Breathing and the Center of Command

The influence of respiration on the Central Nervous System

MASTER - THESIS

for obtaining the academic degree

Master of Science

in the study programme Osteopathy

submitted by

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October 2020

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ABSTRACT

Aim: The aim of this narrative review is to investigate, whether there is scientific evidence for the impact of breathing on the CNS and if so, what these effects are and on which levels they are measurable.

Methods: The literature research was carried out in the PubMed database in June 2020. The research produced 23 studies, which were subdivided in 3 topics: CSF motion, brain activity and pain perception.

Results: Strong evidence for impacts of respiration on the CNS was found. Breathing significantly influences the flow of CSF throughout the CNS including all CSF spaces on the cranial and spinal level. Breathholding was found to temporarily supress this flow. It was unambiguously shown, that inspiration generates a cranial CSF motion, conversely expiration leads to a caudal fluctuation, a clear displacement of fluid was found. In addition, it was demonstrated, that the velocities of the flow vary in the different regions of the CNS.

Respiration was found to influence large parts both in cortical and limbic regions, such as amygdala, hippocampus, insula, frontal, parietal and primary olfactory cortices. It influences slow cortical potentials particularly at 10sec/cycle, and infra-slow oscillations, which are involved in the development of resting state networks as the default mode network, which is important for cognitive performance. It has an impact on the excitability of other cortical regions as the primary motor hand area. Phase and pathway of respiration influence limbic functions as emotion discrimination and memory function, inspiration and nasal respiration leading to an increase in both.

It has been shown, that slow and deep breathing have an analgesic effect, and that the phase of respiration might have an influence on pain perception. Expiration leads to the same analgesic effect, however, the results are not entirely invariable.

Keywords:
breathing, central nervous system, Cerebrospinal Fluid, Pain Perception, Brain Activity

ABSTRACT

Ziel: Ziel dieses narrativen Reviews ist es zu erforschen, ob es wissenschaftliche Grundlagen für den Einfluss der Atmung auf das Zentralnervensystem (ZNS) gibt und wenn ja, welche diese, und auf welchen Ebenen sie messbar sind.

Methodik: Die Literaturrecherche wurde in der PubMed Datenbank im Juni 2020 durchgeführt. Die Suche ergab 23 Studien, welche in 3 Themengebiete geteilt wurden: Cerebrospinal Flüssigkeit (CSF), Hirnaktivität und Schmerzwahrnehmung.

Ergebnisse: Es wurden eindeutige Hinweise für den Einfluss von Atmung auf das ZNS gefunden. Sie beeinflusst maßgeblich den Fluss von CSF im gesamten ZNS, in allen CSF Räumen sowohl auf kranialer als auch spinaler Ebene, Anhalten der Atmung unterdrückt diesen kurzfristig. In der Einatemphase kommt es zu einer kranialen Bewegung der CSF, in der Ausatemphase zu einer kaudalen. Die Geschwindigkeiten der CSF variiert in den verschiedenen Regionen des ZNS.

Die Atmung beeinflusst große Bereiche, sowohl in kortikalen als auch in limbischen Arealen, wie Amygdala, Hippocampus, Insula, Frontalem-, Parietalem- und primär olfaktorischem Cortex. Sie beeinflusst langsame kortikale Potentiale, insbesondere bei etwa 10sec/Zyklus, und infra-slow Oszillationen, welche an der Bildung von Ruhezustandsnetzwerken wie dem Default Mode Network beteiligt sind und für kognitive Leistungsfähigkeit wichtig sind. Weiters hat sie einen Einfluss auf die Erregbarkeit anderer kortikaler Regionen wie dem primärmotorischen Kortex für die Hand, und auf limbische Funktionen wie Einordnen von Emotionen oder Gedächtnisleistung, wobei hier Phase (Einatmung>Ausatmung) und Weg der Atmung (nasal>oral) Einfluss haben.

Langsame, tiefe Atmung hat einen schmerzlindernden Effekt sowohl auf Schmerzwahrnehmung als auch -toleranz, die Ausatmung scheint ebenfalls selbigen Effekt zu begünstigen, die Ergebnisse hierzu sind jedoch nicht ganz widerspruchsfrei.

Schlüsselwörter: Atmung, Zentralnervensystem, Cerebrospinale Flüssigkeit, Schmerzwahrnehmung, Hirnaktivität

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1 Introduction

Working on the diaphragm and breathing mechanisms is a central part in osteopathy. Breathing is said to be, apart from the heartbeat, one of the most vital driving forces in our body. In the osteopathic studies, the thoracic diaphragm is taught to have various functions, that are generally accepted, which include respiration, separation of the thoracic and abdominal cavity and therefore it´s function to maintain different pressure gradients in these cavities, as well as the movement (mobility) of the abdominal organs. Furthermore, it is claimed to have effects on numerous other systems, amongst which is the central nervous system (CNS). These basic diaphragmatic functions are well accepted and taught among osteopaths and other medical professionals, as well as shown in medical science. However, it is often difficult for young osteopaths to comprehend the complexity of these physiological processes, not to mention to perceive, what the very experienced therapists are able to sense. Furthermore, many of these sensations are very hard to verify scientifically, which makes it difficult for cranial osteopathy to be considered as based on evidence.

Scientists frequently target the topic of respiration and its effects in the body, yet I have found no studies from an osteopathic viewpoint on this specific subject. Osteopaths speak of sensing breath in almost any body tissue, as well as claim to achieve effects on most levels of the body with the treatment of the diaphragm. The challenge in osteopathic research is making these sensations, which are often subjective and therefore difficult to implement in science, measurable. For this reason, as objectification of sensations is often not possible, and in order to try to render osteopathy more evidence based, it is essential to resort to findings and knowledge from fundamental research and to process and interpret them from an osteopathic point of view.

Although breathing influences many various levels and systems of the body, the decision to solely concentrate on the CNS was consciously made. One reason for this is the fact, that in cranial osteopathy, as one of the three pillars in osteopathy, the CSN plays the largest role. Another reason is, that a quick overview literature research on respiration and the autonomic nervous system (ANS) showed, that not enough literature is available on this topic. The third reason is, that additionally dealing the topic of the ANS would have gone beyond the scope of this thesis.

The CSN is of special interest for me, as there are so many sensations, which are perceptible in cranial osteopathy, which are difficult for me to sense and understand, and, in addition, to scientifically examine. The question, that I am posing myself is which of these perceptible sensations are actually objectively measurable?

Therefore, the aim of this thesis is to investigate the fundamental research literature, that has prior been done on the topic and to process them as an osteopath, in order to provide a more profound understanding of and explanations for osteopathic perception. In addition, objective of this work is to use these findings, in order to derive implications for osteopathic treatment in the various fields. This includes the attempt to derive conclusions and hypotheses for osteopathic working from the basic outcomes. On the basis of an article by Bordoni, Purgol, Bizzarri, Modica, and Morabito (2018), three main areas of interest on this topic were defined, which are: Influence of Breathing on the Flow of Cerebrospinal Fluid (CSF), Influence of Breathing on Brain Activity and Influence of Breathing on Pain Perception.
It is to be said beforehand, that, although this thesis attempts to investigate phaenomena, which are perceived during cranial osteopathy, the referred term of respiration and breathing, which is described during this thesis only refers to thoracic respiration, not the concept of primary respiration, which is used in cranial osteopathy.

2 Theoretical Background

The following chapter will deal with the underlying theoretical and anatomical background, which is needed, in order to enable a better comprehension of this work. It will consider the diaphragm with its anatomical and fascial connections, its arterial, venous and nervous supply.

2.1 Anatomical and Fascial Connections of the Diaphragm

The basic anatomy of the diaphragm is commonly known among osteopaths and therefore need not be explained in detail. Nevertheless, it is important to comprehend several pathways and connections, as they will be important during the course of this work in order to enable the understanding of the ways of connections of the diaphragm and the various systems. Therefore, the openings in the diaphragm and the passing structures, as well as supplying blood- and lymphatic vessels and related nervous structures will be discussed in this chapter.

The human thoracic diaphragm is a continuous sheet of muscle and connective tissue, which separates the thorax and the abdomen, however, there are small openings and passage ways, which are of great importance for the function and supply, on the one hand for the diaphragm itself, on the other hand for adjacent structures. Beside the three main openings, which are the Foramen Vena Cavae (V.Cava Inferior, right R. Phrenicoabdominalis pass through), the Hiatus Oesophageus (Esophagus, Trunci Vagales ant and post) and the Hiatus Aorticus (Aorta Pars Descendens, Ductus Thoracicus), there are smaller gaps in the fascia, which are between the Crus Mediale and Intermedius (Nn. Splanchnicii, V. Azygos, V. Hemiazygos), between the Crus Mediale and Laterale (Truncus Sympathicus, N. Splanchnicus Minor) and the Trigonum Sternocostale (A. and V. Thoracica Interna) (Schünke, Schulte, & Schumacher, 2018). These openings are of great significance, as they build ways of passage and communication between the diaphragm and numerous body structures from the brain to the pelvis and therefore can explain parts of the phenomena of interaction.

Bordoni, Simonelli, and Morabito (2019) pictured the diaphragm as a fascial system, that stands in interaction with various other fascial systems of the body. In fact, they refer to the diaphragm muscle as throughout fascia, as all the diaphragmatic tissues originate from the same mesodermal leaflet. “The diaphragm muscle is a stratification of multiple fascial networks: transversalis fascia, endothoracic fascia, thoracolumbar fascia, phrenic center, epimysium, perimysium, endomysium, basement membrane, extracellular matrix, contractile tissue” (p.4). Especially worth mentioning here is, as Bordoni and Zanier (2013) state, that the fascia transversalis is of great significance, as it sheets the inner layer of the epimysium of the M. Transversus Abdominis, the sheath of the M. Rectus Abdominis, as well as the M. Obliquus Externus and reaches into inguinal and pelvic sections. This is one direct relationship and mechanism, explaining a possible relationship between diaphragm and postural aspects. In addition, the interfascial plane, which is in connection to the diaphragm in the posterior section must be noted. It is described by Lee, Ku, and Rha (2010) that it combines the retromesenteric plane and the retrorenal plane and extends via the mesorectal interfascial plane (or prevesical space) into the pelvis. Previously, the close, synergistic activity of the thoracic and the pelvic diaphragm has been shown in many clinical investigations, as Ferla, Darski, Paiva, Sbruzzi, and Vieira (2016) found profound evidence for in their review on this topic.

Moreover, Bordoni et al. (2019) highlight fascial connections to the periosteum of the vertebrae T11- L4, as well as to the epimysium of M. Quadratus Lumborum and M. Psoas Major. Further direct contacts of the diaphragm are both parietal coatings of the thorax and the abdomen, the pleura pulmonalis and the peritoneum (Bordoni & Zanier, 2013).

The diaphragm is interlinked with a number of thoracic organs through ligamentous connections, such as the base of the lungs (through the pulmonary ligament) and the pericardium (through the Lig. Phrenicopericardiacum), and abdominal organs, as the esophagus (Lig. Prenicoesophagealis), the liver (Lig. Falciforme, Lig Coronarium, Ligg. Triangularia Dextrum and Sinistrum), the stomach (Lig. Gastrophrenicum) the Colong (Lig. Phrenicocolicum) and the Duodenum (Treitz ligament) (Bordoni & Zanier, 2013).

It can be clearly stated, that all the above-mentioned structures are fascially and structurally closely related to the diaphragm and interactions between all the different systems take place.

2.2 Arterial, venous and lymphatic supply

The main blood supply for the superior region of the thoracic diaphragm comes from three pairs of arteries. Coming from the Aorta Thoracalis arise the Aa. Phrenicae Superiores, which supply the largest area of the superior diaphragm, and the A. Subclavia. From there stems the A. Thoracica Interna, which gives off two further supplying vessels, the A. Pericardiacophrenica and the A. Musculophrenica. The inferior parts of the diaphragm are supplied by the abdominal aorta through the left and right Aa. Phreniae Inferiores. Venous Drainage occurs through the Vv. Phrenicae Superiores, which drain into the V. Azygos and V. Hemiazygos, and the Vv. Phrenicae Inferiores, that duct into the V. Cava Inferior (Schünke, Schulte, & Schumacher, 2018).

According to Bordoni and Zanier (2013), the diaphragmatic blood vessels have their vegetative supply from the intercostal nerves and, in addition also from the phrenic nerve, where they play a vascular proprioceptive role.

Lymphatic drainage can be divided into two groups, according to location. The Nll. Phrenici Superiores carry lymphatic fluid from the diaphragm, as well as from the lower parts of the esophagus, the lung and, via a trans-diaphragmatic pathway, also from the liver and drain into the Truncus Bronchomediastinalis and, furtheron into the angulus venosus. Nll. Phrenici Inferiores duct the lymph from the inferior diaphragm, and partially from lower parts of the lungs into the Truncus Lumbalis, from there into the Cisterna Chyli and subsequently from the Ductus Thoracicus into the venous angle (Schünke, Schulte, & Schumacher, 2018).

2.3 Innervation

Concerning the understanding of the diaphragmatic interlinks, the innervation of the diaphragm is of great significance, therefore we must consider two nerves, the N. Phrenicus and the N. Vagus (for the crural area).

In order to attempt to understand parts of the complexity of diaphragmatic interaction, studying the course of the phrenic nerve is essential. Before the nerve arises from the cervical plexus, the brain regions, involved in the transmission to the N. Phrenicus must be considered. Bordoni and Zanier (2013) describe, that the retroambiguus nucleus in the occipital area controls areas in the medulla oblongata, in the case of the diaphragm, the pre-Botzinger complex, a set of medullary interneurons, which hence control phrenic motor units in the ventral horn of the cervical spinal cord.

The phrenic nerve itself arises mainly from the ventral ramus of the fourth cervical nerve, yet also the third and the fifth contribute to the formation. After leaving the cervical plexus, it runs along anteriorly of the M. Scalenus Ant., and passes between this muscle and the M. Sternocleidomastoideus and enters the thorax between the subclavian artery and vein (Banneheka, 2008; Canella et al., 2010).

Jiang, Xu, Shen, Xu, and Gu (2011) investigated the phrenic nerve after the entry into the thorax. It progresses along the anterior surface of the pulmonary hilum and runs between both edges of the Pleura Mediastinalis and the Pericardium and, in this course, it gives off somatosensory branches to both. It then innervates all parts of the diaphragm, except the crural regions, and the Ramus Phrenicoabdominalis passes through it, giving neural supply to the Glisson Capsule, the pancreas and the peritoneum (Schünke, Schulte, & Schumacher, 2018).

Bordoni and Zanier (2013) mention anastomoses of the phrenic nerve and the vagus nerve in the crural region. “It is generally believed that the esophageal afferents of the vagus exert an inhibitory influence on the medullary and phrenic motor neurons” (p. 284). In another article, Bordoni et al. (2018) consider potential anastomoses to numerous other nerves, including the

N. Subclavius, Ansa Cervicais, N.Hypoglossus, N. Accessorius, Ganglion Stellatum, N. Supraclavicularis and the N. Sternohyoideus. It can therefore be concluded, that interaction between all these nerves and, in addition their supply areas, takes place in both directions.

On the other hand, especially considering motor control of the crural diaphragm, the vagus nerve must be investigated. Bordoni and Zanier (2013) state, that recent research implies, that the four nucleic centers, which can be associated with the N. Vagus, are situated in the Medulla Oblongata and are called the Nucleus Dorsalis N. Vagi (visceroefferent fibers for smooth muscles and glands in thoracic- and abdominal organs), the Nucleus Ambiguus (visceroefferent fibers supplying parts of pharynx and larynx), the Nucleus Spinalis N. Trigemini (end of somatoafferent fibers, receiving afferences from R. Meningeus, R. Auricularis) and the Nucleus Tractus Solitarii (end of visceroafferent fibers from epiglottis and gustative nerves). The vagus arises from the medulla, builds the Ganglion Superius N. Vagi, leaves the cranium via the Foramen Jugulare and builds the Gangion Inferius N. Vagi. It runs along with the A. Carotis Communis and the V. Jugularis Interna, passes between the subclavian artery and vein, hence along the esophagus, where left and right vagus anastomose, and passes through the diaphragm at the hiatus oesophageus (Schünke, Schulte, & Schumacher, 2018a; Schünke, Schulte, Schumacher, Voll, & Wesker, 2018b). Anastomoses of the vagus are referred to by Bordoni et al. (2018) “including the sympathetic system at the cervical and abdominal levels and the phrenic nerve, the vagus itself (loop or anastomosis of Galenum) and the nerve XI (Lobstein anastomosis), nerve IX and the ansa cervicalis” (p. 2).

3 Research Question and Methods

This thesis is part of fundamental research, and was written as a narrative review. The included clinical trials were divided into three main groups (CSF, Brain Activity and Pain Perception) and hence subdivided into more precise fields. They were critically assessed, however, no tool for critical appraisal has been utilized, as to my knowledge, there are no such tools specifically designed for fundamental research. As these studies were mostly neither randomized, nor blinded, etc. and the evaluation for this thesis was conducted with regards to content, i.e. qualitative not quantitative, the known critical appraisal tools were very poorly applicable. In order to make the studies comparable nonetheless, a table was generated for the studies of each of the three main chapters, which contains all important baseline data, interventions and outcomes and which are displayed at the end of each of the respective chapters.

3.1 Research Question

Is there scientific evidence for the impact of breathing on the central nervous system? What are these effects and on which different levels are they measurable?

3.2 Literature Research

The literature research was conducted on 17.6.2020 and 18.6.2020. As this work is based on fundamental research, the literature search was only made in the PubMed database. The reason, that this was only done for this one database, is, that most articles for fundamental research in the medical field can be found there and no studies concerning osteopathic or physiotherapeutic interventions were required. The article of Bordoni et al. (2018) gave inspiration to the literature research, which will consequently concentrate on three main areas: the motion of CSF, activation of brain areas and, as pain is generated in the CNS, pain perception. The keywords were therefore selected and filters applied as displayed in Table 1:

Table 1: Literature Research

Total	Human	English	German	2000-2020	Review	Results after filter	double	Meet Criteria
(Respir*[Title]) AND (CSF[Title] OR (Cerebrospinal Fluid[Title]))								
162	93	74	80	34	1	33	0	9
(Inspiration*[Title]) AND (CSF[Title] OR (Cerebrospinal Fluid[Title]))								
1	1	1	1	1	0	1	0	1
(Breathing[Title] OR Respiration [Title]) AND (activ*) AND brain NOT Disorder								
744	193	170	177	129	38	92	1	4
(Breathing[Title] OR Respiration [Title]) AND (deactiv*) AND brain NOT Disorder								
4	3	3	3	3	0	3	0	1
(Breathing[Title] OR Respiration [Title]) AND (potentials) AND brain NOT Disorder								
264	89	83	86	57	14	43	4	2
(Respir*[Title]) AND (cortical[Title]) (most excluded because about disorders)								
123	49	45	45	34	2	32	0	0
(Breathing[Title] OR Respir* [Title]) AND Pain[Title] NOT Therapy								
118	66	51	54	39	0	39	1	6

Table 1: Keywords used for the literature research; the above line states the exact notation, which was used, the line below shows how many studies remained, after having applied the respective filter. The filters were applied in the order from left to right, as shown in the table: Human, English, German, 2000-2020, Review (were excluded), Double.

The literature research left 10 studies for the topic of CSF, 7 for Brain Activity and 6 for Pain Perception, which were included for this review. As mentioned in the introduction, the topic of respiration and the ANS was not taken into account, the brief overview literature research, carried out with the keywords: (Autonomic Nervous System[Title] OR ANS[Title]) AND (breath*[Title] OR Respir*[Title]), applied with all the above- mentioned filters, produced 7 studies, of which only 2 would have met the in- and exclusion criteria, as most studies, that were found investigated the ANS in combination with pathologies.

3.3 Criteria for Inclusion

Objective of this work was to investigate the effect of breathing on the CNS in its physiology, not the pathophysiology. Therefore, criteria for inclusion were studies, that examine respiration or the thoracic diaphragm, which only consider normal breathing mechanisms. Due to language barriers of the author of this work, only research was included, which is written in either english or german language.

Requirements such as randomized controlled trial (RCT) were consciously not made, as in fundamental research, mostly no interventions are examined, rather body functions and interactions, so there are little RCT´s available.

3.4 Criteria for Exclusion

Criteria for exclusion, were all studies, that examine animals or cadavers, studies, studies that investigated pathophysiology and pathology, and, in consequence, studies that examined humans after surgery and in postoperative conditions. In addition, research considering any form of therapy was excluded. Clinical trials, which look upon a reverse effect (i.e. effect of the psyche on breathing mechanisms, effect of brain activities on respiration, etc.), were also be excluded.

One additional criterion for exclusion was the year of publication. The studies, investigating these topics, to a great part require technical equipment such as magnet resonance imaging (MRI), electroencephalogram (EEG) or other imaging techniques, which are under constant technical improvement. It was therefore assumed, that older studies, may not be well comparable to the newly conducted research in form of technical demands. Hence, one further criterion for exclusion was defined as studies older than the year 2000. In addition, only clinical trials were taken into account, reviews excluded.

4 Breathing and the Central Nervous System

Concerning the impact of the diaphragm on the CNS, three topics will be considered: The Cerebrospinal Fluid (CSF), the influence of diaphragmatic action on brain activity and the influence of the diaphragm and breathing on pain perception.

4.1 Breathing and the Impact on the flow of Cerebrospinal Fluid

On the topic of breathing and the flow of CSF, ten studies were extracted from the literature research. As to the knowledge of the author of this work there is no tool for critical appraisal applicable for studies in fundamental research and in order to make the outline data better comparable, these studies will be displayed in Table 2 at the end of this chapter 4.1.

4.1.1 Indications for respiratory influence on CSF flow

According to Dreha-Kulaczewski et al. (2015), respiration is the most essential regulator for CSF flow in the entire ventricular system and considerably larger than the cardiac-related component. They performed a study using in a real-time MRI technique on 10 healthy subjects, while they were performing different breathing protocols (1. pace-controlled normal breathing, 2. breath holding for 12 sec., 3. forced inspiration through a black box), in order to observe CSF flow in the different parts of the ventricular system. The observations, that have been made were on the one hand, a pulsatile flow component, which could be associated with the heart rate, and a second component, which gave a stronger CSF flow, which can be ascribed to respiration. For the first breathing protocol it was clearly found, that respiration was the main source of CSF flow, especially in the third ventricle, where findings were most consistent. The third protocol with resisted inspiration, however, showed that only inspiration was found to produce a great CSF flow, the effect was not found for expiration and the cardiac component only had a small impact on the flow. Their conclusion, that inspiration is the main driving force for CSF flow, was underlined, as it was found in the second protocol, that in the breath holding sequence, the component of the respiratory driven CSF flow was completely suppressed.

A similar effect concerning respiratory related CSF flow and breathholding was shown by Chen, Beckett, Verma, and Feinberg (2015) and Kao, Guo, Liou, Hsiao, and Chou (2008). In addition, Chen et al. (2015) also showed clear modulations of the flow, which differ at various breathing rates, and which were obtained above the cardiac-related modulations.

The same distinction between respiratory and cardiac driven CSF flow was investigated by Yatsushiro et al. (2016). A 2-Dimensional Phase Contrast MRI was carried out on 7 healthy volunteers, with an abdominal pressure sensor applied, while they were asked to breathe in different intervals of 6, 10 and 16 seconds according to an audio signal, where an overall of 56 seconds of imaging information was collected. The authors also clearly show, that there is a measurable difference in cardiac and respiratory-driven motion of CSF. The results of this study imply, that the distribution of these two components in the overall CSF motion varies along the different intracranial regions, for example, in the anterior spinal subarachnoid space, CSF flow was predominantly cardiac-driven, in contrast respiratory component was higher near veins, such as the Sinus Rectus.

The prior- mentioned studies investigated CSF motion on the level of the cranium. Daouk, Bouzerar, and Baledent (2017) examined the influence of these both components on blood- and CSF flow on a spinal level. They performed MR imaging in a 2 dimensional fast field echo planar imaging on 16 healthy subjects. According to the authors, this technique enables the analyzation of blood and CSF flow almost in real time. Regions of interest were defined as the jugular vein, the internal carotids and the spinal canal at the level of C2-3 during normal, spontaneous breathing. As part of this study investigates blood flow, not CSF, the results for this part will not explicitly be mentioned, as it is not productive for the research question. Concerning CSF flow, the authors have found the respiratory component to have more effect on the flow, however, both cardiac and respiratory components seem to have a minor impact on the overall flow of CSF.

This partially stands in contrast to the findings of Dreha-Kulaczewski (2015), who claimed respiration to be the main driving force of CSF flow. It is to be said, however, that the region of interest for the CSF flow was defined differently in those two studies, Daouk et al. (2016) regarding it at a cervical and Dreha-Kuaczewski et al. (2015) at a cranial level, which makes comparison difficult. In addition, Daouk et al. (2016) themselves argue, that the site of measurement in their trial might not have been the most beneficial, as the spinal canal is surrounded by rigid structures, which can possibly decrease the flow, whereas CSF measurement in the brain directly might be more susceptible to flow changes and measurements.

4.1.2 Localisation of CSF flow

One aspect, which was studied in various experiments, was the localization, in which respiratory changes in CSF flow were measurable. Kao et al. (2008) investigated the spatiotemporal patterns of respiration on 12 healthy volunteers, using dynamic echo planar imaging. The researchers obtained magnetic resonance images during two trials, firstly during normal breathing and secondly during 2 cycles of breath holding for 20 sec. The results from this study show, that respiratory-driven CSF flow was especially demonstrable in the vicinity of the ventricles, in CSF spaces and the Sinus Saggitalis whereas the cardiac components in the motion during normal breathing were (additionally to the above-mentioned) found to be in the vicinity of intracranial vessels and the Plexus Choroideus.

As mentioned in the previous chapter, Dreha-Kulaczewski et al. (2015) examined the influence of respiration on the flow in the entire ventricular system. It can be stated, that the most consistent measurements were made for the third ventricle, nevertheless, in all other parts of the ventricular system, i.e. the lateral ventricles, the aquaeduct and the fourth ventricle, respiration was clearly found to be the main driving force. An interesting fact, which partially contradicts findings in other studies, is, that the authors express the opinion, that the aquaeduct is the least suitable structure to examine for the CSF flow. The reason, which is mentioned is the close proximity to various different, possibly confounding, structures, eg. various brain tissues, and therefore the exposure to interferences from selfsame. The authors state, that in their study, at the site of the aquaeduct, the CSF flow showed a large variability within and across the subjects, presumably due to brain movements.

By means of example, in contrast, in the study by Takizawa, Matsumae, Sunohara, Yatsushiro, and Kuroda (2017), the aquaeduct and the Foramen Magnum were of special interest. Asynchronous 2D-PC technique (MRI) was carried out in 7 healthy volunteers, while the respiratory rate, through an additional pressure sensor, and the heart rate, through an echocardiogram, was simultaneously monitored. Subjects were required to control their breathing rate in accordance with audio guidance in 6s, 10 s and 16 s cycles for a total of 55 seconds. From the obtained data, the waveforms were separated into respiratory and cardiac components (through frequency range) and hence the maximum velocity for both components were identified. Part of the outcomes of this study will be discussed in due course in chapters 4.1.3 and 4.1.5. Some findings of this study are in partial contrast to those of Dreha-Kulaczewski et al. (2015), who clearly found the respiratory component to be of greater impact than the cardiac. Takizawa et al. (2017) disagree and state, that at both examined sites and in all breathing patterns, the cardiac component of CSF motion is significantly larger than the respiratory in terms of velocity. Nevertheless, they describe, that in terms of displacement of CSF, respiration has the greater impact, which again seems in partial accordance to the above findings.

In contrast to the other studies, which are discussed in this chapter and which deal with localisations inside the cranium, Friese, Hamhaber, Erb, Kueker, and Klose (2004) are occupied with CSF motion on the spinal level. A dynamic echo planar imaging MRI study was carried out on seven healthy subjects on five different levels in the spinal canal (C1, C2/3, C6/7, T5 and T12) during eight minutes of normal respiration, while heart and breathing rate were simultaneously monitored using a pulsoximeter and a respiration belt. The data were then processed and the different curves interpreted. The main site for CSF fluctuations was clearly found to be in the anterior subarachnoid space in the entire cervical region, this distinct pattern was not found in the thoracolumbar region, where the site of the flow showed large individual variations. The flow of CSF was shown to be respiration-related on all levels, in the upper cervical region it was found to be 19%, in the lumbar region 28%. These findings are underlined by results from Dreha-Kulaczewski et al. (2018), who also showed, that for inspiration the effect of respiration on CSF motion is apparent on all spinal levels, whereas for expiration it is most evident in the lower thoracic spine (T6-L2).

In conclusion it can be said, that there seems to be good evidence for respiratory impact on CSF flow in all parts of the CSF spaces, which include the ventricular system, as well as the subarachnoid space and the cisterns, the sulci and the central canal of the spinal cord on all levels, as well as the Sinus Saggitalis.

4.1.3 Velocity of CSF flow

The next aspect concerning CSF flow, which will be investigated, is the flow velocity. Takizawa et al. (2017) found that both regions of interest, the Sylvian Aquaeduct and the Foramen Magnum, the cardiac component of CSF motion was significantly larger concerning velocity in all investigated breathing rhythms. In terms of displacement, however, in both regions, the respiratory component was significantly larger compared to the cardiac. The authors argue, that one possible reason for the fact that the cardiac related CSF motion is predominant over the respiratory considering velocity, is that this may help in maintaining CSF pressure in the cranial cavity. On the other hand, they state, that in terms of displacement, where the respiratory component is predominant over the cardiac, this may facilitate a good substance exchange between brain parenchym and CSF spaces. Although no differences have been found in terms of CSF velocity or displacement concerning the various breathing rhythms (in 6sec, 10sec and 16sec/ cycle), significant variations within the curve have been found between 6sec and 16sec/ cycle for both respiratory and cardiac components, which again gives evidence for the impact of respiration on CSF fluctuation.

Concerning flow velocities, Chen et al. (2015) are to be mentioned. They examined the CSF flow of 9 healthy subjects with real-time MRI, with focus on velocity imaging in the cisterns, the foramen Magendie, the Foramen Monro, the fourth ventricle and the aquaeduct, while simultaneously monitoring respiration. Participants were asked to perform a series of breathing patterns from slow to fast and breathholding, that were controlled by a visual pattern on screen. The respiratory influence on CSF flow was found both in terms of direction and speed. The authors showed clear modulations of the flow, which differed at various breathing rates, and which were obtained above the cardiac-related modulations. Throughout the whole brain, during slow breathing, the flow velocities were found to vary, meaning they are greater in craniocaudal and anteroposterior direction, and lower in the area of the sulci. As in most of the other studies, the low frequency modulation (<0.5 Hz) of the CSF flow was clearly ascribed to respiration. Both, the cardiac- and the respiratory components were measured, yet no conclusion has been drawn by the authors concerning predominances.

Moving down along the course of the CNS, flow velocities were found to be most in the upper cervical area, with a maximum at C2/3 and to decrease in caudal direction along the spine (minimum at C6/7 and T5). However, the flow was increased again in the thoracolumbar region (Friese et al., 2004).

4.1.4 Direction of CSF motion

The CSF flow, particularly in the aquaeduct, was investigated for a total time of 120sec using an echoplanar imaging technique (MRI) on 22 healthy subjects by Klose, Strik, Kiefer, and Grodd (2000), while heart rate was monitored via a pulse oximeter and respiration through a respiration belt. This procedure enabled to identify the existence of flows, but not the direction of the flow, for this reason, a single volunteer study with different MR imaging had to be conducted in order to establish the direction. The outcomes of this study showed, that the flow of CSF in the cranial direction was maximum during the post-inspiration phase, vice versa, the caudal flow of the CSF was found to be maximum at the end of expiration. According to the authors, this is explicable as a compensation mechanism on the level of the cranium for changes in the intrathoracic pressure (IP) during respiration, as the IP is reduced in inspiration, the blood flow from the cranial veins is increased, and hence the CSF compensates for this reduction in cranial fluid volume.

Despite varying slightly in details, these results are similar to those obtained in the study by Yamada et al. (2013), who carried out a special Time-SLIP MRI scan on 10 healthy volunteers, which were in turn asked to inhale and exhale deeply to a maximum (cycles lasting about 6 sec) and hold their breath, while rate of respiration and heart rate were monitored simultaneously. In order to validate the results, acquired from the MRI, an additional flow phantom study was carried out. They showed, that a significant motion in the cranial direction of CSF took place in the ventricular system, as well as in the subarachnoid space (prepontine cistern toward suprasellar cisterns), especially in the beginning of deep inspiration (in comparison to Klose et al. (2000), where the cranial directed motion was maximum in the post-inspiration phase). Consequently, a caudal flow was imaged in the above-mentioned systems during the early phase of exhalation. The results seem to vary slightly, however Klose et al. (2000) only speak of the peak measurement, while Yamada et al. (2013) describe a general cranial motion during inspiration, therefore the results are not contradictory. These results are further supported by Chen et al. (2015), who similarly found a flow of CSF in the cranial direction during inspiration and, in turn, a caudal flow during expiration.

Equally, the same pattern of motion has been presented on a spinal level by Dreha-Kulaczewski et al. (2018) and by Friese et al. (2004). The latter speak of a systolic downward movement of CSF and, in consequence, a diastolic upward movement of CSF in the spinal canal. During late expiration, the systolic downward movement was found to be enhanced, whereas in early inspiration, the diastolic upward movement was found to be increased. The authors therefore describe expiration to lead to a downward CSF output through the Foramen Magnum and vice versa, inspiration to lead to an upward motion.

Dreha-Kulaczewski et al. (2018) obtained data from 19 healthy subjects during a real-time-contrast flow MRI, with an additional respiration belt, while the participants performed a breathing protocol. This protocol required them to either breathe deeply for 4 cycles (2,5 seconds forced inspiration, 2,5 seconds forced expiration) or breathe normally. In all breathing conditions, it was found, that inspiration causes a flow of CSF in cranial direction on all spinal levels, and, in turn, expiration causes a caudal flow. For inspiration this effect is apparent on all levels, whereas for expiration it is most evident in the lower thoracic spine (T6-L2). During the forced breathing, this pattern is shown to be significantly larger, than during the normal breathing, however, it is clearly identifiable in both conditions. Through this imaging technique changes in CSF flow velocities are displayed, which is influenced both by the flow itself and the lumen of the vessel. By showing, that the lumen in the subarachnoid space did not significantly change during the different phases of respiration, neither in normal nor in forced breathing, the authors conclude, that the measured change in flow velocities are solely due to shift in CSF flow, not chances in lumen of the space.

4.1.5 Displacement of CSF

One further point, which has been investigated is the displacement and direction of CSF. For this aspect, Takizawa et al. (2017) have clearly found, that respiration is the greater driving force in comparison to the heart rate. They suggest, that the displacement of CSF enables a good substance exchange between brain parenchym and the CSF spaces. Their calculated displacement of CSF, in the cranial direction at the different breathing cycles, is between 1.24±0.23mm and 1.47±0.54mm at the aquaeduct and between 5.05±3.14mm and 6.14±3.55mm at the Foramen Magnum. For the caudal direction, very similar results were found. In this study, cranial and caudal directed displacement caused by both cardiac and respiratory components are examined, however, no statement can be made as to the direction of movement during the respiratory phases.

Yamada et al. (2013) discuss, that the distance between the maximum displacement of inhalation and exhalation was then measured and was stated as 16.4±7.7 mm cranial and 11.6±3.0 mm caudal in the prepontine region. Also during breath holding small, fast movements in the cranio-caudad direction were displayed (3.0±0.4 mm cranially and 3.0±0.5mm).

The results for the displacement from these two studies differ to a greater extent. One possible cause for these differences may be the varying imaging and data processing techniques, the validity of both, however, can unfortunately not be evaluated by the author, as it would require far more detailed knowledge of MRI techniques and MR data processing. Yamada et al. (2013) measured directly from the obtained images, whereas Takizawa et al. (2017) calculated and derived the displacement from velocities, measured in the MRI. Another reason for the differences in results is the fact, that the displacement has partially been calculated in different parts of the CSF spaces.

Takizawa et al. (2017) measured at the Foramen Magnum and the aquaeduct, which, according to Dreha-Kulaczewski et al. (2015), is no favourable site for measuring CSF flow. In contrast, Yamada et al. (2013) measured the flow in the entire ventricular system and the subarachnoid space, yet the results were only displayed for the prepontine cisterne. It can therefore be concluded, that respiration definitely has a significant impact on the displacement of CSF, the amount of which presumably lies somewhere between the results of the above-mentioned studies.

Table 2 Summary of Studies on Respiration and CSF Motion

Title	Author/Year	Subjects	Interventions	Outcomes
Characterization of cardiac- and respiratory driven cerebrospinal fluid motion based on asynchronous phase-contrast magnetic resonance imaging in volunteers	Takizawa et al. (2017)	7 healthy (6m, 1f)	• 2D-PC technique (MRI) • Breathing rate: 6, 10, 16 sec/cycle • Total 55 sec imaging • ROI: Sylvian Aquaeduct, Foramen Magnum • Velocity and Displacement of CSF was investigated	• Velocity of CSF: at both ROI cardiac component significantly larger • Displacement of CSF: at both ROI respiratory component significantly larger • Authors explanation: Cardiac related CSF motion predominant over respiratory, helps maintain CSF pressure in the cavity • Displacement of CSF more respiratory related, good for substance exchange between parenchym and CSF space
Influence of respiration on cerebrospinal fluid movement using magnetic resonance spin labeling	Yamada et al. (2013)	10 healthy (8m, 2f)	• Time SLIP - MRI study • Breathing Rate 6sec/ cycle	• Sign. Cranial CSF motion in ventricular system and subarachnoid space, especially at beginning of deep inspiration, caudal flow during early expiration • Displacement between max. inspiration and expiration was 16.4±7.7 mm in cranial and 11.6±3.0 mm in caudal direction
Detection of a Relation between Respiration and CSF Pulsation with and Echoplanar Technique	Klose et al. (2000)	22 healthy (14m, 8f)	• Echoplanar Imaging Technique-MRI • Total 120 sec Imaging • ROI: Aquaeduct	• Cranial flow max. in post-inspiration phase • Caudal max. in end of expiration
Inspiration is the Major Regulator of Human CSF Flow	Dreha-Kulaczewski et al. (2015)	10 healthy (8m, 2f)	• Real-time MRI • Breathing protocols: 1. Forced breathing 5 sec/cycle 2. Breath holding 3. Forced inspiration 5 sec/ cycle • ROI: ventricular system	• Inspiration most important regulator for flow of CSF (add. Breathholding suppressed this component) • Cardiac Component only minor • Findings especially consistent in third ventricle • Aquaeduct not particularly good site for measurment of CSF flow – underlies many different surrounding forces

Title	Author/Year	Subjects	Interventions	Outcomes
The respiratory modulation of intracranial cerebrospinal fluid pulsation observed on dynamic echo planar images	Kao et al. (2008)	12 healthy (7m, 5f)	• Dynamic echoplanar imaging- MRI • Normal breathing, 2 cycles of breathholding 20 sec each	• Respiratory-driven CSF flow in vicinity of ventricles, CSF spaces and Sinus Saggitalis • Influence of breathing on CSF flow confirmed, as during breathholding respiratory rhythms temporarily suppressed
Dynamics of Respiratory and Cardiac CSF Motion Revealed with real-time simultaneous multi-slice Epi Velocity Phase Contrast Imaging	Chen et al. (2015)	9 healthy (?)	• Real- Time MRI, velocity imaging in 3 directions • Breathing instructions: “free”, “fast”, “slow”, “breathhold” after inspiration and “breathhold” after expiration • ROI: basal cisterns, Foramen Magendie & Monroe, fourth ventricle, Aquaeduct, Subarachnoid Space	• Respiratory effect on CSF flow in terms of speed and direction • Flow velocities vary throughout brain • Velocities greater in craniocaudal and a/p direction, lower in area of sulci • Inspiration: cranial motion into cavity and lateral ventricles, expiration vice versa
Heart Rate and Respiration influence on macroscopic blood and CSF flows	Daouk et al. (2016)	16 healthy (?)	• 2D fast field echo planar MRI • ROI: V. Jugularis, A.Carotis Interna, Spinal Canal at C2/3 • Normal breathing	• Cardiac influence in A. Carotis larger • Respiratory influence in V.Jugularis larger • CSF flow at spinal level: respiratory component larger than cardiac BUT • Both components minor impact on overall CSF flow at C2/3
The Influence of Pulse and Respiration on Spinal Cerebrospinal Fluid Pulsation	Friese et al. (2003)	7 healthy (4m, 3f)	• Dynamic echo planar MRI • ROI: 5 levels of spine • Total 8 min imaging • Normal breathing	• CSF flow maximum in upper cervical area, decreases caudally, increases thoracolumbar region • Main site for flow ant. subarachnoid space, in thoracolumbar not so clearly displayable • Inspiration: cranial motion, expiration Caudal motion of CSF

Title	Author/Year	Subjects	Interventions	Outcomes
Respiration and the watershed of spinal CSF flow in humans	Dreha-Kulaczewski et al. (2018)	19 healthy (14m, 6 f)	• a real-time phase-contrast MRI • Normal and deep, forced breathing alternately • ROI: spinal canal at all levels	• Inspiration causes cranial CSF flow in all spinal levels, in both breathing conditions (amplitude larger with forced breathing) • expiration caudal flow, most evident T6-L2 • Lumen in subarachnoid space no significant change during respiration → chances in flow ascribable to respiration
Characerization of Cardiac- and Respiratory-driven Cerebrospinal Fluid Motions Using Correlation Mapping with Asynchronous 2-Dimensional Phase Contrast Technique	Yatsushiro et al. (2016)	7 healthy (6m, 1f)	• 2D phase contrast MRI • Breathing intervals: 6, 10, 16 sec/ cycle • Total Imaging 56 sec	• Measurable difference in cardiac and respiratory-related CSF motion • Distribution of which vary along different intracranial regions: • Ant. subarachnoid Space predominantly cardiac-driven • Near veins, eg. In the Sinus Rectus, more respiratory- driven

4.2 Breathing and the Influence on Brain Activity

The next topic, which is to be investigated, is the influence of breathing on brain activity. Seven studies have been extracted from the literature research, the outcomes will be presented in three parts, the first dealing with the localisation of respiratory- related brain oscillations, the second and third going into detail for cognitive and limbic brain areas respectively. The included studies will be shortly summarized in Table 3 at the end of this chapter 4.2.

4.2.1 Localisation of respiration- related brain potentials

To begin with, Smejkal, Druga, and Tintera (2000) investigated the influence of volitional breathing on thereby activated brain regions. 9 healthy volunteers were scanned, using fMRI, while they were in turn calculating (and not cognitively breathing) or breathing in accordance with and acoustic signal, while the respiration rate was simultaneously monitored. It was demonstrated that during volitional breathing, brain activity occurred in both hemispheres of the frontal lobe, likewise in both hemispheres of the parietal lobe, especially in the gyrus postcentralis, in which the somatosensory cortex can be found, and both temporal lobes, particularly in the Brodmann area 22, of which part is involved in the Wernicke area. The authors clearly state, that aim of the study was only to derive topographic information about activated centres, therefore no conclusion can be drawn as to the extent of intensity, or to activation dynamics. They discuss, that the obtained temporal activity could possibly be due to the acoustic signal, which was given in order to dictate the breathing rhythm, rather than the breathing itself. One aspect, which makes interpretation of these results difficult, is the fact, that, both volitional and normal (nonvolitional) breathing were examined, the results displayed, however, were solely on volitional breathing. Therefore, it seems difficult, to draw conclusions about which regions are active during normal breathing, which during volitional breathing, and which activation patterns can be ascribed purely to the cognitive aspect, rather than the breathing.

More precise details as to the localisation of respiration- related oscillations can be concluded from the first part of the study by Herrero, Khuvis, Yeagle, Cerf, and Mehta (2018). Data, obtained from 8 patients with partial epilepsy, who underwent chronic intracranial EEG (iEEG) monitoring, were examined, with intracranial electrodes placed throughout the entire brain for diagnostic purposes. Brain regions, which showed coherence rates to breathing, i.e. brain oscillations, that can be ascribed to breathing were investigated. The subjects were assigned three different tasks, which included natural breathing, volitional breathing, meaning a conscious increase in breathing rate, and an exteroceptive experiment, which meant, that attention was to be shifted to external stimuli. iEEG data was collected, while the breathing rate was simultaneously monitored. It is to be said, that the below-mentioned results represent coherence of brain oscillations and breathing rhythms, they do not, however, automatically imply associated brain functions. It has been shown, that, of the brain areas, that had a high coherence to breathing, 89% were sited in the grey matter, 11% in the white matter and 0% in CSF spaces. According to the authors, 41.3% of all the existent sites in the grey matter had a coherence with breathing and these coherence values were significantly increased during fast breathing. The most invariable results were obtained from the hippocampus, amygdala, insula, frontal, parietal and primary olfactory cortices, which is the same to those, which show interrelation with natural breathing, yet, during fast breathing, the coherence is increased equivalently in magnitude. A fast breathing rate additionally caused higher respiratory-related oscillations, in the premotor cortex, caudal-medial frontal cortex, orbitofrontal- and motor cortex, the insula, superior temporal gyrus and the amygdala. However, the authors discuss, that this increased rate might also be due to the volition behind the breathing, not the breathing rate itself.

The results of this study support those of Smejkal et al. (2000), furthermore, they give a far more detailed insight into this matter. This is, in large part, due to the methods used, iEEG being a very precise way of obtaining data of brain activity, as the electrodes are directly placed onto the site, and no confounding tissues lie between. In addition, it is to be said, that, due to the large period of time of 18 years, that lies between the two experiments, the technical equipment supposedly underwent large technical progress, which might add to the reasons, the obtained data from Herrero et al. (2018) provide greater detail.

Similar results as to the localisation of respiration- associated brain potentials, concerning limbic areas, were obtained by Zelano et al. (2016). It is to be said, however, that in this study only a limited selection of regarded sites was investigated, therefore the comparability is limited. Their study included three experiments, of which the first will be investigated in this chapter, the second and third will be processed in chapter 4.2.3. iEEG data for natural breathing over a 15 min period of time was observed in 7 patients with temporal lobe epilepsy, who underwent diagnostic iEEG observation. In order to be included, the electrode placement specifically had to cover the piriform cortex, the amygdala and/ or the hippocampus. The results of this experiment clearly show, that electrical fluctuations, that were respiration- related with the normal breathing-cycle take place, in all three monitored sites, which corresponds to the findings by Herrero et al. (2018).

Further investigated sites of respiration- related cortical potential are in the frontal, slightly lesser in parietal, prefrontal and occipital regions of the brain (Hinterberger, Walter, Doliwa, & Loew, 2019), as well as the primary motor hand area (Ozaki & Kurata, 2015). In contrast, respiration leading to a deactivation of the Posterior Midline Region (PMR), resulting in a negative default mode effect was found (Huijbers et al., 2014).

To sum these findings up, it can be said, that breathing has a significant impact on brain activity, as well in cortical- as in limbic regions, the magnitude this coherence being clearly dependent on the breathing rate, with lower coherence values for natural breathing and higher values for faster breathing.

4.2.2 Respiration associated potentials in cortical areas

In order to enable a thorough understanding of the following research, definition and explanation of the terms Infra- slow oscillations (ISO), as well as resting state networks (RSN) and Slow Cortical Potentials (SCP) is vital. According to Watson (2018) “The ISO, [is] defined as a brain electrical rhythm with maximal spectral power in the frequencies from 0.01 Hz to 0.1 Hz” (p.1) that “lies in a temporal domain between typical brain sleep/wake state shifts and faster oscillations” (p.1). They are involved in the formation of resting state networks, which are involved in numerous neural tasks, reaching from sleeping state to cognitive function. Of these resting state networks around six different individual networks have been identified to the current time (Watson, 2018). Heine et al. (2012) state, that “The most widely studied resting state network (RSN) is the default mode network (DMN), encompassing precuneus/posterior cingulate cortex (PCC), mesiofrontal/anterior cingulate cortex (ACC), and temporoparietal junction areas” (p.1). ISO are in the frequency range between 0.01 Hz and 0.1 Hz, Hinterberger et al. (2019) investigate SCPs, which they define as below 1 Hz. They explain, that a negative SCP leads to an increased neuronal function, and, in turn, a positive SCP decreases cortical excitability. (p.2).

With the aim of investigating these infra- slow oscillations in the brain in synchronization with breathing, Karavaev et al. (2018) recruited 13 healthy subjects for an EEG experiment. The experiment consisted of three different phases: paced breathing, with linearly increasing frequency from 0.05 Hz (3bmp) to 0.25 Hz (15 bpm), breathing at 3 fixed frequencies 0.08 Hz (4,8 bpm), 0.12 Hz (7,2 bpm) and 0.21 Hz (12,6 bpm), and natural breathing. The authors showed that there is a clear synchronization of respiration and infra-slow oscillations in the brain with phase- and frequency locking during a paced breathing rhythm. Especially between 0.095-0.12 Hz (5.7-7.2 bpm – 11,5 sec -8,3 sec breathing intervals) the synchronization was shown to be very strong on a 1:1 level. In addition, it was found, that different brain regions showed different degrees of respiration-related infra-slow synchronization, the left occipital area showing the highest.

Similarly, Hinterberger et al. (2019), who investigated the influence of breathing on Heart Rate Variability (HRV) and SCP, showed, that a respiration pace of 10sec/ cycle had a particularly high activation of slow cortical potentials. EEG data, as well as HRV and respiration were measured from 37 healthy volunteers, who performed tasks of paced breathing with the aim of investigating respiration- induced slow cortical potentials (SCP) and their correlation with

HRV. After baseline recordings, subjects were asked to breathe according to a visual pacemaker for 6sec, 8sec, 10sec, 12sec, 14sec, 6sec per cycle, each breathing rhythm was recorded for 7 minutes. The main outcome of this study is, that a slower breathing rate has a high impact on SCP and HRV. The highest synchrony between SCPs and HRV at a rate of respiration of 10 sec/cycle, where the highest amplitude for both parameters was measured. At this pace, SCP activation of frontal and central regions was especially apparent, the faster breathing rhythms however, only show weak activations of the parietal, prefrontal and occipital regions. One interesting aspect, which was shown by the authors is the fact, that a positive shift in SCP was found during inhalation phase, and vice versa a negative shift during exhalation.
The authors interpret this negative cortical potential before the start of the inspiration as a sort of readiness potential, which acts as initiator for inhalation. According to them, the positive shift of potentials during inspiration may be evidence for the inhibition of other cortical regions, as the default mode network (DMN), which is deactivated during cognitive tasks. The higher amplitude in slow wave potentials may be ascribable to the deactivation of this network through the attentive breathing task.

This deduction, that cortical areas, such as the DMN are inhibited through respiration and thus cognitive function enhanced, likewise was drawn by Huijbers et al. (2014). Their experiment was carried out in three subsequent phases. There was a training phase, a scan phase with memory encoding tasks, where words were presented and the participants had to decide, whether the item is living or no-living alternately during normal breathing or 20 sec breathholding, and finally a post-scan phase, where memory had to be retrieved. The outcomes of this experiment underline a significant phase-locking effect with respiration, and it occurs stronger for items that were remembered in the third phase, than for items, that were forgotten. Phase-locking was defined by the authors as “the relation between respiratory fluctuations and stimulus [words] presentation” (p. 4939), describing the effect, that the respiratory rhythm is altered through an external stimulus. Although this describes a vice versa effect to what the research question should investigate, this outcome might still be of interest, as it shows, that breathing seems to have an effect on memory, what is more, not only on instantaneous, but also on later memory performance. This means, that items seemed to have been remembered significantly better, if respiratory phase-locking took place, rather than for items, where this was not measurable. Of particular interest was the default mode network in the Posterior Midline Region (PMR), which are brain regions that are active during resting state, and in turn, for enabling successful cognitive performance, need to be deactivated. The degree of PMR deactivation is in direct correlation to cognitive output.

In the fMRI a substantial contribution of the breathing cycle to a negative default mode effect in the PMR was found, although a considerable amount of this effect was still measurable during breathholding. This implies, according to the authors, that there are other components, which influence the default mode network, that are independent of respiration.
One aspect, which makes these studies, which show very similar results, difficult for direct comparison is the fact, that different means of imaging and data acquisition (EEG as well as fMRI) have been utilized. Huijbers et al. (2014) have found respiration- related deactivation in the DMN, however due to the fact that this was an MRI study, no measurements as to the frequency of the oscillations were made. Hinterberger et al. (2019), however, explicitly investigated SCPs in the frequency of below 1 Hz, and through the positive and negative shifts of the potentials derived to the conclusion of the deactivation of this network.
Another aspect, that impedes the comparison, are the different emphasis and study protocols. Hinterberger et al. (2019) concentrated on the effect of different breathing rhythms on the SCPs and the HRV, therefore measured potentials, whereas Huijbers et al. (2014) investigated the cognitive aspect, performing memory tasks and at the same time monitoring fMRI images. In conclusion, however, both authors have derived the same results, hinting that respiration influences the activation and deactivation of the DMN, leading do a change in memory performance.

Concerning the topic of respiration and its influence on cortical potentials, one study by Ozaki and Kurata (2015) are to be mentioned. The effect of normal and deep breathing at rest on the primary motor hand area was observed in eleven healthy volunteers. Transcranial Magnetic Stimulation (TMS) was applied on the primary motor hand area (M1) and motor-evoked potentials (MEP) measured for the corresponding muscles of the forearm of the right hand (M. Abductor Pollicis Brevis, M. Interosseus Dorsalis I, M. Abductor Digiti Minimi, M. Flexor Digitorum Superficialis, M. Extensor Indicis) while CO2 levels were recorded.
An additional experiment was carried out, with aim to examine, whether respiration has an influence on the peripheral nervous system (PNS). Therefore, the N. Medianus was stimulated, and MEPs measured during either normal or deep breathing. The authors showed a correlation between the depth of breathing and the excitability of the primary motor hand area. The condition of deep breathing entails an increased amplitude in MEP in all the observed muscles, in comparison to normal breathing. In addition, MEP latencies were reduced by approximately 1 millisecond. For both parameters, no difference was found between inspiration and expiration phase, which implies, that the effect of deep breathing is not phase dependant.
In the second part of the experiment, no significant changes in amplitude or latency of the action potential (neither sensory nor motor) were observed, which leads the authors to the conclusion, that the changes in excitability through deep breathing occur only in the CNS, not the PNS. The authors suggest, that their results, that the increased MEPs are respiration-

phase-independent can only be applied to the resting state of the subject, not, however, during volitional motor action, where, according to prior research, there is a specific coupling between the phase and the motor act. Furthermore, they state that:

> The present findings endorse and expand the idea of an overall respiration-related enhancement of the motor system, especially as related to the corticospinal pathways: Voluntary deep breathing at rest facilitates the excitability of the motor hand area, and this enhancement of excitability occurs across the full respiratory cycle. (p. 2169).

To sum the findings up, it can be said, that there is good evidence for respiration- associated potentials in cortical areas. The most consistent findings were that a slow breathing rate of approximately 10 sec/ cycle has a large influence on Slow- and Infra- slow cortical potentials. At this pace, the highest synchrony between SCP and HRV was demonstrated. A positive shift in SCP during inspiration, as well a negative shift during expiration was found, leading to the conclusion, that respiration influences the activation pattern of the Default Mode Network and therefore influencing memory performance, which is also confirmed through fMRI images. The excitability of the primary motor hand area was shown to be respiration dependant, deep breathing resulting in an increased MEP amplitude and reduced MEP latency, an effect, which seems to be independent of the respiration- phase.

4.2.3 Influence of respiration on limbic functions

According to Krämer (2010), the hippocampus, Gyrus Cinguli, Gyrus Parahippocampalis, amygdala and the Corpus Mammilare are generally accepted as parts of the limbic system. Some authors also seem to include the Rhinencephalon, including, among others, the piriform cortex, parts of the amygdala and the bulbus olfactorius. The limbic system controls parts of our affective behaviour, is involved in impulse regulation, as well as learning, memory generation and -retrieval.

Zelano et al. (2016) studied the influence of respiration on the limbic system, with special view to respirational phases and pathways in three separate experiments. For the first part, 7 patients with temporal lobe epilepsy, where intracranial electrodes were placed in the piriform cortex (part of the olfactory cortex), the amygdala and/or the hippocampus, were asked to breathe naturally for 15 min, throughout which time iEEG data was obtained. It was shown, that electrical fluctuations take place, that were phase- synchronal with the normal breathing-cycle, as well in the piriform cortex, as in the amygdala and hippocampus, especially in the inspirational phase of nasal breathing ("Diversion from nasal to oral breathing led to a disorganization of limbic oscillatory synchrony in all three brain regions" (p. 12464)). The authors suggest, that the, comparably slow pace of human breathing, causes infra- slow oscillations, and the air, that rhythmically enters through the nose, can evoke neural oscillations throughout the entire limbic system. They assume, that these low-frequency oscillations through nasal respiration can act as a carrier rhythm, upon which higher-frequency activity can occur in the limbic areas. In the second part of their experiment, 70 healthy subjects (some with instruction to breathe nasally, some orally and some nasally with open mouth) were shown rapidly switching pictures with faces expressing either fear or surprise, which were to be categorized by the subjects as fast as possible. Reaction time was measured, along with respiration phases.

The third part of the experiment consisted of healthy subjects, being presented with 180 pictures and told, they would be required to remember them later, and, after 20 min break, being shown the same pictures along 180 "new" ones, and asked to recall, whether they have seen them before or not, while respiration was, again, monitored. The authors state, that the "nasal route of respiration offers an entry point to limbic brain areas for modulating cognitive function. … [and] that respiratory phase and route have a significant influence on emotion discrimination and recognition memory" (p. 12464). This means, it was found, that the distinction of emotions (through the facial expressions), as well as the recognition of previously shown pictures, was significantly better during inspiration, in comparison to expiration, (for the memory recognition, inspiration was significantly beneficial for both encoding and retrieving of information), and similarly, they were considerably better in nasal breathing (compared to oral breathing). Respiration via the oral pathway caused a significant reduction in cognitive performance.

Focused more on the cognitive aspects of respiration-related changes in limbic functions, Huijbers et al. (2014) carried out their fMRI experiment in combination with memory encoding tasks, which is mentioned in the previous chapter. In accordance with the results from Zelano et al. (2016), they demonstrate a good correlation between respiration and cognitive performance and, in addition, not only immediate, but also later memory retrieval. In particular, the authors ascribe the increase in memory function to a phase- locking phenomenon between respiration and memory encoding. A large part of this increase in cognitive performance is ascribed to a deactivation of the default mode network in the posterior midline region through the respiratory cycle by the authors, which is described in more detail in the previous chapter.

In conclusion, there is strong evidence, that respiration has an impact on brain activity in many areas of both in cortical and limbic regions, the respiratory phase and route being able to influence abilities such as memory performance and emotion discrimination.

Table 3 Summary of Studies on Respiration and Brain Activity

Title	Author/ Year	Subjects	Methods	Outcomes
Nasal Respiration Entrains Human Limbic Oscillations and Modulates Cognitive Function	Zelano et al. (2016)	3 studies: 1. 7 patients temporal lobe epilepsy	• Intracranial electrodes (iEEG) • ROI: Piriform Cortex, Amygdala, Hippocampus • Natural breathing • Total Imaging 15 min	• Electric fluctuations phase-synchrone with breathing cycle • In piriform cortex, amygdala, hippocampus • Especially in inspiration phase and by nasal breathing • Oral breathing leads to disorganization of limbic oscillatory synchrony in all 3 brain regions
		2. 70 healthy	• 3 groups: breathe nasally, orally, nasally with open mouth • Shown pictures faces – emotion discrimination between surprise and fear • Reaction time and respiration phases obtained	• Emotion discrimination and memory recognition significantly influenced by phase and pathway of respiration • Inspiration leading to increased ability • As well as nasal breathing • Oral breathing leads to significant reduction in cognitive performance (p. 12464)
		3. ?	• Same breathing instruction • 180 pictures – should remember • 20 min break • Same pictures mixed with 180 new • Recall whether already seen	
Brain activation during volitional Control of Breathing	Smejkal et al. (2000)	9 healthy (4m, 5f)	• fMRI • normal breathing or paced breathing while calculating	• through paced breathing: activation in both hemispheres of frontal and parietal lobe (especially Gyrus Postcentralis) and temporal lobes (Gyrus Cinguli, Insula, Caput Nuclei Caudati) • no mention of difference of activation by normal and volitional breathing • no mention as to the phases, in which these activations occur

Title	Author/ Year	Subjects	Methods	Outcomes
Breathing above the brain stem: volitional Contral and attentional modulation	Herrero et al. (2018)	8 with partial epilepsy (4m, 4f)	• intracranial EEG monitoring • natural breathing, increasing breathing rate, breathing with attention to external stimuli • ROI: entire brain	• Of areas with coherence to respiration: 89% in gray matter • 41.3% of all sites in the gray matter had coherence, which increased during fast breathing • Especially in hippocampus, amygdala, insula, frontal, parietal and primary olfactory cortices • Same sites activated, increase in amplitude through faster breathing • Faster breathing additionally: higher oscillations in premotor cortex, caudal-medial frontal cortex, orbitofrontal- and motor cortex, insula, superior temporal gyrus, amygdala
Respiration Phase-Locks to Fast Stimulus Presentations: Implications for the Interpretation of Posterior Midline "Deactivations"	Huijbers et al. (2014)	26 healthy (6m, 20f)	• fMRI • semantic memory encoding • normal breathing or breath holding	• large effect of breathing cycle on default mode network deactivation in Posterior Midline Region (deactivation associated with better cognitive performance) • respiratory phase-locking occurs and is stronger for later remembered items than forgotten
The effects of voluntary control of respiration on the excitability of the primary motor hand area, evaluated by end-tidal CO2 monitoring	Ozaki et al. (2015)	11 healthy (6m, 5f)	• Motor-Evoked Potentials (MEP) measured in forearm muscles while transcranial magnetic stimulation performed on primary motor hand area (M1) • Normal and deep breathing	• Deep breathing entails increased amplitude in MEP in all forearm muscles • MEP latencies slightly reduced with deep breathing • Effect not phase- dependant - No difference between inspiration and expiration • Changes in excitability only in CNS, not in PNS
Synchronization of infra-slow oscillations of brain potentials with respiration	Karavaev et al. (2018)	13 healthy (?)	• EEG • Paved breathing with linearly increasing frequency 0.05 Hz-0.25 Hz, breathing at 3 different rates 0.08 Hz, 0.12 Hz, 0.21 Hz, natural breathing	• clear synchronization of respiration and infra-slow oscillations • between 0.095-0.12 Hz synchrony strong (1:1) • different brain regions showed different degrees of synchronization

Title	Author/ Year	Subjects	Methods	Outcomes
The brain´s resonance with breathing – decelerated breathing synchronizes heart rate and slow cortical potentials	Hinterberger et al. (2019)	37 healthy (17m, 20f)	• EEG and HRV measured • Breathing: 6, 8, 10, 12, 14 sec/cycle • Aim: respiration- induced Slow Cortical Potentials (SCP) • Total recording: 7 min	• Slow breathing rate high impact on SCP and HRV • Highest synchrony at 10 sec/cycle, where - Good activation in frontal and central regions - Positive shift in SCP during Inhalation - Negative shift in SCP during Exhalation • This may be evidence for deactivation of default mode network

4.3 Breathing and the Influence on Pain Perception

One further important aspect, concerning the influence of breathing on the central nervous system, concerns pain perception. It is widely agreed in the medical society, that slow, conscious breathing can have an analgesic effect, however, many studies, which underline this, are carried out examining various forms of meditative breathing, not normal breathing. For this reason, the results are difficult to generalize and to apply to persons, who do not practice forms of meditation. Therefore, it seems necessary to examine studies, which investigate the influence of breathing on pain perception for this population. The literature research has produced six studies, which will be examined and discussed during this chapter, the outline data will be displayed in Table 4 at the end of this chapter 4.3.

The effects of slow breathing on pain perception and autonomic responses were investigated by Zautra, Fasman, Davis, and Craig (2010) , who applied a thermal pain stimulus to 27 women with fibromyalgia, as well as 25 healthy women, while they underwent either normal or very slow respiration. Pain intensity was asked and affective responses were measured after each trial.
As the research question is only concerned with physiology, only the outcomes for the healthy participants will be taken into account, those concerning the patients with fibromyalgia are not discussed. The authors showed, that the slow breathing condition significantly lowered the perceived pain intensity, furthermore, a good positive correlation was found, meaning, the higher the pain stimulus, the higher the analgesic effect. In addition, a lower affective response was found during pain sensation, when participants practiced a slow breathing rhythm. One aspect, which makes interpretation and generalization of these results difficult is the fact, that only women were taken into account. According to Wiesenfeld-Hallin (2005) pain perception differs between males and females, as sexual hormones influence sensitivity to pain. This means, that during the course of the menstrual cycle, tolerance and threshold to pain fluctuates. However, as the authors do not mention any attempt in order to carry out the procedure only during a standardized phase in the menstrual cycle, the results are vulnerable to bias through hormonal influences and it therefore makes comparison more difficult.

In a similar way, thermal pain threshold and tolerance was measured using a thermode on the forearm for 20 healthy subjects, where the gender distribution was almost equal, who underwent five different breathing protocols, by Chalaye, Goffaux, Lafrenaye, and Marchand (2009). This protocol included natural breathing, slow deep breathing, rapid breathing, distraction via video game and heart rate (HR) biofeedback (inhaling, when HR was increasing, exhaling when it was decreasing), while simultaneous monitoring of electrocardiogram (ECG) and respiration through a piezo electric respiratory belt was carried out.

Analgesic effects, meaning a higher pain threshold compared to natural breathing, were found only for the slow deep breathing, the HR biofeedback and the distraction condition, for natural and rapid breathing, no such effect was present. Similar results were found for pain tolerance with the exception, that distraction had no significant effect. Summing up, it can be said, that both conditions, slow breathing and HR biofeedback, which means breathing paced through the heart rate, had the greatest reduction in pain sensitivity, while additionally resulting in the largest heart rate variability. The authors also argue, that through the attentive breathing, cognitive factors might have played a role in the analgesic effect, yet, they state, that during rapid breathing, no such effect was shown, therefore the cognitive factors do not seem to outweigh. They hypothesize, that one possible explanation for the slow breathing effect is, that due to the pressure gradients, fluctuations in blood pressure occur. Baroreceptors sense these fluctuations and transmit the information via cranial nerves IX and X into the brain, especially the Nucleus Tractus Solitarius. Meller, Stiehm, Malinowski, and Thieme (2016) state, that this nucleus is in a network along with other brain stem and cortical regions, which contribute to the modulation of anxiety, sleep and pain. This study investigated the influence of different breathing rates on pain perception, they did not, however, examine, whether the phases of respiration have an influence.

The problem of interference of cognitive factors and therefore possible bias, was also discussed by Jafari et al. (2016). The investigation whether there is a detectable difference in self-reported pain (measured by the NRS) and nociception (measured through the Nociceptive Flexion Reflex – NFR) between spontaneous- and paced breathing, as well as whether breathholding can reduce the selfsame was aim of their study. Data was collected from 32 healthy volunteers, who underwent spontaneous breathing as well as different breathholding trials, to evaluate respiration through a chest belt, to evaluate the NFR through EMG recordings through two electrodes on the M. Biceps Femoris and for self-reported pain with help of the NRS, while Electro-cutaneous pain stimulation was applied at the N.Suralis of the ipsilateral leg.

Self-reported pain was found to be significantly lower during breathholding in comparison to natural breathing. The authors discuss, that this effect may be due to the required attentiveness during the different breathholding trials, as well as the fact, that the pain stimuli were more predictable during this phase, which is, through various research, believed to lead to reduced pain ratings. In contrast, this study showed an (not significant) increase in the NFR during breathholding in comparison to natural breathing, which the authors potentially explain by either the increased attention on the painful stimuli or elsewise because "instructed breath-holds relates to a potential subthreshold facilitation of alpha motoneurons." (p. 56) This means, that muscles, which are in connection with breathholding, may possibly enhance the NFR. Nevertheless, it has been found, that the depth of breathhold affects the NFR, breathholding at mid- inhalation produced a significantly higher NFR in comparison to breathholding at full-range in- as well as exhalation. In contrast to other findings such as Arsenault, Ladouceur, Lehmann, Rainville, and Piché (2013) and Iwabe, Ozaki, and Hashizume (2014), the phase of spontaneous respiration (inspiration vs. expiration) was not found to have a significant impact on pain perception (a slight reduction was found in expiration, but not significant). One aspect, which makes this study difficult for comparison, is the fact that Jafari et al. (2016) carried out this experiment for the lower extremity, whereas all the other studies examined the upper extremity, which arises the question of the transferability of the results to other regions of the body.

In accordance with the above- presented results, the effect of Slow, deep breathing (DSB) on pain perception, autonomic activity and mood processing was investigated by Busch et al. (2012) in a long-term study on 16 healthy subjects. Two Mesocycles of six weeks each, each of which examined a different DSB technique (attentive DSB and relaxing DSB), were carried out with a rest period of six months in between, as to avoid any carry-over effects. Each Mesocycle consisted of one supervised training per week (six in total) and measurements, measuring thermal detection threshold, pain threshold for cold and hot stimuli, skin conductance level (SCL – measurement for autonomic activity) and mood states, were carried out on three separate occasions during the Mesocycle. Breathing rate was given at around 7 cycles/ min (8,5 sec/ cycle) for both interventions. aDSB was carried out with subjects required to breathe, so that their breathing rate and depth fitted an ideal breathing curve on a monitor, whereas during the rDSB mesocycle, subjects were asked to focus on the experience of breathing and were externally paced by verbal instructions. It was shown that both thermal detection- and pain threshold were significantly increased, as well as skin conductance level decreased during the rDSB breathing sessions, which implies an overall reduction in pain perception. No such changes were acquired during the aDSB, however. For both conditions, a similar reduction in negative feelings was found. The skin conductance level was found to be decreased by 18% in the rDSB trial, which implies an overall reduction in autonomic activity. One major drawback of this study, as the authors argue, that it is not clearly possible, to distinguish, whether the measured effects were due to respiration or rather to overall relaxation. Nonetheless they still conclude from the overall results, that conscious deep and slow breathing is an effective way to influence pain and autonomic processing.

Summarizing the outcomes of this study, it can definitely be said, that there is an effect of respiration on pain processing, whether only through relaxation or directly through the breathing mechanisms itself, but clearly slow, deep breathing influences pain threshold and -perception.

A clear influence of the respiratory cycle on pain perception, in accordance with brain potentials and sympathetic responses was shown by Iwabe et al. (2014). Noxious Stimuli were inflicted via intraepidermal electrical stimulation on the dorsum of the left hand on 10 healthy subjects, while simultaneously EEG, ECG, Sympathetic Skin Responses and Co2 was measured during normal breathing. Data for Subjective Pain perception at different thresholds was then collected.
It was demonstrated, that subjective pain perception was stronger during inspiration phase and, in addition, that sympathetic skin response, associated with a higher pain level, was larger in inspiration. In accordance, the amplitude of evoked potentials in the EEG was also larger during inspiration, and the amplitude proved to be correlating to the subjective pain perception. The authors assume, that one reason for the analgesic effect of expiration may be that serotonergic neurons in the Nucleus Raphe Inferior, which is influenced by respiration, may have a phasic gating effect for nociceptive inputs at the height of the spinal cord, which results in pain suppression during expiration. It can therefore be concluded, that expiration has a beneficial effect on all these parameters, leading to a reduced sense of pain, less sympathetic skin responses, as well as reduced evoked potentials in the brain.

The above findings are in slight contrast, to what Arsenault et al. (2013) have found. Transcutaneous electrical stimuli were applied the sural nerve of 20 healthy subjects in different breathing conditions (slow breathing with slow inspiration, slow breathing with fast inspiration, normal breathing with fast inspiration), while subjective pain and anxiety were recorded, along with EEG and cardiac measurements and RIII-reflex measurements (Spinal nociceptive activity). Unexpectedly, subjective pain was found to be significantly lower during inspiration, but it was not influenced by breathing patterns. In contrast to these findings, the RIII-reflex amplitude, which measures spinal nociceptive activity, was found to be greater in amplitude during inspiration, which implies, according to the authors, that the prior-mentioned hypoalgesic effect during inspiration might rather be due to cerebral and cognitive mechanisms, than to respiration itself. The authors are well aware of one drawback of the study design, which might confound results, which is, that auditively cued respiration might be distracting and therefore attention of the subjects might have been directed elsewhere, and not to the painful electric impulse. Due to the fact that the RIII-reflex showed an increased spinal nociceptive activity during inspiration, it can be assumed, that these results are still in accordance with the outcomes of Iwabe et al. (2014).

One aspect, which has to be critically regarded in all the above studies, is the fact, that the procedures all included a cued, and controlled breathing. All the above authors discuss, that the cognitive processes involved in the processing of these instructions might shift attention towards the cue rather than the painful stimulus, however, they mostly argue, that this effect is

only small, so the results seem to be valid. Another factor, which should be considered, is the fact, that both gender and cultural aspects have an influence on pain perception, which makes the studies not completely comparable. Three studies were carried out on the northern American continent, two in Europe and one in Asia, therefore many cultures and peoples are not represented through the sample of studies examined in this thesis.
One more aspect, which impairs the applicability of the above- mentioned results, is the fact that the pain stimulus was either thermal or an electric impulse. For this reason, the outcomes cannot be completely generalized and applied to all kinds of pain sensations.

To conclude, it is obvious, that physiological respiration is an essential factor in the perception of pain. Especially slow, deep breathing has a strong beneficial effect on pain threshold and tolerance, and exhalation seems to reduce pain perception, along with pain-associated brain potentials, sympathetic skin responses and spinal nociceptive activity.

Table 4 Summary of studies on Respiration and Pain Perception

Title	Author/ Year	Subjects	Methods	Outcomes
The respiratory cycle modulates brain potentials, sympathetic activity and subjective pain sensation induced by noxious stimulation	Iwabe et al. (2014)	10 healthy (10m, 0f)	• Intraepidermal electrical stimulation • EEG, EKG, Sympathetic Skin Response, Subjective Pain measured • Normal, nasal breathing	• Respiratory cycle influence on pain perception, brain potentials and sympathetic skin response • Amplitude of Potentials in EEG larger in inspiration, amplitude correlating to higher subjective pain • Expiration is linked with a decreased subjective pain perception, as well as a lower amplitude of evoked potentials and a reduced sympathetic skin response
Pain modulation induced by respiration: Phase and Frequency Effects	Arsenault et al. (2013)	20 healthy (11m, 9f)	• Transcutaneous Electrical Stimulation on N. Suralis • Slow breathing with slow/fast inspiration, normal breathing with fast inspiration • Subjective Pain, Anxiety, EEG, RIII Reflex	• Subjective Pain significantly lower during inspiration, not influenced by breathing patterns, (according to authors, effects seem to be small) • RIII Reflex (Spinal Nociceptive Activity) found greater in amplitude during inspiration → according to authors hypoalgesic effect during inspiration possibly/likely due to cognitive mechanisms
Respiratory Effects on Experimental Heat Pain and Cardiac Activity	Chalaye et al. (2009)	20 healthy (11m, 9f)	• Pain through thermode on forearm • Natural, slow deep, rapid, distraction, heart rate biofeedback breathing • ECG, respiration monitored	• Slow, deep breathing and biofeedback showed greatest reduction in pain sensitivity, largest HRV, Pain threshold higher • Authors indicate, that respiratory-induced hypoalgesia, is due to different neurobiological mechanisms than hypoalgesia through pure distraction • Phase effects were not investigated
The effects of slow breathing on affective responses to pain stimuli: An experimental study	Zautra et al. (2010)	17f with fibromyalgia 25f healthy	• Heat stimulus • Either normal or very slow respiration • Subjective Pain and affective response measured	• Slow breathing reduced subjective pain, lower affective response • The higher the heat stimulus, the higher the analgesic effect • (research question of this work concerns physiology, only outcomes for healthy subjects displayed)

Title	Author/ Year	Subjects	Methods	Outcomes
The Effect of Deep and Slow Breathing on Pain Perception, Autonomic Activity and Mood Processing – An Experimental Study	Bush et al. (2012)	16 healthy (3m, 13f)	• 2 Mesocycles à 6 weeks, inbetween 6 months without intervention • Mesocycle: 1 supervised training/week; in one attentive, other relaxing deep breathing (aDSB, rDSB) • Thermal detection- and pain threshold for cold/ hot, skin conductance level, mood state • DSB: 8,5 sec/cycle	• Thermal detection- and pain threshold significantly increased during rDSB, not aDSB • Difficult to differentiate whether analgesic effect through breathing or rather overall relaxation • Conscious deep and slow breathing is an effective way to influence pain and atonomic processing
Respiratory hypoalgesia? Breath-holding, but not respiratory phase modulates nociceptive flexion reflex and pain intensity	Jafari et al. (2016)	32 healthy (10m, 22f)	• Electro cutaneous pain stimulation on N.Suralis • EMG of M. Biceps Femoris, Subjective Pain, respiration measured • Normal breathing, various breathholding trials	• Subjective Pain significantly lower during breathholding → authors argue possibly due to increased attentiveness, and the higher predictability of the pain stimuli • Not significant increase in Nociceptive Flexion Reflex (NFR) (pain withdrawal reflex) during breathhold • Phase of respiration no significant influence on pain perception (slight reduction found during expiration, but not significant)

5 Discussion

In the following chapter, the results, as well as the thesis itself will be critically evaluated and the relevance for osteopathy will be highlighted. It will be divided into three parts, a brief summarization and discussion of the results, implications for osteopathy and a critical reflection on the thesis itself.

5.1 Summarization and Discussion of Results

Summarizing the results from chapter 4, it can be concluded, that there is strong scientific evidence, that respiration is well measurable along the entire CNS. Every single examined study confirmed the hypothesis, that respiration is measurable on various levels and functions of the central nervous system.

Concerning the motion of CSF, all examined studies confirm an overall impact of respiration on the flow, to various degrees. According to Dreha-Kulaczewski et al. (2015), inspiration is the main driving force for CSF flow in normal breathing and breathholding supresses this flow, a phenomenon, which was similarly found by Chen et al. (2015) and Kao et al. (2008). On the other hand Daouk et al. (2017) state, that, although the respiratory component seems to outweigh the cardiac in terms of influence on CSF motion, both components only seem to influence the flow on a minor degree. As mentioned in chapter 4.1.1 the comparability of these studies is difficult, as different regions of interest were examined, on the one hand in the cranium, on the other at a cervical level, and therefore the results are prone to differ. However, all the above- mentioned examined studies agree on the fact, that a clear respiration- related motion of CSF is measurable in the CNS.

The flow of CSF in the cranium is measurable along the entire ventricular system, as well as in the CSF spaces (Kao et al., 2008; Dreha-Kulaczewski et al., 2015) and the Sinus Saggitalis (Kao et al., 2008), and on the spinal level especially in the anterior subarachnoid space in the cervical region (Friese et al., 2004), however it is measurable on all spinal levels (Dreha-Kulaczewski et al., 2018). As to the direction of the flow, the authors (Klose et al., 2000; Yamada et al., 2013; Dreha-Kulaczewski et al., 2018; Friese et al., 2004) of all studies examining this aspect agree, that inspiration leads to a cranial, upward motion of CSF and expiration to a caudal, downward movement. Takizawa et al. (2017) claim that in terms of velocity, the cardiac component is predominant over the respiratory and argue, that this fact might help in maintaining the pressure in the CSF system. Chen et al. (2015) measured both components in the ventricular system, however, no statement is made, as to which has the greater impact. They claim, that the velocity of CSF flow varies throughout the different regions in the brain, being greater in cranio- caudal and anterio- posterior direction, and smaller around the sulci. On the spinal level, flow velocities were shown to be maximum at C2/3 and decreasing moving caudally along the spine (Friese et al., 2004). Displacement of CSF motion during the respiratory cycle was clearly verifiable, the exact results of the two studies differ to a large degree, though. Takizawa et al. (2017) speak of cranial motion between 1.24±0.23 mm and 1.47±0.54 mm measured the aquaeduct and the Foramen Magnum (similar in caudal direction) at various paced breathing rates, whereas Yamada et al. (2013) mention measurements of 16.4±7.7 mm cranial and 11.6±3.0 mm in the ventricular system and the subarachnoid space, carrying out deep breathing and breathholding sequences. As mentioned in chapter 4.1.5, comparison and exact determination of which of the results are more exact is difficult, as the regions of interest are not identical, the imaging and further data processing, as well as presentation of the data differ. Nonetheless, the conclusion can be drawn, that a displacement takes place in the CSF system, which is respiration- driven and measurable.

In conclusion, it has been shown in this thesis, that the osteopathic claim of sensing breathing in the CNS in terms of CSF flow seems verifiable. Respiration has significant effects on the flow of CSF, and breathholding temporarily suppresses the related flow. The influence of respiration was confirmed in every single examined study. The impacts can be seen throughout the entire CSF spaces, including the ventricular system, the subarachnoid space and the spinal cord on all levels. Generally, inspiration causes a cranial, and expiration a caudal motion of CSF. The flow velocities vary in the different areas in the cranium and a clear displacement of CSF is measurable.

The second aspect, which was investigated in this thesis is the influence of respiration on brain activity. Respiration-associated activity in normal breathing can be seen in large parts (41.3%) of the grey matter, and throughout cortical and limbic regions. Among those are the amygdala, insula, hippocampus, the frontal, parietal and primary olfactory cortices, which gave the most invariable results in the iEEG. During fast breathing, additional activity can be observed more in frontal regions and, as the magnitude of the coherence of respiration and brain activation were shown to be dependent on the breathing rate, the coherence values increased during fast breathing (Herrero et al., 2018). These sites of respiration- related brain activity were also partially confirmed by Zelano et al. (2016), who only investigated iEEG regions of interest in the limbic system. These findings, obtained through iEEG, which provides very accurate measurements, indicate good evidence for respiration- related activities in cortical and limbic areas.

Karavaev et al. (2018) confirm through conventional EEG, that different regions in the brain show different degrees of synchronization with respiration. In particular, they showed that breathing induces infra- slow oscillations, especially for breathing rhythms between 5.7 and

7.2 cycles/ min. As explained in chapter 4.2.2, these ISO are involved in the development of resting state networks, such as the default mode network, which play an important role in cognition, which leads to the inference, that breathing can influence cognitive function. This assumption is further supported by Huijbers et al. (2014), who showed through their fMRI study, that the normal breathing cycle has a strong effect on deactivation of the DMN in the posterior midline region. Deactivation of this network is associated with a better cognitive performance, the degree of deactivation being in direct correlation to cognitive performance. In addition, they found, that respiratory phase- locking is measurable and significant in memory function, as it was found to be stronger, for words, that were later remembered. Similar to the findings by Karavaev et al. (2018), Hinterberger et al. (2019) also show through EEG data, that a slow breathing rate has a high influence on slow cortical potentials, in particular a breathing rate of 10 sec/ cycle, which corresponds to 6 cycles/ min, showed the highest synchrony between respiration and the brain potentials. They give further support to the assertion, that respiration affects the deactivation of the DMN and therefore cognitive function, as they found that inspiration evokes a positive shift and expiration a negative shift in SCP. The authors argue, that the positive shift may be evidence for the inhibition of other regions in the cortex, such as the DMN. Ozaki and Kurata (2015) showed, that breathing influences the excitability of the cortical region of the primary motor hand area, as deep breathing increased the amplitude of Motor- Evoked Potentials (MEP), as well as MEP latencies in forearm muscles. This leads the authors to the hypothesis, that respiration can generally enhance the entire motor system.

It was found by Zelano et al. (2016), that limbic functions are influenced by respiration. On the one hand, they gave evidence for this through iEEG recordings in the limbic system during natural breathing for 15 min, where clear respiration- related oscillations were measureable there. On the other hand, through the second and third experiment, they gave evidence, that emotion discrimination and memory recognition were significantly influenced by phase and pathway of respiration, inspiration leading to increased capability of both functions and nasal breathing leading to the selfsame. Oral respiration, on the contrary, was found to result in a significant reduction in cognitive performance.

As mentioned previously in this chapter, Huijbers et al. (2014) draw the same conclusions, that respiration influences cognitive function, from their study, however they did not specifically investigate neither phase or pathway of breathing, but rather state, that the breathing cycle altogether influences the deactivation of the DMN and that phase- locking with respiration leads to significant improvement in memory performance.

The last aspect, which was investigated in this thesis is the influence of breathing on pain perception. It was demonstrated by Zautra et al. (2010), that slow respiration, in comparison to normal breathing, significantly decreased subjective pain intensity. Furthermore, it was found, that the greater the pain, meaning a higher pain stimulus, the higher the analgesic effect of respiration. Similarly, Chalaye et al. (2009) state, that the condition of slow, deep breathing, as well as breathing according to biofeedback in accordance with the heart rate, led to an increased pain threshold, as well as increased pain tolerance.

The results from the study by Busch et al. (2012), who investigated two ways of deep, slow breathing, which were either attentive or relaxing, are very similar, however the procedures and aims differed to a great extent, making a comparison difficult. It was found, that relaxing DSB increased the thermal detection and pain threshold, as well as it reduced skin conductance level, which is a parameter for autonomous activity and is associated with pain perception. One very interesting aspect concerning this study however, is, that the measurements were obtained over a period of six weeks, suggesting, that rDSB on a regular basis can lead to overall longer- term changes in these parameters. The phase of respiration was shown to have a clear influence on pain perception by Iwabe et al. (2014). According to them, inspiration leads to a higher pain perception, as well as an increase in sympathetic skin response and an increase in the amplitude of evoked potentials. Conversely expiration led to a decrease in all three parameters. Only a non- significant influence of phase on pain perception was found by Jafari et al. (2016), however the trend seemed to support the assumption, that expiration leads to a decrease in subjective pain. Additionally, it was found, that perceived pain was reduced during a breathholding sequence, this, however, was potentially ascribed by the authors to the cognitive aspect of the sequence. Arsenault et al. (2013) on the contrary, found inspiration to lead to a decrease in subjective pain. The authors themselves argue, that this result is probable to be due to cognitive factors, rather than an analgesic effect itself, especially considering the fact, that the amplitude of the RIII reflex, which is an indicator for spinal nociceptive activity, increased during inspiration. In conclusion, it can be summarized, that there is good evidence, that slow, deep breathing has an analgesic effect, expiration phase seems to have the same effect, however the results, which underline this, are not all consistent.

5.2 Implications for osteopathy

The fact, that respiration is clearly measurable throughout the CNS is of high significance for osteopathy, as it underlines the sensations of osteopaths, who claim to sense respiration in most tissues, and therefore this thesis is a small contribution in the effort of making osteopathy and osteopathic perception, in particular in cranial osteopathy, more evidence based.

In this thesis evidence was provided, that inspiration leads to a cranial motion of CSF in the ventricular system, as well as in all other CSF spaces on the cranial and spinal level (Klose et al., 2000; Yamada et al., 2013; Chen et al., 2015; Friese et al., 2004; Dreha-Kulaczewski et al., 2018) an increase in spinal nociceptive activity (RIII-reflex) (Arsenault et al., 2013), an increase in pain-associated brain potentials (Iwabe et al., 2014), and an increase in sympathetic skin responses to pain (Iwabe et al., 2014). On the other hand, it is to be said, that during inspiration cognitive and emotional abilities such as emotional discrimination and memory performance seem to improve, more precisely this means, that words, which were remembered during inspiration, were better recalled later on, than for expiration. For the latter abilities, the pathway of respiration seems to be of great influence, nasal respiration enhancing them, oral breathing leading to a disorganization of limbic oscillatory synchrony and to a significant reduction in cognitive performance (Zelano et al., 2016). Conversely expiration leads to the opposite effects.

These findings are of significant relevance for osteopaths, especially in the fields of paediatrics, neurology, psychiatry and pain management. It has to be mentioned, that the below stated are assumptions drawn by the author of this work from the results of the above-mentioned studies, they do not, however, display any direct results or conclusions from the authors of the mentioned studies.

The outcomes of these studies imply, that one possible way of working on and influencing the limbic system is by treating the diaphragm and improving breathing mechanisms and patterns. As the results reveal, that breathing-related oscillations in the limbic system occur and associated functions such as memory performance or emotion discrimination alter during respiratory phases. It can therefore be hypothesized, that, through treating diaphragmatic- and breathing dysfunctions, a positive effect on the overall limbic system can be achieved. This can be relevant for instance in the field of psychiatry as for anxiety disorders or developmental disorders such as autism. It has been shown, that emotion-processing processes are influenced by breathing phases, which leads to the assumption, that, for patients with problems in this field, treatment on the diaphragmatic level and improving breathing mechanisms, possibly with focus on inspiration, can be beneficial. What is more, memory performance significantly improved during inspiration, which can be interesting in the fields of paediatrics for children with learning difficulties, likewise also for treatment of neurologic patients, who struggle with cognitive issues.

As it has been found, that oral respiration is unfavourable for these abilities, it seems important to integrate the evaluation the pathway of respiration into the clinical examination of patients, with difficulties in these functions. Subsequently, if deficits or dysfunctions are found in this regions, one implication for osteopathy is to try to open these pathways, in order to facilitate a free nasal respiration and in consequence, have a possible positive impact on memory performance and learning skills.

It has been suggested by Ozaki and Kurata (2015), that an “overall respiration-related enhancement of the motor system” takes place and “this enhancement of excitability occurs across the full respiratory cycle” (p.2169). This hypothesis and integration of breathing and treatment of the diaphragm therefore possibly is of interest for osteopaths in various fields, with the aim of improving and enhancing motor functions, such as in the treatment in intensive care units with patients with an overall low excitability, in the work with athletes or the work with children in their physiological motor development.

One further implication for osteopathy, which is not new, nonetheless very important, is the application of breathing in the field of pain management. The results of these studies show, that a person does not have to be practiced in meditative breathing, in order to achieve analgesic effects through respiration. In particular, the focus should be laid on a slow, and deep expiration. This is shown to have positive effects on overall pain perception, a reduction in pain threshold and tolerance, a reduction in pain associated brain potentials, sympathetic skin responses and a reduction in spinal nociceptive activity.

5.3 Critical Reflection on the Thesis

The examined studies, despite all their previously discussed individual limitations, all support the assumption, that breathing is measurable throughout various parts of the central nervous system. The results of this thesis, however, have several limitations, which will be discussed during this chapter.

On the one hand, the fact, that the studies availed themselves of different methods of testing, such as MRI, EEG or MEP seems very beneficial to the validity of this thesis, as one effect often is verified through more than one method of measurement, which potentially highlights different aspects, yet confirmed one another. On the other hand, this aspect makes the studies very difficult for comparison, as no actual values or images can be opposed to each other, and therefore only the deductions, made from the respective data were comparable. This made the assessment and weighing of the results challenging, and in some cases, not possible. Likewise, the fact, that often, although similar procedures and methods of testing were used, different regions of interest in the CNS were investigated, which often only enabled juxtaposing the results, but not opposing them. This arises the question, if studies, which received slightly contradictory results, but have examined different regions of interest, would have come to similar outcomes, if they had investigated the exact same areas.

One aspect, which restricts the outcomes of this thesis, is the fact, that all studies have been made in the resting state, with the subjects either prone or sitting in a chair. For this kind of research, with imaging techniques and other susceptible technical equipment required, no other means of procedures would be possible, nonetheless, the results therefore must be limited to the resting state. As during osteopathic treatment, the patient mostly lies in a resting state, however, and osteopaths sense the breathing during selfsame, the results still seem to be applicable to this setting.

One further limitation of the results is, that all studies were carried out in an artificial environment, in hospitals or laboratories. Moreover, the patients were informed on the procedures, and were aware, that the experiments were carried out, in order to investigate respiration and its impacts on their body. As the studies investigated influences of breathing on the CNS, and brain activities in particular are influenced by cognitive processes, the awareness of the subjects, that breathing was examined, may possibly have influenced the results.

Another factor, which possibly limits the results of this thesis, is the fact, that in many studies, paced or cued respiration was examined. On the one hand, this was intended and consciously chosen, in order to obtain information as to how different breathing rhythms affect different variables in the CNS and to get an impression for general trends. On the other hand, the results obtained by paced breathing firstly do not automatically represent normal breathing and secondly the cued breathing involves cognitive processes, which possibly influences the results. This appears to be a minor issue for CSF fluctuations, which are regulated by physical processes, but it possibly is a major issue for the topic of brain activity and pain perception, as in both cognitive issues can possibly confound the outcomes. It can be said, however, that not all studies utilized cued breathing, and those, investigating a normal, physiological breathing rhythm to large parts seem to support the obtained results with cued respiration.

As to the topic of pain perception, possible limitations of this thesis include gender and cultural bias in the examined studies, which were not investigated and discussed in this thesis. Furthermore, it is to be said, that the experiments were carried out under laboratory conditions, therefore the pain stimuli had to be artificially produced. The most common procedures for this are thermal or electric stimuli. Strictly speaking, the results of this thesis are limited only to thermal and these nociceptive stimuli, not, however, to all other perceivable pain sensations.

The second aspect, which gives possible limitations to the results of this thesis are distortions caused by the methodology of this narrative review itself. The first point concerns the research question, which was chosen and deliberately narrowed down by the author of this work, who is no expert in neuroanatomy or neurophysiology. Due to this fact, it is possible, that the choosing of the research question and therefore the basis for this work were not perfectly and sufficiently professionally selected. A widening of the research question for example to the entire body would have provided extremely interesting insights, however it would have gone beyond the scope of this master thesis.

Moreover, due to the fact that the author of this work had to research prior to defining the aims and hypothesis in order to obtain the necessary background knowledge for this thesis, the list of keywords for the literature research was chosen after having read several articles on this topic. For this reason, it is very likely, that studies were not included, which would have met the inclusion and exclusion criteria, but were not found, as they did not show up during the literature research with limited keywords. An attempt has been made in order to double- check with synonyms, such as for the topic of brain activity, not only the term activity, but deactivation, oscillation and potentials were used.

One point, which limits the results of this thesis is the fact that the author of this work processed and interpreted the given studies not as a neuroscientist, but rather with the knowledge and the perspective of an osteopath. On the one hand, this possibly distorts the selection of the included studies, but as the aim of this thesis is to gain knowledge for osteopathic studies, this point does not seem to weigh so much. On the other hand, however this can possibly distort the collection and interpretation of the results, as well as the conclusions, which were drawn.

This leads to the next aspect, which is to be discussed, that, as previously mentioned, the author of this work is no expert in this field, therefore criteria for inclusion and exclusion were chosen according to her knowledge and judgement. This implies, that to some extent these might not all have been perfectly chosen and suitable. By means of example, the fact, that only studies were included, which were published in the last 20 years, by argumentation that the required studies all depended on technical equipment and due to the fact, that this equipment underlies constant technical improvement and therefore the comparability would not be sufficient, might lead to a distortion in the results, as the possibility exists, that there are studies, which are older and still provide valid and interesting insights in this topic.

The literature research was limited to the knowledge of the author of this work. It therefore was defined beforehand, that the word breathing or respiration has to be explicitly in the title of the respective study. Especially in such complex fields as neuroscience, the more detailed studies might often not have these words explicitly in the title, but rather examined to such an elaborateness, that they did not include these keywords in the title and therefore would not have shown up during the literature research with such limited keywords. Nonetheless, it is to be said, that the studies, which were recruited from the literature research seemed sufficient in order to answer the research question, although further studies might have improved the insight and outcomes.

Additionally, the risk of conformational bias, as well as overconfidence bias and bias blind spot might have distorted the processing and interpretation of this thesis. This leads to one additional factor, which is to be considered, that, due to partially lacking thorough background knowledge, the results from the studies could to some parts only be processed on a rather superficial level, and not to the profound level, which might have been required and which would have required detailed insight in radiology and imaging methods, as well as neuroscience. However, as the target group for this thesis are not neuroscientists but osteopaths, and the research question was defined accordingly, the level of proficiency seems sufficient.

In addition, the fact, that this work was written by an osteopath, might partially lead to a belief bias, so that plausible conclusions might be drawn, although they are actually not deducible from the results. As previously mentioned, in osteopathic studies, it is taught, what and how sensations are perceivable. Therefore, coming from these studies, it is possible, that deductions were made according to prior accepted knowledge, rather than directly made from the results themselves.

The power of the predication of this thesis is diminished by the fact, that, to the knowledge of the author of this thesis, no tool for critical appraisal exists for the assessment of fundamental research. For this reason, it is highly difficult to critically and objectively evaluate the studies, which would render the predication of this thesis more systematic. In an attempt to compensate for this, however, the studies were summarized in tables, in order to at least display the outline data and make them comparable. As already mentioned before, the comparability in general is limited, due to the fact that different aims, methods and technical equipment were used.

In conclusion, it can be said, however, that, despite all its limitations, both of the included studies and the thesis itself, that sufficient good evidence has been produced and provided, in order to sufficiently answer the research question and to show, that breathing is well measurable along the entire central nervous system, on various levels.

6 Conclusion

This thesis processed the research question, whether respiration was measurable in the central nervous system and if so, to what extent and on which levels. The answer to this question, to which all examined studies agree, clearly is yes, breathing definitely is measurable and has great influence on the CNS. These impacts include the motion of CSF, various activities in the brain in cortical and limbic regions, as well as the processing of pain perception. These findings underline the osteopathic claim, that respiration is perceivable in the CNS.

Breathing significantly influences the flow of CSF throughout the entire CNS including all CSF spaces on the cranial and spinal level. Breathholding was found to temporarily supress the respiration- related flow. It was unambiguously shown, that inspiration generates a cranial directed motion of CSF, conversely expiration leads to a caudal fluctuation and a clear displacement of the fluid was found. In addition, it was demonstrated, that the velocities of the flow vary in the different regions of the CNS.

During normal breathing, respiration- related activation can be found in large parts (41.3%) of the grey matter both in cortical and limbic regions. These include the amygdala, hippocampus, insula, frontal, parietal and primary olfactory cortices. Fast breathing additionally activates frontal regions, the magnitude of coherence to respiration being dependant on the breathing rate.
Breathing strongly influences slow cortical potentials, the highest synchrony being at a breathing rate of 10 sec/ cycle, and in addition, infra- slow oscillations, which are involved in the development of resting state networks as the default mode network in the posterior midline region, the deactivation of which is strongly required in cognitive processes. It was found that the normal breathing cycle strongly influences the deactivation of this DMN. Moreover breathing has an impact on the excitability of other cortical regions such as the primary motor hand area, which leads the authors of the same study to the hypothesis, that generally breathing can enhance the entire motor system. One further interesting aspect, which was found in this thesis, is that limbic functions such as for example emotion discrimination and memory function are influenced by respiration, especially by the phase and pathway of breathing, inspiration generally enhancing these functions and nasal respiration being more beneficial than oral.

Concerning the topic of respiration and pain perception, it has been confirmed, that slow and deep breathing have an analgesic effect, and that the phase of respiration might have an influence on pain perception. Expiration leads to the same analgesic effect, however, the results are not entirely invariable.

The target group for this thesis are osteopaths and with regard to this group, this thesis hopefully provided interesting insights in this topic. On the one hand, it provides evidence, that changes in structures of the CNS throughout the breathing cycle definitely take place and therefore that osteopathic perception, that respiration is palpable in this system was to a little extent made more visible. On the other hand, it is a small contribution in the effort in making osteopathy and especially cranial osteopathy more evidence based.

This thesis only focused on a small section, but as breathing is one of the most vital functions in the human body, there is so much more to be examined. As the impact of breathing is so well measurable in the CNS, it can be hypothesized, that the impacts are much more far-reaching. It would be of great interest therefore, to further investigate the influence of breathing on other body systems and functions such as whether similar effects can also be measured in the peripheral or the autonomous nervous system. Whether it has measurable impacts on the interstitial tissues, the other diaphragms in the body or on metabolic activity in the all levels of the body. How it influences our cardiac and lymphatic system or how it influences postural functions.

This thesis has only focused on the question, whether and how respiration is measurable in the CNS. The question would further be highly interesting, whether these detected respiration-associated fluid motions and electrical potentials also have other functional influences for example on brain metabolism. Another interesting question, which arises, is whether and which influences of breathing on other body systems are measurable.

The topic of this thesis and all these other questions and issues are of great significance for osteopathic research, as they potentially underline many important aspects for osteopathy, provide a deeper insight and understanding for osteopathic perception and therefore create a profounder, more evidence- based background.

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Tables

Abbreviations

A/ Aa	Arteria/ Arteriae
ACC	mesiofrontal/ anterior cingular cortex
ANS	Autonomic Nervous System
ant	anterior
C	Cervical Vertebra
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DSB/ aDSB/ rDSB	Deep Slow Breathing/ attentive DSB/ relaxing DSB
ECG	Electrocardiogram
EEG	Electroencephalogram
fMRI	Magnetic Resonance Imaging
HR	Heart Rate
HRV	Heart Rate Variability
Hz	Hertz
iEEG	intracranial EEG
IP	Intrathoracic Pressure
L	Lumbar Vertebra
Lig/ Ligg	Ligamentum/ Ligamenta
M	Musculus
MRI	Magnetic Resonance Imaging
N/ Nn	Nervus/ Nervi
NFR	Nociceptive Flexion Reflex
Nl/ Nll	Nodus Lymphaticus/ Nodi Lymphatici
NRS	Numeric Rating Scale
PCC	precuneus/ posterior cingulate cortex
PMR	Posterior Midline Region
post	posterior

R	Ramus
RCT	Randomized Controlled Trial
ROI	Region of Interest
sec	second(s)
T	Thoracic Vertebra
V/ Vv	Vena/ Venae