). This results in highly-interconnected high-degree nodes in the network. Such a structure makes the network more resilient to node failure. Factors like trust, attractiveness and mutual understanding might represent similar network connection-preferences in the social network. These factors might therefore be underlying the property of self-organization of the social network.

The neuronal network, on the other hand, indeed has shown signs of self-organization. It is unclear yet what mechanisms are underlying this property. In other words, it is unknown what factors like "trust" and "attractiveness" in the social network are to the neuronal network. However, the presumption that such underlying mechanisms also play a role in the neuronal network suggests that we should look differently at the working of the brain as discussed in Chapter 1 (Part I); that is, the neuronal network might not merely aim for cost-efficient information transfer, but show characteristics related to self-organization as well. This may affect studies of brain networks, in the sense that they should not merely account for patterns of simultaneously active brain regions when considering interventions (e.g., medication).

By ignoring the underlying mechanisms (possibly characteristics of self-organization), much information is filtered out by graph theory, resulting in an exponential loss of resolution. It was concluded from the brain project that graph analysis may not be sensitive enough to detect possible local aberrations of the migraine neuronal network. However, it might be the case that we simply lack important information (again, possibly characteristics of self-organization) to properly define and compare the networks. Yet, as said in the Chapter 9, it might not be able to fully capture the interactions that govern such behavior.

1.2 The next step

The most important finding of this synthesis, is that both the social network as well as the neuronal network might have underlying layers of network characteristics that are hard to capture by network analysis. Possibly, these characteristics are associated with the property of self-organization. In this section, the comparison continues in light of the current projects.

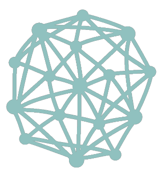
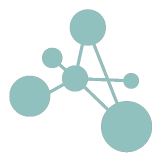
Concerning the method of data collection, two points of discussion are made. The first point is about the distinction of the functional networks. In the social network project, no distinction was made between the different functional networks (i.e., the psychosocial mechanisms), in order to account for all possible pathways through which the locus of control would occur. As explained in Chapter 2 (Part I), the psychosocial mechanisms are to the social network what brain functional networks, like the resting-state network, are to the brain. However, we only measured the resting-state functional network in the brain, as if we were only measuring social support in the social network. In other words, we only measured part of the entire functional network in the brain, and it might well be possible that migraine accesses the network through multiple pathways simultaneously. The neuronal network is thought to display more functional networks than the resting-state, many of which we do not yet know. Similarly, the social network might consist of more functional networks too, other than those listed by Berkman et al. (2000).

Secondly, with the approach of graph theory, only the tip of the iceberg is recorded. In case of the neuronal network, only activity in the outer layer of the brain was captured by our macroscale approach. Besides, information of brain activity was lost by respectively volume conduction, functional connectivity measures and the use of the minimum spanning tree (see Part II). It was the other way around within the egocentric social network: a microscopic approach was used by taking the ego as the starting point. However, the data were recovered at only one point in time. Both cases are just small parts of the entire network, which might also explain why possible characteristics of self-organization (which is a property of the entire system) are so hard to detect.

The next step could be to reduce information loss in graph analysis. Within brain network studies, this is done by simultaneously considering EEG and MRI, in order to combine a high time resolution (EEG) with a high space resolution (MRI). Considering the social network, the same line of thought could be followed. We can increase the time resolution, by asking patients to keep daily track of their headache-specific locus of control and/or social network. Furthermore, the space resolution might be enlarged by considering the alters' networks as well, or at least the alters' perspectives on the relationship with the ego.
Furthermore, medical interventions are not carried out without the support of extensive research. As such, the discovery, development and marketing of new drugs

is a lengthy process. Besides, physicians do not simply provide medication to any migraine patient, for the simple reason that it might be harmful to the patient. Similarly, we do not carry out any intervention in the brain as long as we are not entirely sure what that intervention does to the brain. So why do we simply apply every form of intervention in the social network of the migraine patient? That is, why does literature state that patients should be actively involved in their own care for migraine, while the psychosocial interventions appear to be just as unstable as migraine medication is to the brain? Therefore, we propose that communication interventions should be considered carefully, preferably supported by research concerning the social network and/or the headache-specific locus of control.

Table 1.1: Summary of the synthesis

Brain		Patient	
System			
	The network shows self-organizing behavior, but not known by what characteristics	Network characteristics like trust and attractiveness play a role in the network, possibly due to self-organization	
Data collection			
	Not all functional networks are known, and migraine might work through multiple functional networks simultaneously	The locus of control works through multiple psycosocial mechanisms simultaneously, but possibly there are more psychosocial mechansism than currently known	
Interventions			
	Medical interventions carried out carefully	Interventions by means of communication not carried out carefully	

1.3 Thinking in network terms: revised

Network analysis is a suitable mathematical tool to compare systems on their performance and cost-efficiency. However, it should be used for systems that can be expressed in ways of mathematics, such as a power network. Network analysis, and graph theory in specific, filters the complex part out of complex systems: it flattens what cannot be flattened. Yet it can provide valuable insights into these complex systems, which would not have been discovered without network analysis. As such, we now believe that the brain works according to similar rules as many other complex systems, like bird flocks or the social network. In fact, it even provided the basis for the analogy central to this thesis. However, when it comes down to intervening the network, we cannot rely on graph theory. The loss of information due to the method is too harmful in order to use the network as a basis for interventions. Network analysis should therefore be used in moderation, and the users should be aware of how little it can mean.

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APPENDICES

A Large overview of the 128-channel EEG cap layout

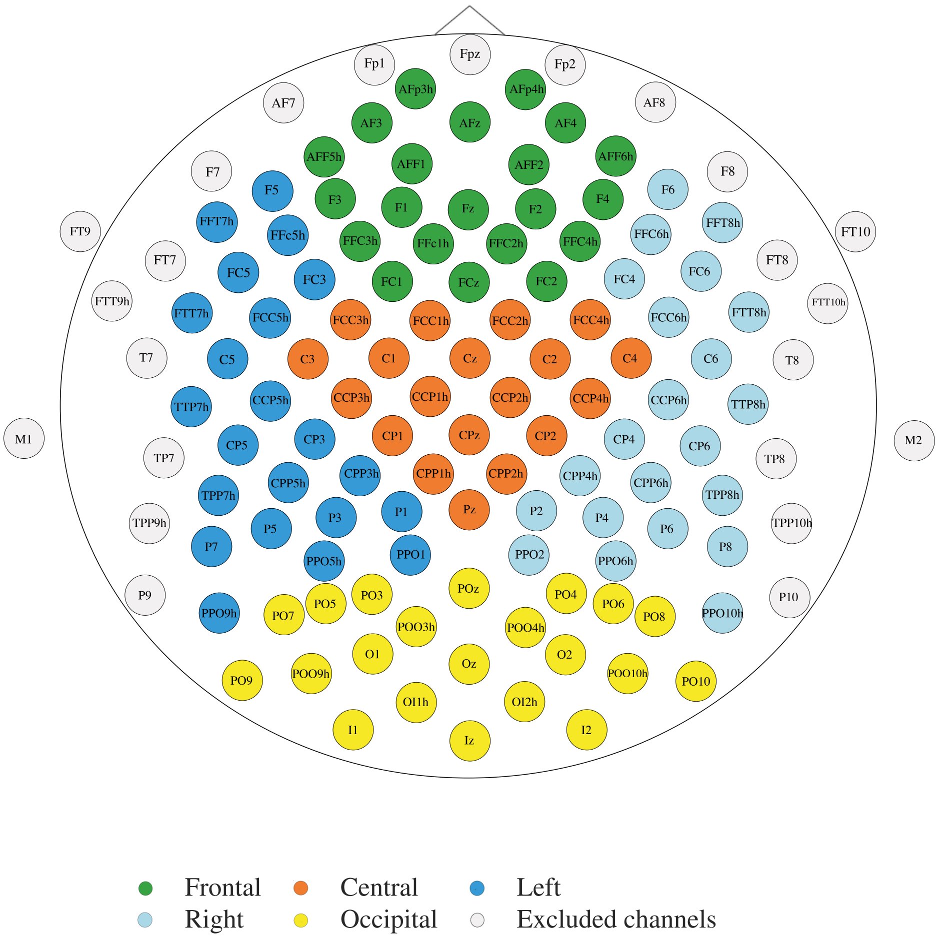

Figure A.1: Layout of the 128-channel EEG cap. Colors indicate which channels (i.e., nodes) belong to which cluster. Gray channels were excluded from analyses, as scalp contact at these positions was suboptimal in most participants.

B Functional connectivity methods in Euler notation

Oscillations are described by three pieces of information: frequency, power and phase. The phase angle of a signal reveals information about the timing of frequency-band-specific activity, or the position along a sine wave of certain frequency at any given time point; that is, if the timing of two oscillations is similar, then their phase angles will have similar values. This piece of information is used as the basis for phase-based connectivity methods, like coherence and the phase-lag index (PLI). Both of these measures of synchronization are based on the *difference* in phase angles between two signals at a certain time-frequency point. Thus, in the case of frequency-band-specific data, the amount of synchronization between two signals over certain period of time (epoch) can be calculated by averaging the differences in their respective phase angles over all time points.

As phase angles are circular, the averaging of phase angle values is not straightforward. Phase angles can, however, be represented as vectors on a unit circle in the complex plane. Euler's formula (Me^ik, in which *M* is the magnitude and *k* the direction) provides a way to represent the phase information in polar space. Therefore, the phase angle difference between two signals at a certain time-frequency point can be represented by a vector on the unit plane. For all time points in frequency-band-specific data, this will result in a distribution of vectors on the unit circle.

It is the distribution of these vectors which reveals information about synchronization among the signals; that is, if the timing of the oscillations measured by the EEG electrodes is similar at each point in time in both EEG signals, then their phase angle differences will have similar values and the distribution will be clustered (see Figure B.1). On the contrary, if phase angle differences show varying values, then the distribution of their respective vectors will be more uniform.

To calculate the amount of uniformity, the vectors in polar space representing the phase angles (not the phase angles themselves) are averaged. The length of this average vector reveals how close the vectors are. In other words, the length of the average vector represents the amount of clustering of the vectors. This method forms the basis of coherence and is known as *intersite phase clustering* (ISPC). It is mathematically described by equation B.1:

$$ISPC_f = *n^{-1} \sum_{t=1}^{n} e^{i(\phi_{tx} - \phi_{ty})} \tag{B.1}$$

in which *n* is the total number of time points (in this case the number of time points per epoch), the summation operator combined with n^{-1} represents the average, $\phi_{tx} - \phi_{ty}$ represent the phase angle difference of channels *x* and *y* at time point *t* and e^i originates from the Euler formula providing the complex polar representation of the phase angle difference at frequency *f*.

Spectral coherence

Spectral coherence, like ISPC, reveals the amount of clustering of the (average) vectors representing phase angle differences. The difference between both methods, is that spectral coherence is scaled by power values. In Euler notation, this gives B.2:

$$S_{xy} = *n^{-1} \sum_{t=1}^{n} |m_{tx}||m_{ty}|e^{i\phi_{txy}} \tag{B.2}$$

in which m_x and m_y are the analytic signals of *x* and *y* respectively (Cohen, 2014).

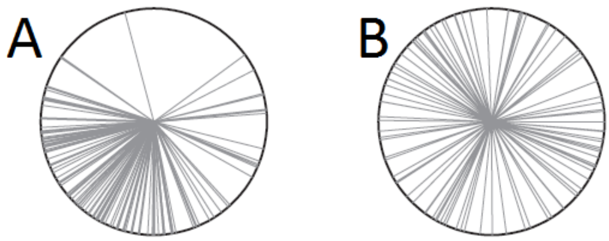

Figure B.1: Example of a unit circle in the complex plane representing the phase angles of many electrodes at a certain time-frequency point. A) The vectors are slightly clustered around a certain value. B) The distribution is quite uniform (Cohen, 2014).

C Degree correlation

Degree correlation indicates whether nodes tend to connect to nodes with the same or similar degree. The network is assortative if high-degree nodes connect to other high-degree nodes and similarly, low-degree nodes connect to other low-degree nodes. The network is disassortative if high-degree nodes connect with low-degree nodes, resulting in a hub-and-spoke network. More generally, degree correlation indicates if the number of links between high-degree and low-degree nodes is systematically different from what is expected by chance. The probability that two nodes with degrees k and k' by chance link with each other is given by equation C.1:

$$p_{k,k'} = \frac{kk'}{2m} \tag{C.1}$$

in which m is the total number of links in the network (in this case, the MST).

The probability that a randomly chosen node will have degree k is given by p_k. However, if a randomly chosen path in the MST was followed, then the node at its end will have a degree according to a probability distribution of kp_k: high-degree nodes have more links and, therefore, the distribution is biased towards nodes of high degree. Degree correlation is about the *remaining degree*, the number of edges leaving the node other than the one that was followed. The remaining degree is one minus the total degree, giving a probability distribution of $(k+1)p_{k+1}$. Normalizing this distribution gives equation C.2:

$$q_k = \frac{(k+1)p_{k+1}}{\sum_j jp_j} \tag{C.2}$$

in which j is the remaining degree at the other end of the edge and $\sum_j jp_j$ can be understood as the expected value of the remaining degree distribution. Equation C.2 is the probability that a randomly selected path in the MST has a node with degree k at its end.

The joint probability distribution of the two nodes at the ends of a path in the

MST with remaining degrees k and j is given by the degree correlation matrix e_{ij}. The degree correlation matrix has the following two characteristics (equation C.3):

$$\sum_{jk} e_{jk} = 1 \qquad \sum_{j} e_{jk} = q_k \tag{C.3}$$

The amount of assortativity is given by equation C.4:

$$\langle jk \rangle - \langle j \rangle \langle k \rangle = \sum_{jk} jk(e_{jk} - q_j q_k) \tag{C.4}$$

where $\langle ... \rangle$ indicates the average over the total number of links. In order to compare the amount of assortativity among MST's, the measure is normalized by the variance $\sigma_q^2 = \sum_k k^2 q_k - [\sum_k k q_k]^2$ of the distribution q_k. Hence, the (normalized) degree correlation is (equation C.5):

$$r = \frac{1}{\sigma_q^2} \sum_{jk} jk(e_{jk} - q_j q_k) \tag{C.5}$$

r has a value between -1 and 1 and is negative for disassortative MST's and positive for assortative MST's (Newman, 2002).

D Minimum spanning trees and critical nodes per participant

MINIMUM SPANNING TREES AND CRITICAL NODES PER PARTICIPANT

COHERENCE - Migraineurs

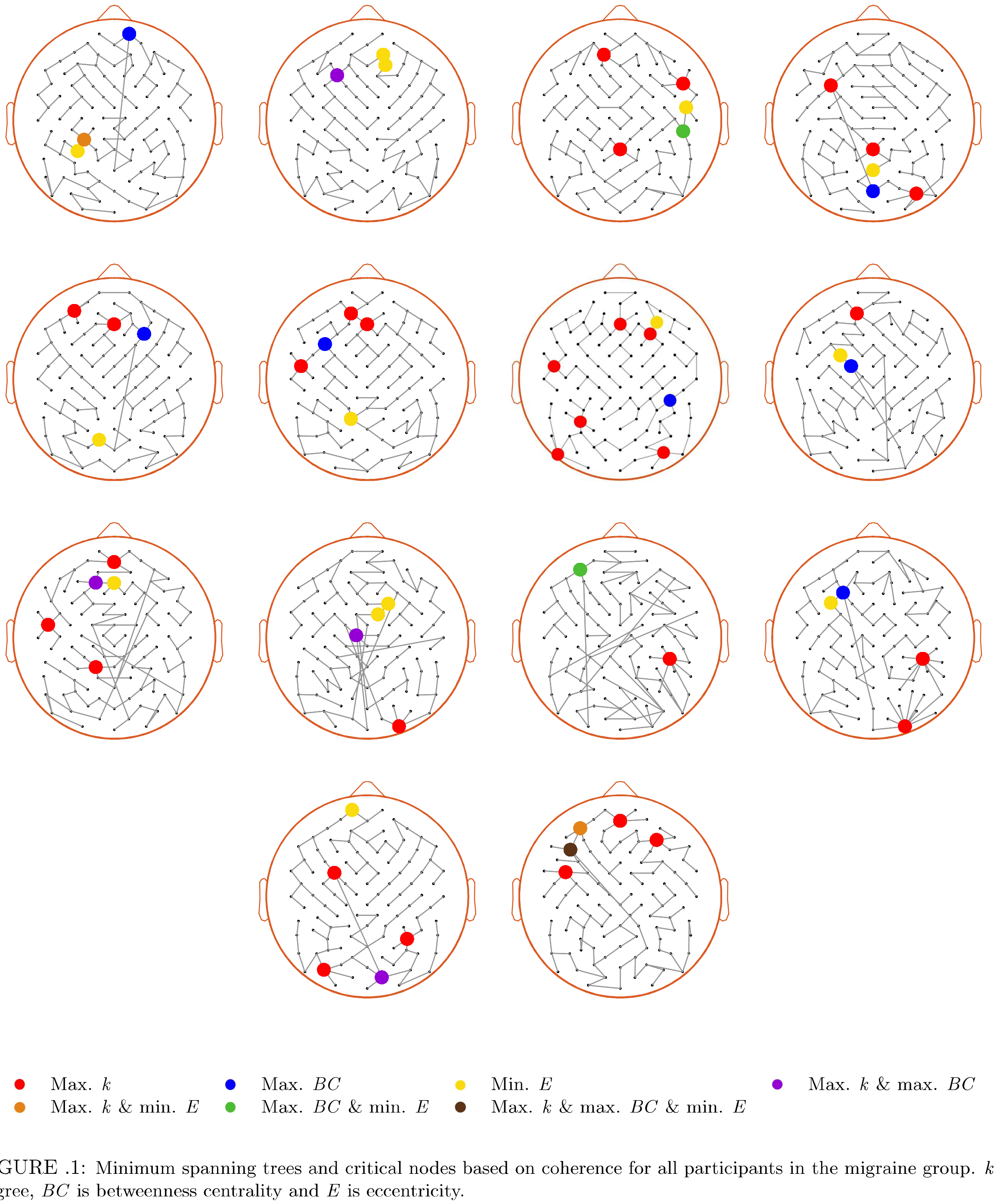

FIGURE .1: Minimum spanning trees and critical nodes based on coherence for all participants in the migraine group. k is degree, BC is betweenness centrality and E is eccentricity.

COHERENCE - Controls

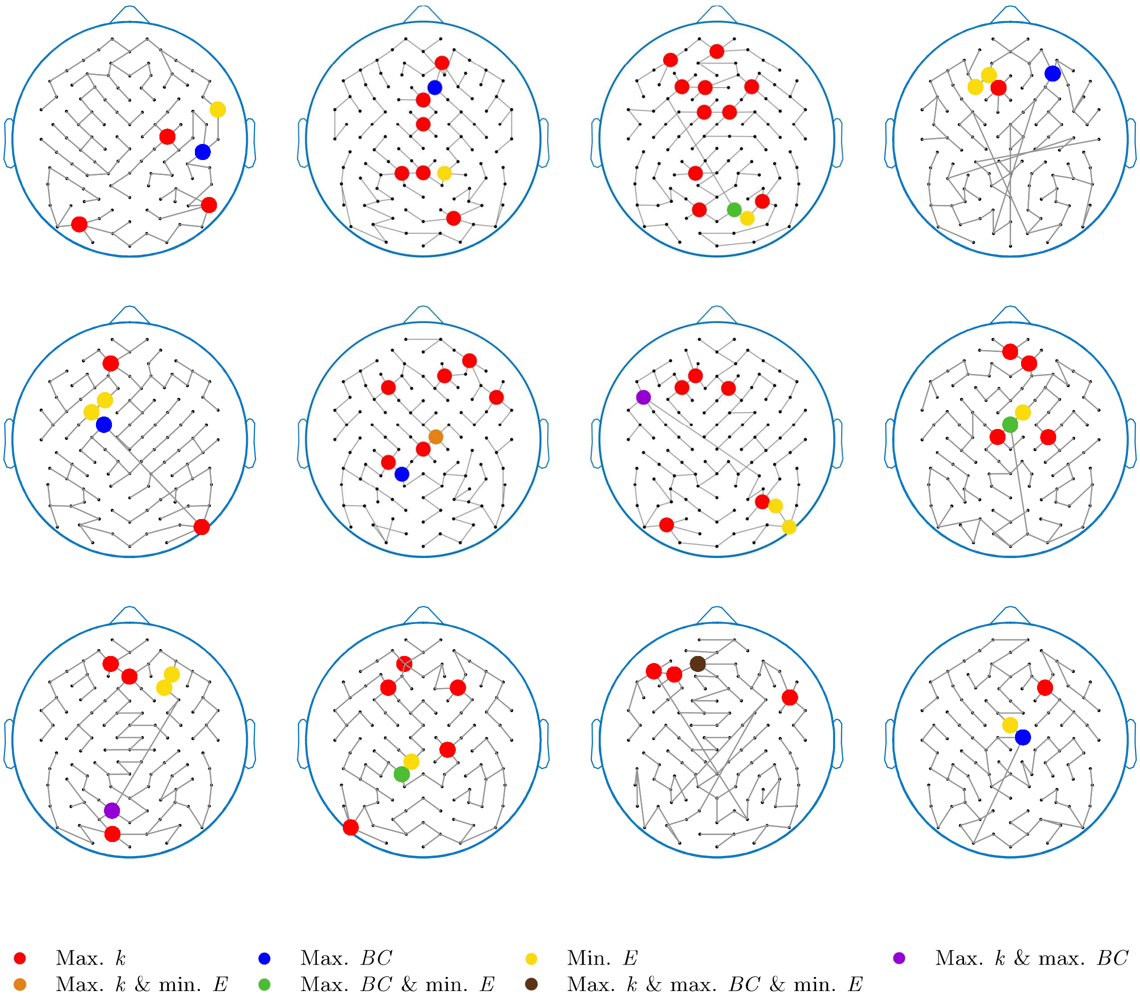

FIGURE .2: Minimum spanning trees and critical nodes based on coherence for all participants in the control group. k is degree, BC is betweenness centrality and E is eccentricity.

PHASE-LAG INDEX - Migraineurs

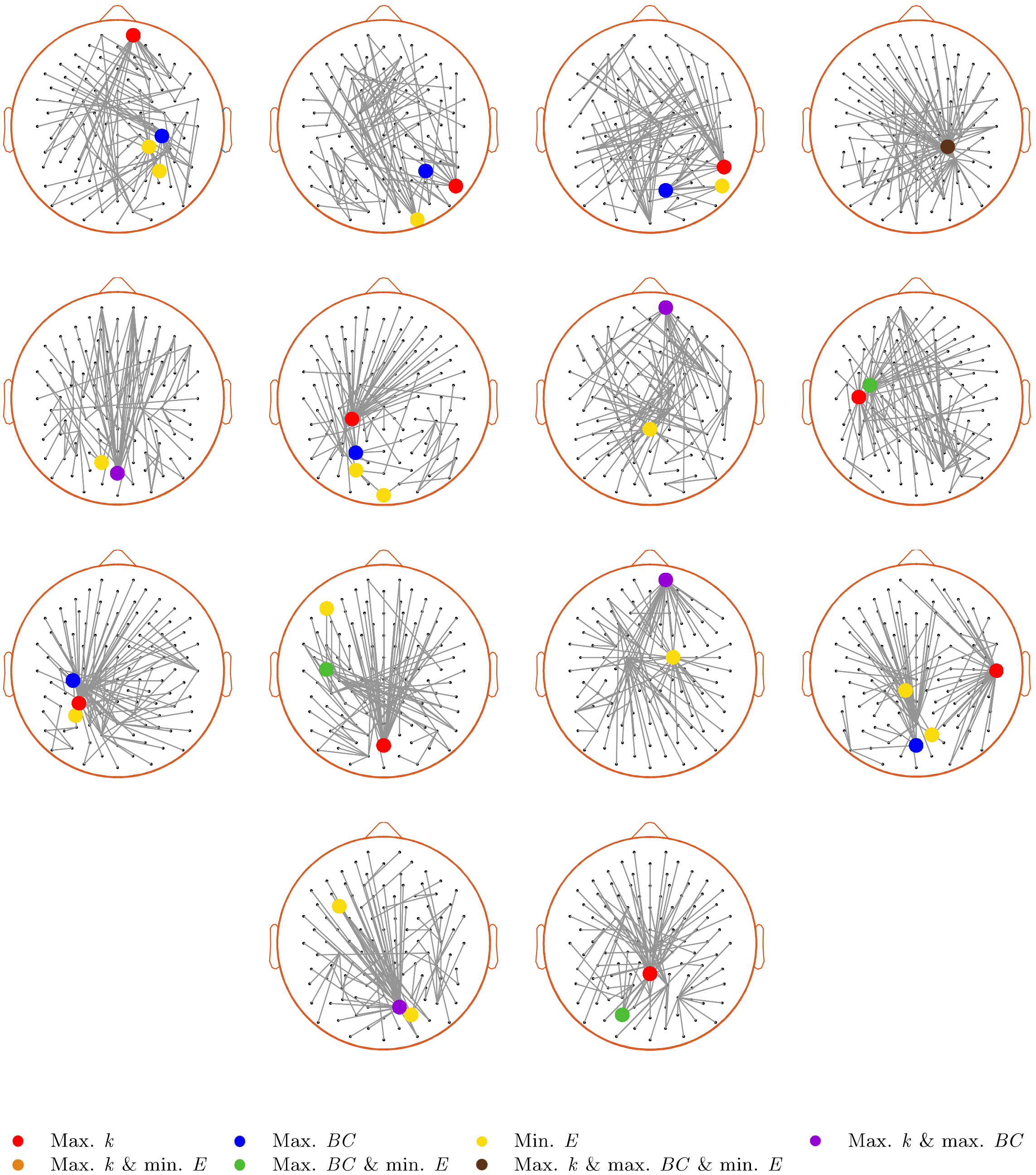

FIGURE .3: Minimum spanning trees and critical nodes based on phase-lag index for all participants in the migraine group. k is degree, BC is betweenness centrality and E is eccentricity.

PHASE-LAG INDEX - Controls

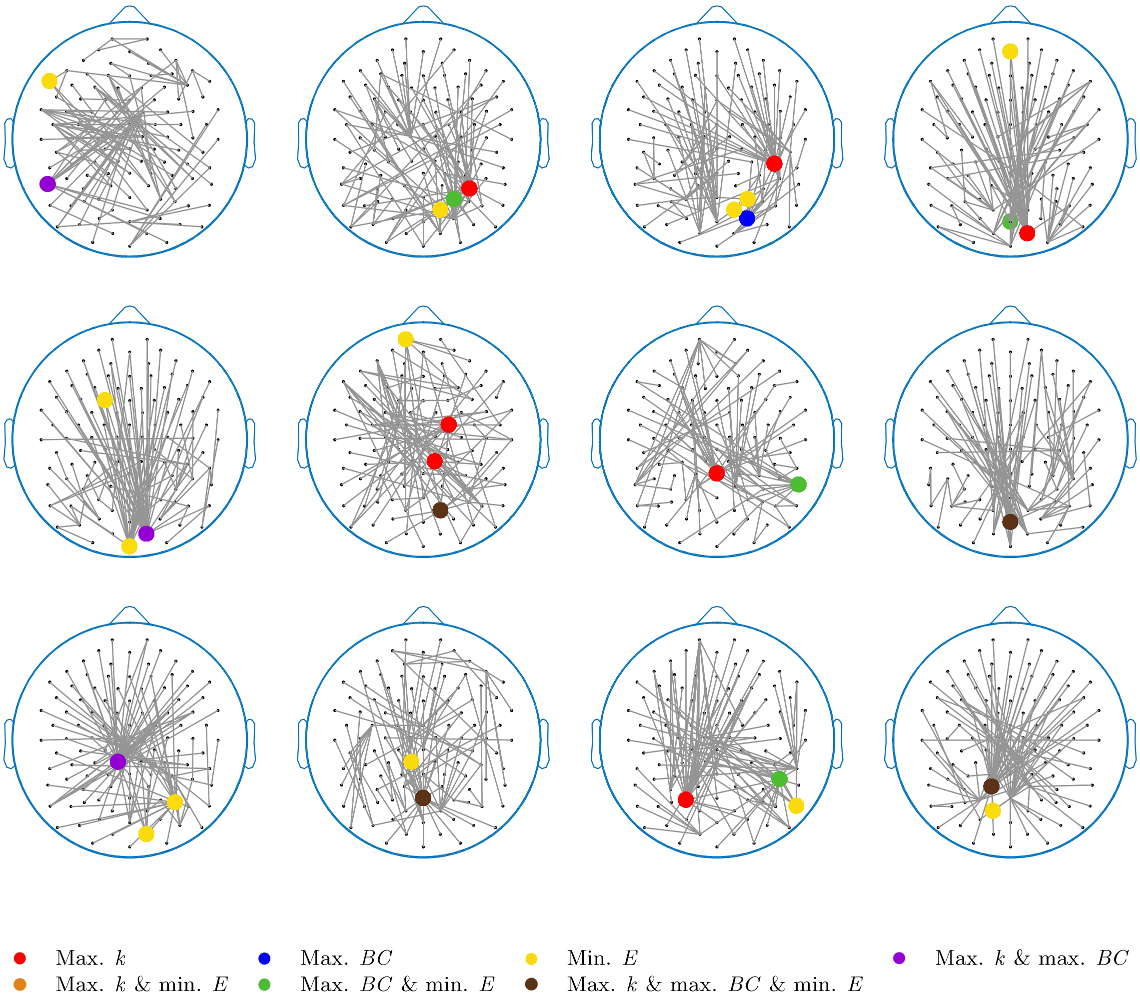

FIGURE .4: Minimum spanning trees and critical nodes based on phase-lag index for all participants in the control group. k is degree, BC is betweenness centrality and E is eccentricity.

E Overlap

OVERLAP

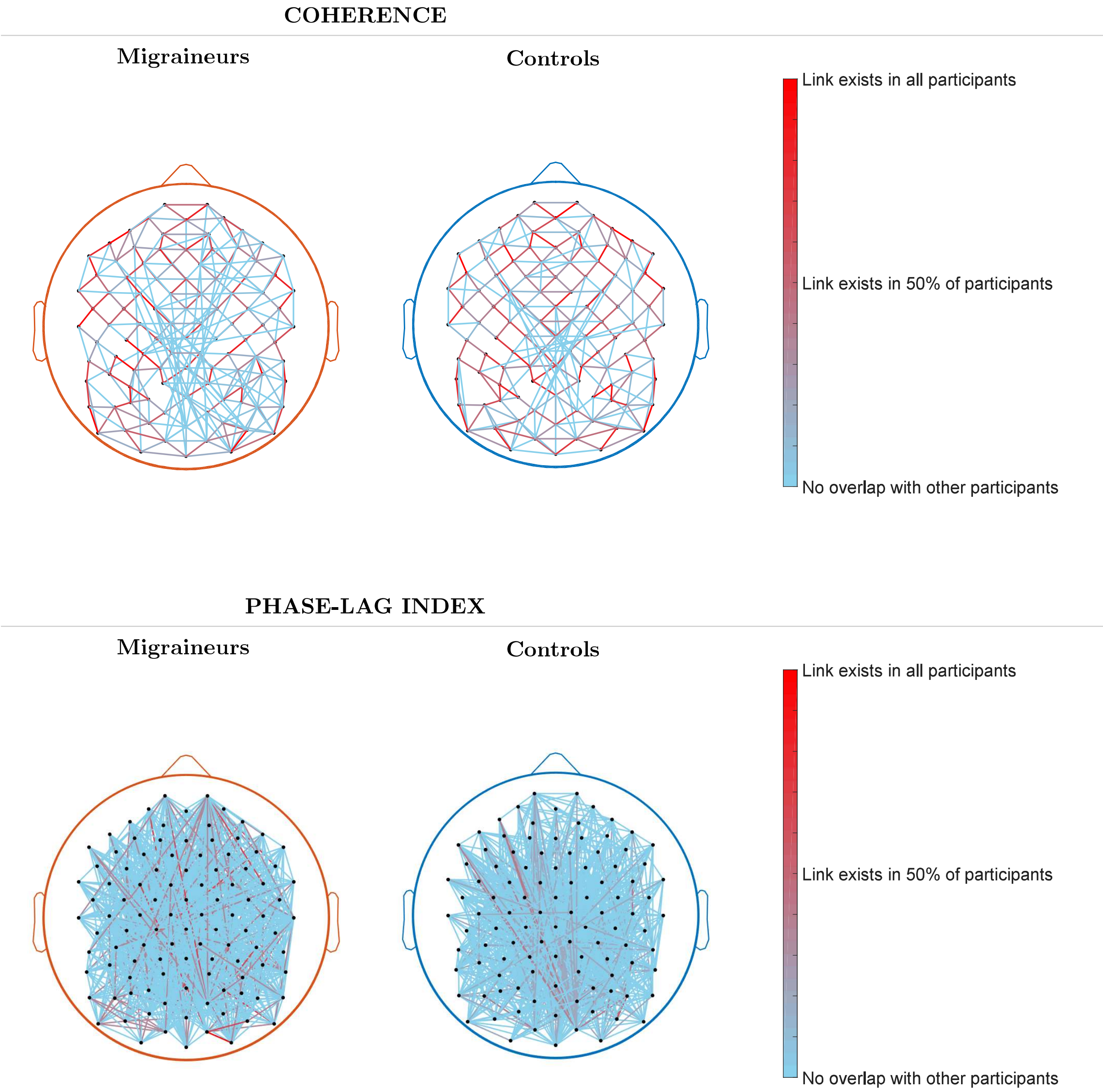

FIGURE .5: Overlap of MST links of all participants per group. Red links indicate that the particular link exists in all participants (in that group), while light blue links appear only in individual participants.

F Headache-specific locus of control questionnaire

The headache-specific locus of control questionnaire Dutch version can be found in this Appendix. The questions relating to the three subscales are as follows (Willekens et al., 2018):

1. Internal LoC: 2, 4, 5, 7, 11, 17, 19, 21, 26, 28, 32.
2. Medical professional LoC: 6, 8, 10, 12, 14, 15, 16, 22, 24, 27, 30.
3. Chance LoC: 1, 3, 9, 13, 18, 20, 23, 25, 29, 31, 33.

Instructies: Deze vragenlijst geeft inzicht in de klachten die u ervaart door de hoofdpijn. Hieronder staan 33 stellingen waarmee u het eens of oneens bent. Naast iedere stelling staan de getallen 1 tot en met 5. Hiermee geeft u aan in welke mate u het eens of oneens bent met de stelling. De 1 staat voor "Volkomen oneens" en de 5 staat voor "Volkomen eens". Omcirkel het getal dat correspondeert met de mate waarin u het eens of oneens bent met de stelling. Zorg ervoor dat u achter *alle 33 stellingen* een getal heeft omcirkeld. *Slechts één getal per stelling* kan worden omcirkeld. De antwoorden die u geeft zijn uw persoonlijke mening. Er zijn dan ook geen goede of foute antwoorden mogelijk.

1 = Volkomen oneens
2 = Gematigd oneens
3 = Neutraal
4 = Gematigd eens
5 = Volkomen eens

1	Als ik hoofdpijn heb is er niets wat ik kan doen om het beloop te veranderen	1	2	3	4	5
2	Ik ben in staat een deel van mijn hoofdpijn te voorkomen door het vermijden van bepaalde stressvolle situaties	1	2	3	4	5
3	Ik ben compleet machteloos met betrekking tot mijn hoofdpijn	1	2	3	4	5
4	Ik kan hoofdpijn soms voorkomen door niet overstuur te raken	1	2	3	4	5
5	Wanneer ik zorg voor voldoende rust heb ik minder vaak hoofdpijn	1	2	3	4	5
6	Alleen mijn arts kan mij aanwijzingen geven om mijn hoofdpijn te voorkomen	1	2	3	4	5
7	Mijn hoofdpijn is soms erger omdat ik overactief ben	1	2	3	4	5
8	Mijn hoofdpijn kan minder erg zijn wanneer medische professionals mij goede zorg verlenen. (Artsen, zusters, etc.)	1	2	3	4	5
9	Ik heb geen enkele invloed op mijn hoofdpijn	1	2	3	4	5
10	De behandeling van mijn arts kan mij helpen tegen hoofdpijn	1	2	3	4	5
11	Wanneer ik mij zorgen maak of pieker over iets heb ik een grotere kans op hoofdpijn	1	2	3	4	5
12	Alleen al een bezoek aan mijn arts helpt tegen mijn hoofdpijn	1	2	3	4	5
13	Ongeacht wat ik doe: als ik hoofdpijn zal krijgen, dan krijg ik het ook	1	2	3	4	5
14	Regelmatig contact met mijn arts is de beste manier voor mij om controle te krijgen over mijn hoofdpijn	1	2	3	4	5
15	Wanneer ik hoofdpijn heb dien ik een medische deskundige te raadplegen	1	2	3	4	5
16	Het zorgvuldig volgen van de door mijn arts uitgeschreven medicijnenkuur is de beste manier om hoofdpijn te voorkomen	1	2	3	4	5
17	Wanneer ik teveel van mijzelf vraag krijg ik hoofdpijn	1	2	3	4	5
18	Geluk speelt een grote rol bij het bepalen hoe snel ik zal herstellen van hoofdpijn	1	2	3	4	5
19	Door er voor te zorgen dat ik niet overactief of geïrriteerd raak voorkom ik veel hoofdpijn	1	2	3	4	5
20	Het niet krijgen van hoofdpijn is voornamelijk een kwestie van geluk	1	2	3	4	5
21	De dingen die ik doe beïnvloeden de kans op hoofdpijn	1	2	3	4	5
22	Gewoonlijk herstel ik van een hoofdpijn na het ontvangen van goede medische zorg	1	2	3	4	5
23	Ik heb een grote kans op hoofdpijn, ongeacht wat ik doe	1	2	3	4	5
24	Wanneer ik niet de juiste medicatie heb, heb ik last van hoofdpijn	1	2	3	4	5
25	Vaak heb ik het gevoel dat wat ik ook doe ik toch hoofdpijn zal krijgen	1	2	3	4	5
26	Ik ben zelf verantwoordelijk voor het krijgen van hoofdpijn	1	2	3	4	5
27	Wanneer mijn arts een vergissing maakt, ben ik degene die daaronder lijdt door hoofdpijn	1	2	3	4	5
28	Mijn hoofdpijn wordt erger wanneer ik met stress te maken heb	1	2	3	4	5
29	Wanneer ik hoofdpijn krijg moet ik de natuur gewoon zijn gang laten gaan	1	2	3	4	5
30	Professionele medische deskundigen zorgen dat ik geen hoofdpijn krijg	1	2	3	4	5
31	Ik heb simpelweg geluk wanneer ik een maand geen hoofdpijn heb	1	2	3	4	5
32	Wanneer ik niet goed voor mezelf zorg heb ik een grote kans op hoofdpijn	1	2	3	4	5
33	Het is een kwestie van toeval of ik hoofdpijn krijg	1	2	3	4	5

G Patient attributes questionnaire

Leids Universitair Medisch Centrum

TU Delft

Nummer: …………………….

<u>Onderzoek naar het sociale netwerk van migraine patiënten</u>

Geslacht: □ m □ v

Geboortedatum *(DD/MM/YYYY)*: ……/……/…………

Ik heb migraine **met/zonder** aura

Ik krijg een aura in ……….% van de gevallen *(Indien van toepassing)*

Aantal jaren migraine: …………………….

Gemiddeld aantal migraineaanvallen per maand: …………………….

Gemiddeld aantal dagen hoofdpijn per maand: …………………….

U bent (waarschijnlijk) door uw huisarts doorverwezen naar het LUMC. Van het LUMC heeft u een brief ontvangen waarin u uitgenodigd werd om online vragenlijsten in te vullen, alvorens een afspraak gemaakt kon worden. Heeft u deze vragenlijst direct ingevuld (zonder herinnering), of heeft u eerst een herinnering van het LUMC gekregen?

□ Direct
□ Herinnering

Leids Universitair Medisch Centrum

TU Delft

Voor het omgaan met mijn migraine pas ik de volgende tactieken toe / heb ik in het verleden de volgende tactieken toegepast *(let op! Meerdere antwoorden mogelijk)*:

Consult bij…

- ☐ Huisarts
- ☐ Hoofdpijnverpleegkundige
- ☐ Hoofdpijnspecialist
- ☐ Apotheek
- ☐ Psycholoog
- ☐ Osteopaat
- ☐ Homeopaat
- ☐ Acupuncturist
- ☐ Anders

Medicatie, namelijk…

- ☐ Paracetamol
- ☐ Ibuprofen
- ☐ Medicatie voorgeschreven door een arts
- ☐ Homeopathische middelen (vitaminen of mineralen)
- ☐ Anders

Algemene tactieken, zoals…

- ☐ Fel licht vermijden
- ☐ Bepaald voedsel, alcohol of koffie vermijden
- ☐ Lawaai vermijden
- ☐ Op bed liggen
- ☐ Naar huis gaan van werk
- ☐ Massage
- ☐ Warme of koude doek op het hoofd leggen
- ☐ Ontspanningsoefeningen
- ☐ Stress vermijden
- ☐ Regelmatig eten en slapen
- ☐ Anders

Informatie of ondersteuning zoeken bij…

- ☐ Familie
- ☐ Vrienden
- ☐ Collega's
- ☐ Hoofdpijnpatiëntenvereniging
- ☐ Internetpagina's
- ☐ Apps
- ☐ Facebookpagina of andere sociale media
- ☐ Anders