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Back to the roots: the role of sensory sensitivity and respiration pattern variability in mental health

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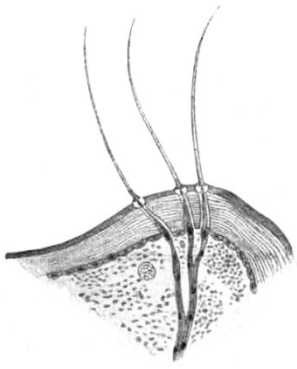

vibrissae of *Cyrtomaja Suhmi* in a drawing of the year 1903 (R. Hertwig ‘Zoologie’, Jena); cilia and hair cells are widespread in living beings including humans, they are used for locomotion, cleaning, in several sense organs, and can even be found in the lung

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1 INTRODUCTION

Imagine you slowly get up in the morning on a normal day in your life. Maybe you take a deep breath, stretch your arms and legs and then your whole body - and the feeling of a good day comes into your mind: a light warm breeze touches your skin and you see nice little clouds dancing in the sunny sky while in the garden bumble bees, flying around the floating willows, hum calmly and the smell of freshly brewed coffee wafting up your nose reminds you it's your partner's turn to prepare breakfast today. You take another deep breath, slowly meandering barefoot over the comfortably warm red paving tiles to the terrace.
All of that is to a great extent sensory perception including body perception and of course respiration and respiration control. Not only does a day set off to a good (or maybe a bad) start accompanied by that, but our whole life is highly based on these fundamental survival related competencies. Even more puzzling it is that those are rarely addressed in individuals who have problems having a good day or face other mental health issues.

1.1 Sensory perception and sensory sensitivity

It is very difficult to imagine what life would be like without sensory perception. Even standing would not be possible as we could not feel that our feet touch the ground, the current position of different body parts in relation to others or of our body in the environment. This becomes very obvious from the following quote by the philosopher and cultural ecologist David Abram (Abram, 2009):

Sensory perception is the silken web that binds our
separate nervous systems into the encompassing ecosystem.

Sensory perception is crucial for survival in many aspects as we need to perceive and react within seconds even in highly complex situations. This for example enables us to sidestep a crossing car while walking. Therefore, the vast abundance of stimuli present in the environment must be filtered by relevance to not get overwhelmed and near-threshold stimuli must be perceived very quickly. Of course this is only possible if enough informative stimuli are present. We highly rely on sensory stimulation and long-term sensory deprivation usually leads to severe symptoms like hallucinations

and anhedonia (Daniel, Lovatt, & Mason, 2014). Sometimes sensory deprivation is even used for torturing and then might also contribute to the development of post-traumatic stress disorder (el Sarraj, Punamaki, Salmi, & Summerfield, 1996).

Sensory perception is directly related to our emotions like enjoying the taste of our favorite dish of our childhood (Hanssen & Kuven, 2016) or when listening to our favorite music makes us happier (Radstaak, Geurts, Brosschot, & Kompier, 2014) and indirectly when the interpretation of and behavior in complex situations starts with the sensory perception thereof (Pleger & Villringer, 2013). Social behavior is therefore also highly related to sensory sensations as we need sensory input to interpret social situations. Thus, sensory input influences our mood and responses quite more than just via regulating our facial expressions, movements or body language with feedback (Kawase, 2014; Wood, Lupyan, Sherrin, & Niedenthal, 2016). So, as we can see, sensory perception affects mood and social life, but interestingly, the opposite seems to be true, too, as mood has been reported to influence sensory perception. For example, fear decreased tactile sensitivity whereas a positive context facilitated auditory discrimination (Kelley & Schmeichel, 2014; Pinheiro, Barros, Dias, & Niznikiewicz, 2017). Furthermore, a sensory perception like listening to music can also influence another sensory perception like the judgment of brightness, possibly via attribution of emotions to different brightness conditions influenced by music (Bhattacharya & Lindsen, 2016). By activating emotions, sensory processing is also relevant in social interactions. This shows how strongly our senses are associated to our emotions and our social life.

One of the first descriptions of human senses was already made by Aristotle in his *Parva Naturalia - de sensu et sensibilibus* naming the visual, auditory, olfactory, gustatory, and tactile sense. More recently, also thermoception and nociception with their highly related processing pathways (Green, 2004), as well as the vestibular sense and proprioception - specified as the relative position and strength of one's own parts of the body - were described as significant human senses.

Importantly, sensory processing also acts unconsciously. The olfactory and gustatory sense can be seen as a chemical sense which also includes the perception of pheromones that is often not directly recognized by people but also has a great impact on behavior (de Groot, Smeets, Kaldewaij, Duijndam, & Semin, 2012) and therefore also on well-being. Comparably, in the visual sense one can find intrinsically photosensitive retinal ganglion cells which are maximally sensitive to blue

light. These cells built a receptor system in which light perception is not directly recognized by humans but is part of the regulation of their circadian rhythm, hormone secretion, body temperature, sleep, alertness, mood and cognition (Dijk & Archer, 2009).

The ability of adequate and adaptive sensory perception can vary between individuals and is decisively influenced by sensory sensitivity (Aron & Aron, 1997). Sensory sensitivity describes the responsiveness of an individual to sensory stimuli and the individual processing intensity of sensory information (Zamoscik et al., 2017). In the context of this concept of sensory sensitivity, proprioception is seen as one part of body perception which additionally includes the perception of hunger, thirst, illnesses and injuries, and the appropriate use of and control over one's movements and muscle tension. Sensory sensitivity seems to predict children's reactivity to both happy and angry emotions of other people (Weeland, Van den Akker, Slagt, & Putnam, 2017) which already emphasizes its importance for mental processes and human behavior.

1.2 Respiration and respiration pattern variability (RPV)

From a simplified biological view, adequate respiration is the inspiration of oxygen and the expiration of carbon dioxide in a regular cycle of about one breath every 4-5 seconds. Respiration is regulated by pulmonary stretch receptors, which are found in the lungs and monitor respiratory rate and depth (Chen, Marchenko, & Rogers, 2010). Additionally, primarily the partial pressure of carbon dioxide in the blood regulates respiratory drive (Chowdhuri & Badr, 2017). *Dum spiro, spero* (while I breathe, I hope) is a modern paraphrase of ideas from Cicero in *Epistulae ad Atticum* IX 10.3 pointing also to other aspects of respiration than simply biological ones. In several cultures respiration is also seen as much more than that. For them the role of respiration for human life is also fundamental in mental processes as expressed by the Buddhist monk and writer Thích Nhất Hạnh (Hạnh, 2016):

Breath is the bridge that connects life to consciousness,
the bridge that unites your body to your thoughts.

Whenever your mind becomes scattered,
use your breath as the means to take hold of your mind again.

Respiration is highly adaptive to changes in physical demands like during sports or professions like in mining or firefighting (Donovan & McConnell, 1999) and can be self-regulated to some extent (Hakked, Balakrishnan, & Krishnamurthy, 2017). But also during mental distress breathing changes (Anderssen, Nicolaisen, & Gabrielsen, 1993) which might reflect anticipated physical demands like 'fight or flight' or during sleep a passive defense response (Anderssen et al., 1993). This may also be explained by the association of alterations in respiration and anxiety. Individuals with greater anxiety levels show higher respiration rates and shorter inspiration and expiration times during rest (Kato, Takahashi, & Homma, 2017), and respond with an initial inspiration to fearful stimuli rather than initial expiration as present in individuals with low anxiety (Klorman, Wiesenfeld, & Austin, 1975). Not only in these cases respiration control is necessary to not get overwhelmed by emotions or exaggerated anxiety resulting maybe in panic and/or hyperventilation (Clark, Salkovskis, & Chalkley, 1985). Importantly, under uncomfortable breathing due to higher inspiratory load, reduced cognitive ability was found in healthy participants (Nierat et al., 2016) which further emphasizes the need of respiratory control and maybe training to be able to cope with stressful situations. During such situations, respiration rate and ventilation as well as cortisol levels are higher and additionally boosted if physiological stress and psychological stress are combined (Webb et al., 2008). Therefore, miners, divers and firefighters for example train themselves to react with a focus on regular breathing in challenging situations (Feuerwehr-und-Katastrophenschutzschule, 2012; Linder & Simha, 2016; Redl, 2010). Something similar is also used in guided breathing tasks in which healthy participants learn to change their respiration and feel more relaxed (Van Diest et al., 2014) or reduced their pain perception (Arsenault, Ladouceur, Lehmann, Rainville, & Piche, 2013). The general population can learn to regulate breathing for example in deep breathing or yoga exercises (Goldstein et al., 2016; Perciavalle et al., 2017) which at least in mindfulness breathing training might also be related to body perception (Kerr, Sacchet, Lazar, Moore, & Jones, 2013) and in diaphragmic breathing (a mind-body practice) to cortisol levels (Ma et al., 2017). Of note, associations of respiration with pain and body perception point to the possible relation of sensory sensitivity and respiration.

As described above, respiration follows a regular cycle. Upon demand, this cycle can vary in duration (respiration rate) but also in the size of amplitude (deepness of

breath) as well as respiration pauses between cycles. All of those variations can be seen as a pattern of the respiration cycle. Those patterns can be very diverse for different individuals and situations, here termed respiration pattern variability (RPV), which can be described via different parameters like the relative standard deviation/coefficient of variance. Specific respiration patterns seem to distinguish between different emotions (Bloch, Lemeignan, & Aguilera, 1991) showing the strong association of respiration and emotions and with that possible influences on mental health.

1.3 Sensory sensitivity and RPV in mental health and illness

Recently, it was hypothesized that “respiration, via multiple sensory pathways, contributes a rhythmic component to the ongoing cortical activity” in the human brain linking higher cortical functions, sensory processing and respiration (p. 1; Heck et al., 2016). As alterations of higher cortical functions are related to mental health it is not surprising that sensory sensitivity and RPV do not only influence well-being of the healthy population but also impact mental health problems may be mutually influencing each other.

Intuitively when we are asked about stress, we relate it to sensory feelings like stress-induced analgesia (Amit & Galina, 1986) and to variations in respiration when we experience anxiety or sadness (P. Sharma, Morris, & Adams, 2016). Pathological states of anxiety, especially panic disorder, seem to be highly associated to respiration, showing as hypersensitivity to carbon dioxide and hyperventilation including feelings of dyspnea (Gorman et al., 1988; Papp, Klein, & Gorman, 1993). A similar relationship can also be found in healthy individuals who were induced with negative mood and then reported higher sensory and affective scores of dyspnea (P. Sharma et al., 2016). In addition, in chronic respiratory diseases depression (Asnaashari, Talaei, & Haghigh, 2012; Fan & Meek, 2014; Kunik et al., 2005) and anxiety (Fan & Meek, 2014) symptoms are twice as much compared with non-respiratory related chronic diseases (Ali, Stone, Peters, Davies, & Khunti, 2006; Spijkerman et al., 2005), so it was proposed that respiration trainings might also show an impact on mental health in these patients (Fan & Meek, 2014). Interestingly, first studies reported beneficial effects of guided breathing for anxiety (Wannemueller

et al., 2016; T. Yamada, Inoue, Mafune, Hiro, & Nagata, 2017) and might hint to the possible positive influence of increased respiration control on mental disorders.

In the literature there is some evidence that sensory sensitivity seems to be important in various mental problems and disorders including depression and autism which are in the focus here (Asperger, 1944; Hilton et al., 2010; Luisier et al., 2015; Remington & Fairnie, 2017; Zamoscik, Huffziger, Kühner, & Kirsch, 2015; Zamoscik, Mier, Schmidt, & Kirsch, 2016) but also in attention-deficit hyperactivity disorder (Fuermaier et al., 2017; Lufi & Tzischinsky, 2014; Puts et al., 2017), anxiety disorders (Rodic, Meyer, Lieb, & Meinlschmidt, 2016) like post-traumatic stress disorder (Clancy, Ding, Bernat, Schmidt, & Li, 2017), somatoform and pain disorders (Cornelissen et al., 2014; Katzer, Oberfeld, Hiller, Gerlach, & Witthoft, 2012), and pain in healthy individuals (Weissman-Fogel, Granovsky, & Bar-Shalita, 2017). Pain and other highly sensitive experiences can also lead to overstimulation and overwhelming situations and with that the experience of stress (Scheydt & Needham, 2017) and accompanied altered respiration. Interestingly, pain perception in healthy people seems also to be related to tryptophan respectively serotonin availability (Martin et al., 2017). Of note, tryptophan (the essential precursor of serotonin) seems also to be related to body perception (Dalkner et al., 2017). Several health problems including autism and mental disorders like anxiety and depression are associated with an altered tryptophan or serotonin system (Kaluzna-Czaplinska, Gatarek, Chirumbolo, Chartrand, & Bjorklund, 2017). These alterations are also associated with alterations in the melatonin production, as melatonin is synthesized from serotonin. Since the production of melatonin is strongly dependent on light conditions and thereby on sensory processing of light, it provides a link between sensory sensitivity, the tryptophan/serotonin system and mental disorders. More precisely, melatonin production is suppressed by light (Lewy, Wehr, Goodwin, Newsome, & Markey, 1980; Pfeffer, Korf, & Wicht, 2017) leading to higher serotonin levels during day light conditions at which higher serotonin levels are related to better mood and used as a pharmacological intervention target (Hieronymus, Emilsson, Nilsson, & Eriksson, 2016). Interestingly, not only the seasonal subtype of depression seems to improve with day or blue light exposure (Baxendale, O'Sullivan, & Heaney, 2013; McCullough & Lehrer, 2017; Meesters, Winthorst, Duijzer, & Hommes, 2016; Sekiguchi, Iritani, & Fujita, 2017; Terman, 2007; Tseng et al., 2016; Viola, James, Schlangen, & Dijk, 2008). It can be assumed that this effect works through a sensory mechanism acting

via melanopsin expressing retinal ganglion cells which seem to contribute to brain responses to light modulated by the brainstem and suggest a broad involvement of light in the regulation of brain function (Vandewalle et al., 2007). Converging findings suggest that circadian dysfunction or disturbance alters the function of brain regions involved in emotion and mood regulation (Bedrosian & Nelson, 2017). This further emphasizes the core importance of sensory sensitivity and respiration which seem to be highly related and embedded in our body functions and mutually influencing various features relevant for well-being and mental health.

1.4 Autism and sensory sensitivity

Autism is a pervasive neurodevelopmental disorder in which social interaction and communication are altered and individuals often show a tendency to display repetitive behaviours and have narrow interests. Currently, autism is seen as spectrum disorder or spectrum condition to respect the broad variation in symptoms and intensity of difficulties in daily life. About 1% of the world population is autistic (Hossain et al., 2017; May, Sciberras, Brignell, & Williams, 2017) and often experience different mental health problems like sleep disturbances (Devnani & Hegde, 2015), depression (Fortuna et al., 2016), or suicidality (Zahid & Upthegrove, 2017), not infrequently hidden for outsiders as one can see in autobiographical accounts by autistic people (Brauns, 2002; Mukhopadhyay, 2000; Willey, 1999). Therefore, problems and strengths might not be easy to recognize and to take care of.

Interestingly, in the new 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM; APA, 2013) sensory features are for the first time included into the criteria for the diagnosis of autism, emphasizing the increasing recognition of the importance of the sensory system in mental health care. Although autism care has improved over the last decades, e.g. in including ideas (amongst others sensory features) of autistic individuals to a greater extent (Hodgetts, Richards, & Park, 2017; Mottron, 2017), support and new concepts for interventions are still needed (Kripke, 2016) also in regard to well-being of relatives (Padden & James, 2017).

High sensory sensitivity which is very prevalent in autism (Markram & Markram, 2010) can lead to increased levels of stress and further have important consequences in social situations (Hilton et al., 2010; Miguel et al., 2017) and

memory. More precisely, in healthy participants it was found that positive autobiographical memories contain more sensory details (D'Argembeau, Comblain, & Van der Linden, 2003) but in addition for autism multiple sensory features seem sometimes to be experienced as traumatic and can even lead to post-traumatic stress disorder (Haruvi-Lamdan, Horesh, & Golan, 2017). The negative experience of sensory stimulation might also be related to other mental health problems in both, autistic individuals and relatives. For example, it could happen that a relative of an autistic person feels rejected and sad because the autistic person does not hug her or him due to sensory over responsiveness. This might also have influence on the autistic person when he or she recognizes sad mood in the relative and/or due to that when the autistic person forces her- or himself to hug the other person although this might further increase sensory overstimulation. Therefore, deeper understanding of sensory sensitivity could help autistic individuals and their environment e.g. by recognizing altered social contact also as a consequence of altered sensory sensitivity being part of autistic cognition and feeling. Besides from negative effects of sensory sensitivity on mood and memory, interestingly, from autobiographical accounts by autistic people there are also clues that sensory experience might positively affect memory processes (Brauns, 2002; Mukhopadhyay, 2000) possibly via increased involvement of sensory features in the life of autistic individuals. Together with the findings of the importance of sensory features for memory in general and hints for the importance in autism this leads to the hypothesis that sensory sensitivity might have a great impact on autobiographical memory processes in autism as well. This point is addressed in the first study (page 17) reported in the present thesis. In an independent sample, further details of sensory sensitivity including body perception ability in autism are shown in the middle section (page 37) of this thesis.

1.5 Depression, sensory sensitivity and RPV

Major depressive disorder is a mental disorder characterized by lasting pervasive feelings of low mood, guilt, and worthlessness. Lifetime prevalence of depression rates range from about 12 to 20% (Carta et al., 1995; Hamdi & Iacono, 2014) combined with high rates of relapses within one (53%; Ali et al., 2017) and three

years (49%; Timm et al., 2017) pointing to the high relevance of intervention research.

As already shortly mentioned, major depressive disorder has been associated with aberrant respiratory patterns and sensory sensitivity. Importantly, altered autobiographical memory was also repeatedly reported for depression (Champagne et al., 2016; Wilson & Gregory, 2017), related to respiration when looking on related stress experience of negative memories, and associated with sensory sensitivity. In detail, as already shortly mentioned in healthy participants for sensory features it was found that positive autobiographical memories contain more sensory and contextual details than neutral or negative memories (D'Argembeau et al., 2003). Additionally for depression, negative autobiographical memories appear to be more salient and remembered in a more general way (Champagne et al., 2016; Wilson & Gregory, 2017) and seem to be related to worse outcome (Raes et al., 2008). This might hint to an important role of sensory features in autobiographical memories which are, especially in depression, an emotional challenge containing various negative emotions also influencing respiration.

There are several studies which found an association between depressive symptoms and respiration. Induction of negative emotions in healthy individuals led to higher respiratory variability (Rainville, Bechara, Naqvi, & Damasio, 2006; Vlemincx, Van Diest, & Van den Bergh, 2015; Vlemincx, Vigo, Vansteenwegen, Van den Bergh, & Van Diest, 2013). Importantly, people can learn to increase respiratory control (Goldstein et al., 2016; Perciavalle et al., 2017) which might also be related to body perception (Kerr et al., 2013), a sensory feature. As already mentioned, in diseases with respiratory problems higher depression symptoms and even depression rates were found (Asnaashari et al., 2012; Kunik et al., 2005). In addition, lower respiratory sinus arrhythmia, which reflects the increase of the heart rate during inspiration and its decrease during expiration as an expression of parasympathetic activity, was associated with depression (Ellis, Shumake, & Beevers, 2016) and relapse rates (Kovacs et al., 2016) which might suggest RPV to be not only an important factor in depression but possibly a vulnerability mechanism. Since all these findings relate altered respiration to mood and depressive symptoms or even depression diagnosis, one could suggest that improvement of respiratory control could be a promising intervention strategy possibly influenced by body perception ability.

There is a huge field of research on the underlying neurobiological mechanisms of depression. Recently, the default mode network (DMN) has gained a lot of attention, because of its role in self-referential processes which are disturbed in depression and of course related to autobiographical memory. The DMN is considered the basic brain network involved in self-referential processes including mainly the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC) and the angular gyri (Whitfield-Gabrieli et al., 2011). In depression, increased DMN activity and connectivity was repeatedly found (Berman et al., 2011; M. D. Greicius et al., 2007; Li et al., 2012; Sheline et al., 2009; Sheline, Price, Yan, & Mintun, 2010) and was linked to worse outcome in remitted depression during negative emotional challenge of imagining personal sad life events (Zamoscik, Huffziger, Ebner-Priemer, Kuehner, & Kirsch, 2014). Of note, the DMN is also associated with physiological processes like respiration (Birn, 2012; Birn, Diamond, Smith, & Bandettini, 2006). Respiration pattern variability in depression might therefore possibly also relate to alterations in DMN connectivity even after correcting for physiological artefacts.

Summing up, on the behavioural but also on the underlying biological level there are several hints of the impact of respiration in depression but the associations and possible further influencing factors like sensory sensitivity are currently rarely focused or described in more detail. However, respiration might be seen as a factor mutually influencing various features in depression, possibly acting as a vulnerability mechanism which impacts the reaction to emotional challenge and other stressful situations possibly moderated by body perception ability as a sensory sensitivity feature. A more intense look on the relation of sensory sensitivity, body perception and respiration is addressed in the middle section (page 37) and altered respiration pattern variability and associated DMN connectivity during sad mood induced with personal negative life events in remitted depression is focused on in the second study (page 47).

1.6 Aims

The primary aim of this work is to advance the understanding of two basic biological features in human behavior, sensory sensitivity and respiration pattern variability, with regard to mental health and mental disorders. Further, the possible influence of the sensory sensitivity feature body perception ability is tested for linking both

together. I like to consider these features in a positive way, as they might help in daily life coping and the further improvement of interventions, but also with their role as potential vulnerability mechanisms. The studies are exemplarily done with autism and depression as autism is highly related to sensory alterations and depression seems to be related to altered respiration. Of note, the two features are also discussed with regard to mental health in general. The main underlying hypotheses are:

- Sensory sensitivity is higher and body perception ability lower in autism.
- Sensory features are associated with better autobiographical memory in autism.
- Respiration pattern variability during imagination of negative autobiographical events is higher in remitted depression.
- Higher respiration pattern variability in remitted depression is related to lower mood, worse outcome and greater default mode network connectivity.
- Higher body perception ability is related to a more regular respiration in remitted depression.

2 *STUDY 1* – Early memories of individuals on the autism spectrum assessed using online self-reports

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2.1 Abstract

"When I was one and a half years old I was on a ferry lying on red seats" – While several autobiographical accounts by people with autism reveal vivid memories of early childhood, the vast amount of experimental investigations found deficits in personal autobiographic memory in autism. To assess this contradiction empirically, we implemented an online questionnaire on early childhood events to compare people on the autism spectrum and non-autistic people with respect to their earliest autobiographical episodic memories and the earliest semantic *know event* as told by another person. Results indicate that people on the autism spectrum do not differ from non-autistic people in the age of their earliest *know events* but remember events from an earlier age in childhood and with more sensory details, contradicting the assumption of an overall deficit in personal episodic memory in autism. Furthermore, our results emphasize the supporting influence of language for memory formation and give evidence for an important role of sensory features in memories of people on the autism spectrum.

2.2 Introduction

Autism is a pervasive developmental disorder in which some of the important core processes required for memory formation are impaired. Specifically, memory formation is influenced by difficulties in social interaction and communication, problems in the formation of new scripts, a tendency to display repetitive behaviours, and often narrow interests, which are typical characteristics in autism.

A number of studies on episodic memory report deficits in people with autism (e.g. Bowler, Gardiner, & Grice, 2000; Bruck, London, Landa, & Goodman, 2007; Crane & Goddard, 2008; Crane, Goddard, & Pring, 2013; Goddard, Dritschel, Robinson, & Howlin, 2014; Millward, Powell, Messer, & Jordan, 2000; Souchay, Wojcik, Williams, Crathern, & Clarke, 2013), which seem to be augmented in males in comparison to females, possibly due to differences in verbal fluency (Goddard, Dritschel, & Howlin, 2014). Mostly, these studies included direct social interaction, referred to predefined events or contexts, or asked for autobiographical memories formed later in life than in early childhood. Interestingly, studies differentiating between semantic *know* and

episodic *remember events* have shown, that only the episodic but not the semantic autobiographical memory is impaired in autism (Crane & Goddard, 2008; Tanweer, Rathbone, & Souchay, 2010). For example, Tanweer and colleagues reported that not the entire autobiographical memory is affected in autism (*know events* are preserved), but only those aspects that can be related to the ability to relive one's past, known as autonoetic awareness (*remember*) (Tanweer et al., 2010). The authors concluded that deficits in autonoetic awareness, as well as a broad lack of specificity (which is a lack of specific information on time and place) causes autobiographical deficits in autism. Other authors attributed deficits in autobiographical memory in autism to a failure in the development of self-identity (Crane & Goddard, 2008), or to impairments in Theory of Mind and working memory (Crane, Goddard, et al., 2013). Also, memories of people with autism were shown to include fewer social and emotional details (Brezis, 2015).

Interestingly and contrariwise to the mentioned experimental studies, some individuals with high-functioning autism seem to be able to recall personal events from a very young age (e.g. Brauns, 2002; Lyons & Fitzgerald, 2005; Mukhopadhyay, 2000) and moreover, these memories are rich in sensory detail. Not only are sensory features included in the new diagnostic criteria of the autism spectrum disorder (ASD; APA, 2013), but also has sensory perception been reported to be atypical in 69-100 % of individuals with autism (e.g. Asperger, 1944; Baranek, David, Poe, Stone, & Watson, 2006; Crane, Goddard, & Pring, 2009; Hilton et al., 2010; Leekam, Nieto, Libby, Wing, & Gould, 2007). Since the probability of encoding increases with a stronger involvement in a particular situation (M. A. Conway & Pleydell-Pearce, 2000), one could assume that individuals with autism are better in memorizing sensory details than non-autistic individuals. Concordantly, according to the intense world theory by Markram and Markram (Markram & Markram, 2010), individuals with autism perceive the world more intensely than non-autistic individuals, due to overactive brain circuitry. The authors propose that a hyper-activation in these brain circuitries could account for hyper-perception, hyper-attention, hyper-emotionality, and even hyper-memory in autism. Hence, there seems to be a contradiction between the findings of experimental studies asking mainly for specific memories and free reports of autobiographical memories in autism. From this perspective, it seems possible that people with autism even have improved personal autobiographical memories in free recall or with regard to (sensory) details.

One feature in autism that could be related to memory formation is altered language acquisition. The development of language and narrative structures enables children to encode memories linguistically which in turn improves retrieval of autobiographical memories in adulthood using similar pathways (Eacott, 1999), while sensory memories appear to become less important over a person's lifetime. Studies found linguistic differences in autism with regard to several features. In a study with different narrative tasks, teenage children with ASD used language that is less descriptive and less grammatically complex (King, Dockrell, & Stuart, 2013). In another study, the narratives of adults with high-functioning autism or Asperger syndrome were less well organized and less cohesive compared to the control group, even though the plot of the story was equally well comprehended (Colle, Baron-Cohen, Wheelwright, & van der Lely, 2008). Losh and colleagues (Losh & Gordon, 2014) reported differences in narrative ability in individuals with high-functioning ASD only during semi-structured conversation which included narrative recall, but not when narrating the story from a picture book. The authors suggest that the picture book might be helpful in engaging the strong visual spatial skills of people with autism, thereby providing coherence. The conversation with the experimenter during the narrative recall on the other hand may be more difficult due to the social interaction.

Language and narrative skills are also important for the formation of a self-concept as they facilitate abstraction and reflection. During the process of language acquisition, children begin to form a remembered and cognitive self (e.g. Howe & Courage, 1997). On the basis of this cognitive self, the ability arises to relate current and remembered events to the actual self and to attach importance to events, leading to stronger encoding and integration of memories in an associative network (Howe & Courage, 1997). Conway pointed out, that memory and the self are interconnected, in that autobiographical memories shape the self, and the self-concept together with associated personal goals shapes the types of memories likely to be recalled (M.A. Conway, 2005). In autism, the self-concept seems to be atypical, considering the reduced awareness of own emotions or mental states (Lind, 2010). Supporting the assumption of a diminished self-concept, individuals with autism spectrum disorder show less self-referential processing than control subjects in experimental settings (Henderson et al., 2009; Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007). Self-referential thoughts are closely linked to activity in the medial prefrontal cortex

(mPFC; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). The mPFC also plays a central role in the unifying theory by Ben Shalom (Shalom, 2009), who highlights the importance of the mPFC and its role at the integrative level of different processing levels, suggesting its responsibility for the atypical characteristics in autism. Besides facilitating long-term storage of memories, the mPFC may help to integrate different aspects of an experience by strengthening synapses between relevant neurons (Paz, Bauer, & Pare, 2008). Difficulties of individuals with ASD in integrating different aspects into a coherent composition were also shown in studies on language and narrative skills. Lind and colleagues (Lind, Williams, Bowler, & Peel, 2014) proposed that impaired episodic memory function may be due to reduced scene construction ability, which is independent of general narrative skills.

We used a well-established questionnaire to assess early *know* and *remember events* in free recall (Bruce, Dolan, & Phillips-Grant, 2000; Bruce et al., 2005) to investigate effects of both event types and also possible interaction effects of group and event. We applied this questionnaire for the first time to people on the autism spectrum (AS). Additionally, we measured autistic traits by means of the Autism Spectrum Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). In order to better meet the special needs of this group, we circumvented any social interaction and instead set up an online-study. Based on autobiographical accounts of people with autism and the assumptions made in the intense world theory (Markram & Markram, 2010), but in contrast to many experimental investigations of personal autobiographical memory in autism, we hypothesized that people on the AS remember earlier childhood events when having free choice which memory to recall and no cues are given. In addition, we examined the influence of two specific factors that might contribute to early memory formation: sensory processing and language acquisition.

2.3 Methods

This study was performed in line with the Declaration of Helsinki and the experimental protocols were carried out in accordance with the recommendations of the University of Mannheims' Ethics Committee with written informed consent from all subjects.

The study was conducted via an online survey programmed with the software testMaker (Milbradt, Zimmerhofer, & Hornke, 2007) hosted by the Department Psychology III at the University of Mannheim, Germany. To reach people with autism, the link to the study was posted in four internet forums dealing with autism, and to reach controls the link was distributed via other forums and online platforms. As an incentive to participate in the study, a lottery for four ten-Euro book vouchers was offered.

First, participants answered items consisting of demographic questions about age, sex, German language skills, and education (inclusion criteria: legal age, a high school degree and good German language skills). To investigate the relation between earliest memory and language, participants were asked for their age of language acquisition. Due to the online nature of the study, no diagnoses could be given or confirmed. However, in an attempt to learn about the history of autism diagnosis, participants were asked to report professional autism diagnosis and further neurological or psychiatric conditions. After assessing this information, the AQ and the questionnaire on early childhood events followed.

Participation in this study required the ability to read and write. Furthermore, all participants reported having at least a high school degree and word count of reported *remember events* did not differ between groups (see below). Hence, we consider all people able to complete the study.

2.3.1 Adult autism spectrum quotient

To estimate the number of people with high autism traits in the sample and to verify self-reported diagnoses all participants completed the Adult Autism Spectrum Quotient (AQ) by Baron-Cohen and colleagues (Baron-Cohen et al., 2001). This questionnaire is valid for ages 16 years and above. The German translation by C. M. Freitag (2006) was used with item 17 and 27 in the translation of G. Dammann (2002). Validity and test-retest reliability of the AQ are high (Baron-Cohen et al., 2001). Thus, the AQ is considered a reliable self-assessment screening instrument for autistic traits (Baron-Cohen et al., 2001; Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005).

2.3.2 Participants

The 'autism spectrum' (AS) group included people with high autism traits who scored 26 or higher (as suggested for clinical samples by Woodbury-Smith et al., 2005) in the Adult Autism Spectrum Quotient (AQ) and had a self-reported professional autism diagnosis. The control group (CG) consists of those participants without a self-reported autism diagnosis and an AQ score below 26. In the total sample of 317 people, AS participants were significantly older than control participants, so we decided on not including the whole control group but instead matched groups by age, sex, and education. Final sample size was N=166. The AQ score differed significantly between groups (F(1,165)=1,248.10, p<.001, f=2.76). For a summary of sex, age, education, AQ score, and self-reported neurological and psychiatric diagnoses beyond autism see Table 1.

Table 1: Demographic variables (sex, age, and education), AQ score, and occurrence of self-reported psychiatric and neurological diagnoses beyond autism

	AS group (n=83)	control group (n=83)
sex: male/intersex/female	31/1/51	32/0/51
mean age in years (SD)	36 (10)	36 (12)
mean education in years (SD)	13 (3)	13 (3)
mean AQ score (SD)*	42 (5)	15 (5)
depression*	16	5
AD(H)D*	11	0
social anxiety	2	0
personality disorder	1 schizoid	1 borderline
Tourette syndrome	1	0
epilepsy	4	1

AS: autism spectrum
more than one diagnosis mentioned by one individual is possible
*indicates significant differences between groups (p < 0.05)

2.3.3 Questionnaire on early childhood events

Early childhood memories and sensory characteristics were assessed with the questionnaire developed by Bruce and colleagues (Bruce et al., 2000; Bruce et al., 2005). The questions about *know* and *remember events* with examples, the estimations of ages, the certainty of age estimation (Bruce et al., 2000), and the rating scales of characteristics of the *remember events* (Bruce et al., 2005; Johnson, Foley, Suengas, & Raye, 1988) from the original English questionnaire were translated into German by the authors (translation provided upon request). In this

questionnaire people are asked to report a total of two autobiographical events from childhood: their earliest *know* and earliest *remember event* (including remembered fragment memories). Additionally, participants indicated the estimated ages when the reported events had happened as well as a confidence judgement regarding these age estimations. A description of the two kinds of events and short examples were provided to the participants. The age of events was assessed via the item “Please specify your age at event occurrence as accurately as possible [in years and months]:” including a box in which participants could freely enter the specific age. When participants knew that an event occurred, but could not relive any details relating to it, these events are referred to as *know events.* These events are based on external sources such as photographs or stories told by friends and family. In their description of the *know events* participants had to indicate the source of their memory. *Remember events* are memories that are pure personal recollections specific to time and place; these events could be relived by the participant and relied on no other sources. In addition to freely describing each event in a short paragraph, participants rated the amount of several details of the *remember events* with 20 items (Bruce et al., 2000; Bruce et al., 2005). We focused our analyses on eight of these items for the investigation of the influence of the sensory system and language on the *remember events*. These items comprised questions about the amount of visual, acoustic, olfactory, tactile, and taste components, richness of details of the event, and how often participants had talked or thought about the event afterwards (e.g. “My recollection of the personal event I just described includes visual details:”) on a scale from one (*none/never*) to seven (*very much*). Report order of the two event types was counterbalanced across participants: half of the sample first recounted a *remember event* and corresponding questions, and the other half a *know event*.

Prior to the rating of the events, data from individuals not meeting the inclusion criteria was removed (e.g. participants without high school degree). The reports were randomly ordered, and their identity (*remember* or *know event*, described by an AS individual or not) was concealed. Each event was independently evaluated by two of the authors as to whether it was a *remember event*, a *know event*, or neither. Inter-rater reliability was good (Cronbach’s α =.89). Description of repeated events (like “I was told I was crying a lot when I was a baby”), the autobiographical fact “I was born”, prenatal memories, and not clearly relatable events (e.g. no source was mentioned in *know events*) were excluded from data. Furthermore, two authors

blindly counted and rated several details in the description of the *remember events*. The ratings were partly adapted from Levine and colleagues (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). In the present study we recorded the overall word count and the amount of words related to the self (I, mine etc.), social in-group (we, our etc.), other persons (sister, his etc.), and things (teddy, carpet etc.). We also rated the *remember event* descriptions with regard to the amount of social and sensory details and number of different senses involved. In addition, the number of references to time (e.g. in the morning, 4th birthday), place (e.g. house of grandparents, France), and thoughts and emotions (like proud or sad) as well as whether the memory was a fragment memory or not was rated. Inter-rater reliability was very good (Cronbach's α =.99). Word counts were standardized to 40 words to adjust for slightly different but not significant word counts between groups (please see "External rating of the *remember events*" for total word count numbers). Please see the appendix for a selection of *remember events* from both groups.

2.4 Results

Know events of 53 participants (24 CG, 29 AS) out of the 166 were not used for analyses because no source was mentioned in the description. In some cases (not significantly different between groups, $F(1,165)=0.10$, $p=.754$, $f=0.03$) there was no full stop at the end of the description of the *remember event*, and we assume that occasionally few words were lost in the export procedure. This did not affect any results.

The order of the description of *remember* and *know events* did not affect results of estimation of the age at the time of the event (*remember*: $F(1,165)=0.05$, $p=.816$, $f=0.00$; *know*: $F(1,165)=0.47$, $p=.493$, $f=0.06$). In addition, confidence judgements of the event ages did not differ between report orders (*remember*: $F(1,165)=0.00$, $p=.993$, $f=0.00$; *know*: $F(1,165)=0.13$, $p=.717$, $f=0.03$).

Confidence judgements did not differ between groups for *remember events* ($F(1,165)=0.14$, $p=.707$, $f=0.03$) but they did for *know events* in which the CG was less certain ($F(1,165)=7.76$, $p=.006$, $f=0.26$). Self-reported age of language acquisition differed slightly but not significantly between groups ($F(1,155)=3.01$, $p=.085$, $f=0.14$). Since the number of self-reported professional diagnoses of

depression (F(1,165)=6.79, p=.010, f=0.20) and AD(H)D (F(1,165)=12.53, p=.001, f=0.28) differed significantly between groups (see also Tab 1), these features were included as covariates in all following ANCOVAs to be able to detect and control for possible effects of those variables. In some cases the covariates had a significant effect: In participants with depression, overall word count was greater, the number of thoughts and different involved senses in *remember events* was higher (word count: F(1,165)=5.40, p=.021, f=0.18; thoughts: F(1,165)=7.01, p=.009, f=0.21; senses: F(1,165)=5.80, p=.017, f=0.19). Furthermore, sensory details were reported less often in people with AD(H)D (F(1,165)=5.88, p=.016, f=0.19). Thus, in the following, statistics for these details are additionally reported for the sample without those participants who reported depression and/or AD(H)D diagnosis. Except for the above mentioned small differences, excluding all participants with self-reported depression and/or AD(H)D diagnoses (new n: AS 58, CG 78, age and sex did not differ significantly) did not change the pattern of results. Therefore, we decided to include all participants in the analyses to make results more representative.

2.4.1 Ages of described events

In a mixed design ANCOVA with event (*remember/know*) and group (AS/CG) as factors and reported ages at time of the event as a dependent variable, we found no main effect of group (F(1,109)=1.48, p=.226, f=0.11; Levene's test for homogeneity was not significant: ps >.300), but a significant main effect of event (F(1,109)=45.93, p<.001, f=0.65), and a significant interaction of group and event (F(1,109)=4.17, p=.044, f=0.20). Participants on the AS reported significantly earlier ages for *remember events* than the control participants (F(3,165)=9.34, p=.003, f=0.24), while groups did not differ in the mean age of *know events* (F(3,112)=0.02, p=.890, f=0.00; figure 1).

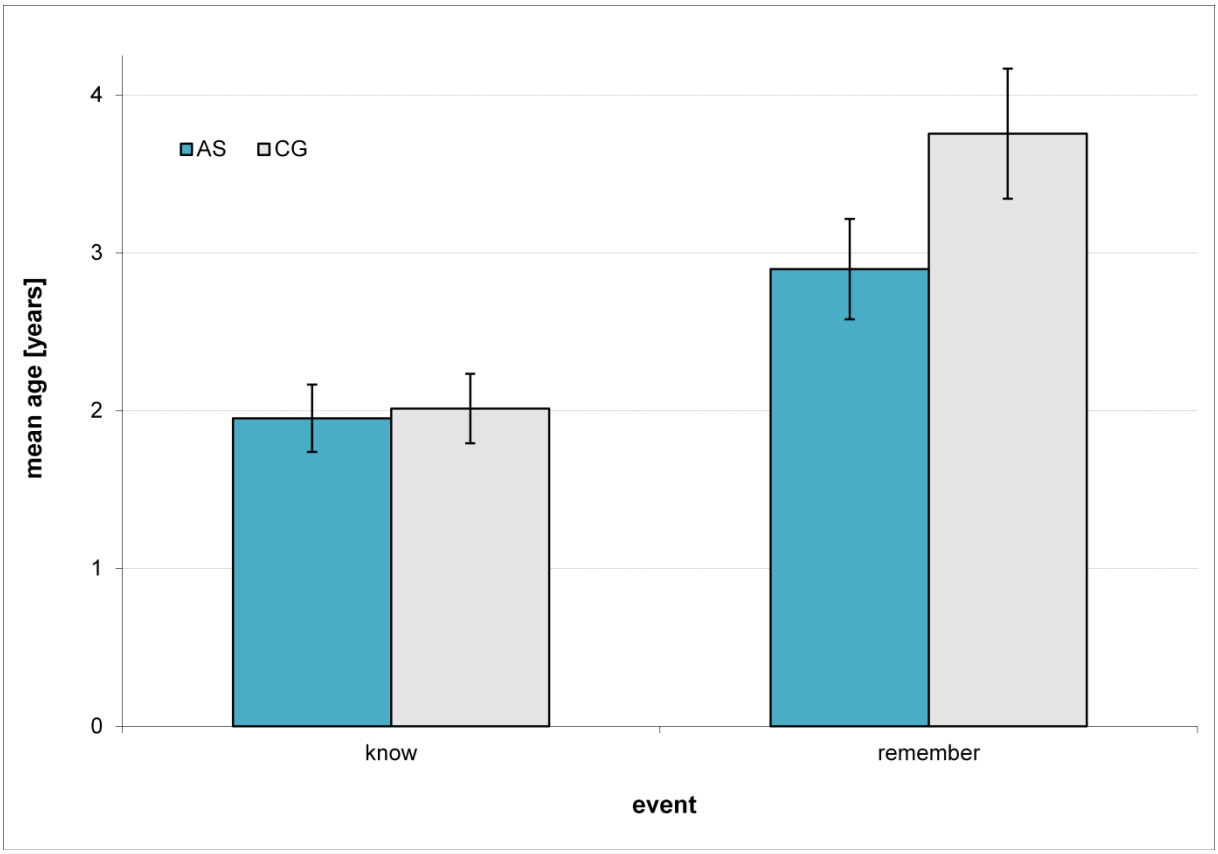

Figure 1: Mean age of the earliest events in participants on the autism spectrum (AS) and matched controls (CG). Error bars indicate ± SE; mean age of *know events* did not differ between groups, mean age of *remember events* of the AS group (M=2.90, SD=1.56) differed significantly compared to the one of the CG (M=3.76, SD=1.41); for further details see text.

2.4.2 Sensory characteristics of the *remember events*

People on the AS remembered more sensory details from their earliest remembered childhood event. Over all senses including visual detail, smell, sound, touch, taste, and richness of details, this relationship was not significant (AS 22.33±7.01, CG 20.00±6.50, F(3,165)=2.19, p=.141, f=0.11). However, the AS group reported significantly more visual detail, sound and richness of details (F(3,165)=10.14, p=.002, f=0.25), whereas depressed participants reported to remember more details related to smell, touch and taste (F(3,165)=5.98, p=.016, f=0.19).

In a correlation analysis, age of earliest *remember event* was related to the amount of reported visual detail in the AS group, but not in the control group (AS: r(83)=-.31, p=.004; CG: r(83)=-.17, p=.130; difference: z=0.95, p=.343).

2.4.3 Language acquisition and language characteristics of the *remember events*

People on the AS reported talking less often about their *remember events* ($F(3,164)=13.25$, $p<.001$, $f=0.29$), while both groups thought equally often about them ($F(3,164)=1.03$, $p=.312$, $f=0.08$). Interestingly however, people reported earlier ages for *remember events* the more often they talked about them (AS: $r(83)=-.27$, $p=.015$; CG: $r(82)=-.22$, $p=.046$). In addition, the age at which participants in the AS group reported first speaking showed a negative correlation with the amount of talking about their earliest *remember events* ($r(78)=-.25$, $p=.029$), while this was not found for the controls ($r(77)=.10$, $p=.374$; difference: $z=2.17$, $p=.030$).

2.4.4 External rating of the *remember events*

Overall word count of the descriptions of *remember events* did not differ significantly between groups (AS 40±27, CG 35±14, $F(3,165)=1.00$, $p=.319$, $f=0.08$; excluding depression/AD(H)D: AS 37±18, CG 34±12, $F(1,135)=1.24$, $p=.268$, $f=0.10$). Furthermore, no group reported more fragment memories (AS: 21 fragments, one not clearly relatable, 61 ‘complete’; CG: 21 fragments, 2 not clearly relatable, 60 ‘complete’). External ratings by the authors showed a similar pattern compared to the internal self-ratings by the participants. Word count of social in-group words and things differed significantly between groups: in the AS group less words referring to the social in-group and more words referring to things were used (social in-group: $F(3,165)=6.91$, $p=.009$, $f=0.21$; things: $F(3,165)=24.48$, $p<.001$, $f=0.39$). However, word counts of references to self or to other persons did not differ between groups (self: $F(3,165)=0.05$, $p=.817$, $f=0.00$; other: $F(3,165)=0.92$, $p=.340$, $f=0.08$). More sensory details were reported in the AS group and they described more different senses from which the details derived (details: $F(3,165)=17.66$, $p<.001$, $f=0.33$, excluding depression/AD(H)D: $F(1,135)=13.09$, $p<.001$, $f=0.31$; senses: $F(3,165)=12.48$, $p=.001$, $f=0.28$, excluding depression/AD(H)D: $F(1,135)=13.21$, $p<.001$, $f=0.31$). Thoughts and emotions were mentioned less often by autistic participants ($F(3,165)=7.78$, $p=.006$, $f=0.22$, excluding depression/AD(H)D: $F(1,135)=4.70$, $p=.032$, $f=0.19$), and also social details were less abundant ($F(3,165)=4.37$, $p=.074$, $f=0.14$; excluding depression/AD(H)D: $F(1,135)=4.52$, $p=.035$, $f=0.18$). Details to time and place, often the measure for specificity, did not

differ between groups (time: $F(3,165)=0.01$, $p=.931$, $f=0.00$; place: $F(3,165)=0.19$, $p=.668$, $f=0.03$). Please see also figure 2.

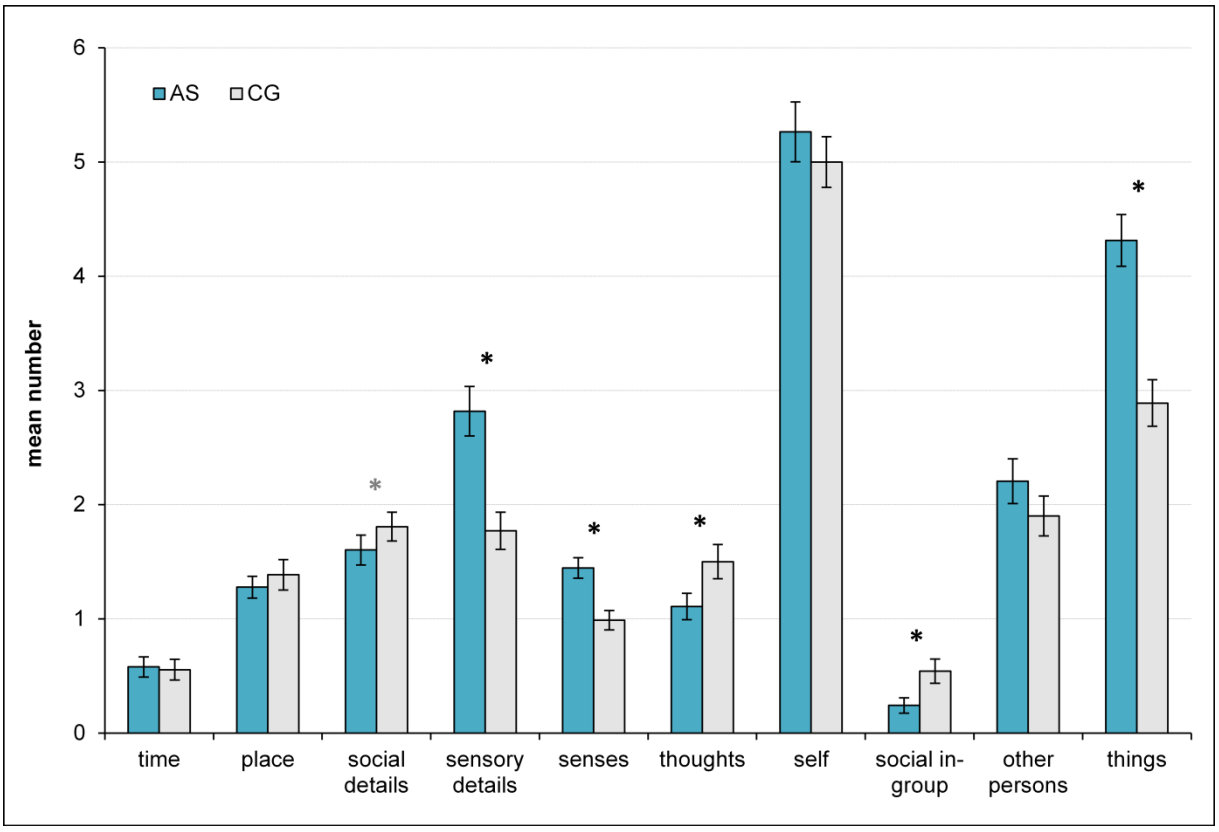

Figure 2: Mean ratings of different aspects and four word counts (self, social in-group, other persons, things) of *remember events* of participants on the autism spectrum (AS) and matched controls (CG). Error bars indicate ± SE; *indicates significant differences between groups ($p < 0.05$), *only significant after exclusion of depression/AD(H)D; for further details see text.

2.5 Discussion

This study aimed to investigate differences in early childhood memories between people on the autism spectrum and controls. We used online questionnaires to better meet the special needs of individuals with autism than it would be possible in a laboratory setting. In addition, in comparison to previous studies on personal autobiographical memory in autism, we asked participants for their earliest *remember* and *know event* without making further restrictions. Based on the intense world theory (Markram & Markram, 2010), in line with the expectation of Lyons and

Fitzgerald (Lyons & Fitzgerald, 2005), and autobiographical accounts written by people with autism (e.g. Brauns, 2002; Mukhopadhyay, 2000), we hypothesized that people on the AS would have earlier autobiographical memories when not being constrained to a specific predefined category or situation. In addition, we were interested in the influence of sensory details and language on early memory formation in autism.

Our results show that participants on the AS remember earlier events and report more sensory details. In addition, the amount of remembered visual details was related to the age of earliest *remember events* in the AS group and supports our prediction of earlier childhood memories in autism and an association of these to sensory processing. Furthermore, the association between more frequent talking about memories and a younger age of the earliest *remember event* in both groups hints also at an influence of language processing on personal autobiographical memory in autism.

Individuals on the AS remembered events from a significantly earlier age in childhood than the control group. The median age of *remember events* in the control group (3.50 years) is comparable to the one found by Bruce and colleagues (3.52 years Bruce et al., 2005) supporting the validity of our measure. Furthermore, groups did not differ in the age of their earliest *know event*. While *remember events* reflect own memories, *know events* reflect memories of episodes other people believe to be important. As *know events* will mainly derive from what seems important to non-autistic people, it is not surprising that the groups did not differ in their age of their earliest *know event*. The age between the first *know* and *remember event* has been proposed to correspond to the end of childhood amnesia (Bruce et al., 2005). According to our data, childhood amnesia seems to end earlier in the AS group than in the control group.

Our results of even earlier remembered childhood memories in autism contradict many previous studies which found mostly deficits in autobiographical episodic memory. It is possible that people with autism performed worse in earlier studies (e.g. Bruck et al., 2007; Millward et al., 2000), because the chosen events did not fit with their interests. The same holds true for the study of Tanweer and colleagues (Tanweer et al., 2010) who also differentiated between *know* and *remember events*. The authors asked their participants to recollect memories from predefined categories like an event linked to a person for example. One might find different

results when asking for other activities (e.g. less social and more sensory related) due to a higher involvement of people with autism in those activities. In the present study participants had free choice which events to report, which avoided a possible bias from using predetermined events. Interestingly, when applying a sentence completion test to participants with autism in a study requiring less social contact (letters) Crane and colleagues (Crane, Lind, & Bowler, 2013) found no evidence for deficits in autobiographical memory either. These findings indicate that people on the AS do not have an overall deficit in autobiographical episodic memory, but might differ from non-autistic people in what they encode and / or remember. Interestingly, specificity or episodicity is often said to be impaired in the memories of people with autism (Tanweer et al., 2010), whereas in the current sample the AS group reported as many details related to time and place as the controls did. Maybe episodicity is preserved due to higher involvement in these self-selected events compared to predefined ones.

Participants on the AS reported more sensory characteristics of their *remember events* compared to the control group, and they included a greater number of different senses, e.g. sound in addition to visual details. The authors' external ratings of the descriptions of the *remember events* revealed the same pattern of results as the self-ratings by the participants. Hence, differences in sensory involvement between people with and without autism could be an explanation for the AS group remembering earlier events. Since people with autism show heightened responses to sensory stimulation (e.g. Asperger, 1944; Baranek et al., 2006; Hilton et al., 2010; Leekam et al., 2007) memory processing via sensory features might be enhanced in adults with autism, which would facilitate retrieval of those memories using sensory pathways. Our results support these assumptions and are also in line with the hyper-perception proposed by Markram and Markram (Markram & Markram, 2010). Even if memories fade similarly over time in both groups, an initially increased attention to and perception of sensory details in the AS group may explain the increased richness and earlier onset of their memories. In addition, earlier memories may also be related to hyper-memory, which may be a starting point for future studies.

This is also in agreement with the increased attention to fine detail (Jolliffe & Baron-Cohen, 1997), leading people with autism to remember details of a situation rather than the global setting. However, we do not know whether children with autism encode more sensory details than non-autistic children or differ only in the ability to

retrieve those details later. It would be interesting for future studies to compare the amount of encoding of sensory details between children and adults with and without autism. As evidenced by Hilton and colleagues (Hilton et al., 2010), who found relations between atypical sensory responsiveness and social behaviour problems in children with autism, sensory inputs must be considered in the development of coping strategies for social problems. Our results suggest that sensory features are also important in memory processes. For this reason and also as sensory perception is atypical in the majority of people with autism, the assessment of patterns of intensity of sensory perception, and consequently the person-specific modulation of sensory inputs might be a useful tool for learning interventions in autism.

We evaluated the memories regarding several social aspects. Participants on the AS reported fewer social interactions and used words indicating group membership such as ‘we’ or ‘our’ less frequently. These results may reflect less engagement or sense of belonging in social situations and consequently fewer reports. This may also explain why some studies using cued recall find poor autobiographical episodic memory in autism, if the cues largely comprise social events or social details. In contrast, memories of individuals on the AS more often referred to things (e.g. toys, furniture, animals), and descriptions were rich in sensory detail.

Remarkably, there are no differences in the number of self- or other-references between groups, so our results do not support an increased self-focus in people on the AS. Group differences however, may simply be caused by differences in narrative styles and also be influenced by the experience that non-autistic people are often not able to relate to the different perceptions, emotions and thoughts experienced by autistic people, which may cause the latter group to keep these mental states to themselves.

Childhood amnesia refers to the phenomenon that early childhood memories are lost, possibly due to fundamental changes in the encoding of events within the first four years of life. One theory of childhood amnesia is based on the predication that children are motivated by different goals than adults. Such differences in motive configuration lead to different levels of involvement in a particular situation, which in turn influences which memories are encoded (M. A. Conway & Pleydell-Pearce, 2000). If these processing levels or motivative goals are established very early or are

not subject to fundamental changes in autism, this different, not-integrative processing may be the reason for the recall of earlier memories.

Another factor that influences the age of the earliest childhood memory is the use of language. While people with autism with typical language development can use language in addition to sensory cues to encode memories, people with autism with delayed language development are possibly limited to just sensory cues for encoding. As retrieval is easier if more pathways are used at the same time (Kast, Meyer, Vogeli, Gross, & Jancke, 2007), one might speculate that people with autism with typical language acquisition can more easily retrieve early autobiographical memories than people with autism with delayed language acquisition. The age of language acquisition should be interpreted with caution, since it is usually learnt from relatives or caregivers, and may differ in accuracy between individuals; however, often times, these early milestones in the development of children are very important to relatives, and thus better remembered or even written down. Furthermore, inaccuracies should be distributed equally over individuals of both groups, likely not influencing our results. As elaborative talk was found to facilitate the development of autobiographical memory skills (Reese, Haden, & Fivush, 1993), it is possible that talking more often about the *remember event* also improves the ability to remember the event later in life. In agreement with the negative correlation between age of language acquisition and the amount of talking about the earliest remembered memory in the AS group, people on the AS remembered even earlier events when they reported talking more about them. In sum, it seems that language also influences autobiographical memories of people on the AS. For this reason, it would be interesting for further studies to include a greater number of people with autism with language delay and to ask for the rating of language features of the *remember events* per se as well as taking into account the ability of several people with autism to comprehend language without using it verbally.

The present study was conducted online. This procedure has several advantages. Laboratory conditions might not be suitable for many individuals with autism as many of them may find social interactions overwhelming and would choose not to participate, resulting in a selection biased sample. In addition, by conducting the survey online, individuals with and without autism may feel less pressure to report socially desirable events. Interestingly, one of the rare studies that found not only deficits but also strengths in the autobiographical memory of people with autism, was

a study in which the memory task was mailed to the participants, allowing them to complete it in their preferred environment instead of a laboratory setting, suggesting a beneficial effect for non-laboratory based assessments of autobiographical memory in autism (Crane, Lind, et al., 2013). Nonetheless, it would be important to compare laboratory and online conditions in reporting early childhood events although it seems likely that the results of age estimation are comparable, as the paper and pencil study of Bruce and colleagues (Bruce et al., 2005) had similar results in the age of the earliest *remember events* for controls (see above).

The drawback of the online approach is that it is not possible to have a diagnostic interview with the participants. So, despite using the AQ as a reliable screening instrument (Baron-Cohen et al., 2001; Woodbury-Smith et al., 2005) and asking participants to self-report professional diagnoses, it is possible that not all people who are included in the AS group have autism and not all people in the control group were non-autistic. However, any potential misclassification of participants in this study would reduce differences rather than accentuating them. Therefore, we assume that our result holds true especially in a more controlled sample. The impossibility of verifying the memories is a limitation of the study. However, reports of false memories are possible for everyone, including relatives. Additionally, this would raise the problem of different involvement of children and adults as well as non-autistic and autistic people, as discussed above. Since a substantial number of first memories in our study would have required verification from non-family members, such as kindergarten teachers, checking every single event is not possible and we would have had to restrict the memories (e.g. situations also experienced and remembered by another available person) which would have led to a biased sample. A further limitation is that only people on the AS who we see as high-functioning and who were able to report their memories were included in the study. So it is not clear whether these results would be the same for people with autism who are not able to report their perception in a way for others to understand. Thereby a new problem emerges, would then the results be due to communication difficulties or altered experience.

In a nutshell, people on the high-functioning AS do not seem to have an overall deficit in personal episodic memory, instead remembering autobiographical memories from an even earlier age in childhood compared to a control group. This could be due to a more sensory based form of memory processing in the AS group, resulting in an improved retrieval of sensory details in adulthood. The findings from

the present study are in agreement with autobiographies from people with autism (e.g. Brauns, 2002; Mukhopadhyay, 2000), the work by Hilton and colleagues (Hilton et al., 2010), Hochhauser and Engel-Yeger (Hochhauser & Engel-Yeger, 2010), and the intense world theory of autism by Markram and Markram (Markram & Markram, 2010), who all assume that sensory features play a major role in autism. Furthermore, also language seems to influence autobiographical memory in autism, as in the AS group an earlier use of language was associated with talking more about the *remember events* and remembering earlier ones. Assessing the pattern of intensity of sensory perception is a potentially useful tool for understanding the heterogeneity of symptoms in autism, developing effective interventional methods, and also of course in day-to-day interactions with people with autism.

2.6 Appendix

A. **Examples of *remember events* of individuals on the autism spectrum (translation by the authors)**

- My earliest memory is that we went on a ferry. The seats were red and I was still so small that I could cross lie on the bench. I didn't feel well.
  [this is the one used in the abstract]
- The fresh peach split into two halves which I ate in kindergarten. Velvety skin, a special texture of the pulp. How the core was furrowed. The orange color of the pulp, the reddish skin.
- Visiting my granny just before she died. At the bedroom door, my mother advised my sister and me to be good and quiet. For the funeral, my mother bought me some dark blue corduroys.
- My earliest memory is about a vacation in southern France. We had a vacation house which was called 'the little house at the ocean'. We went there all the way in the blue Fiat. My brother was still a baby. The sand on the beach was so hot that I burned my feet.

B. **Examples of *remember events* of controls (translation by the authors)**

- On my fourth birthday I had chickenpox, which is why my children's party was canceled. Then my parents drove to a lake with me.

- In kindergarten another child received a worksheet and was praised for its handling. I wanted to please the kindergarten teacher and took a sheet from the desk and filled it in. Unfortunately, I was scolded for it.
- I remember the first holiday with my family. I was three years old. We flew to Crete and my brother and I got an inflatable airplane toy on the plane.
- I sat on the edge of the bed and "read" to my parents from a book, though I could not actually read.

3 Relating sensory sensitivity to respiration

This section includes data that has already been published as well as unpublished data. The published data are from:

Zamoscik, V., Niemeyer, C., Gerchen, M. F., Fenske, S. C., Witthoft, M., & Kirsch, P. (2017). [Sensory Inventory (SI): self-assessment of sensory sensitivity for adults and adolescents]. *Fortschr Neurol Psychiatr, 85*(9), 541-551. doi:10.1055/s-0043-117885

3.1 Introduction

An adequate perception of the environment is one of the main foundations of adaptive behavior and ensures survival. Even if the overall picture is confusing, normally we can assess and respond adequately to dangerous situations within a very short time, by relying especially on acoustic and visual stimuli. For example, this enables us to avoid a snake in the wilderness or a playing child on the street while driving. Therefore, near-threshold stimuli must be perceived quickly in order to generate adaptive responses, while at the same time, the enormous abundance of stimuli present in the environment must be filtered by relevance to not get overwhelmed by the multiplicity of stimuli.

As already mentioned earlier, this ability of adequate and adaptive sensory perception can vary between individuals and is influenced by sensory sensitivity (Aron & Aron, 1997) in which persons with high sensory sensitivity have lower stimulus thresholds (Aron & Aron, 1997; Satow, 1987). However, deviations in the perception and processing of sensory stimuli, as present in overwhelming situations with too many stimuli at the same time or in individuals with a very high sensory sensitivity can also evoke or sustain psychopathological abnormalities and play a central role in the development and course of mental disorders.

First insights on increased sensory sensitivity and decreased body perception ability in individuals with mental disorders were gained (Zamoscik, 2016; Zamoscik et al., 2017). On the one hand, in autism a sensitive sensory perception seems to be associated with anxiety (Lane, Reynolds, & Dumenci, 2012), more intense experience of stress and higher cortisol levels in social situations (Corbett, Muscatello, & Blain, 2016) and related to the severity of social impairment (Hilton et al., 2010). Yet, in autism, body perception as one part of sensory sensitivity has not often been focused on. Interoceptive awareness which can be seen as somehow overlapping to body perception was recently reviewed for autism with the tendency towards hyporeactivity (DuBois, Ameis, Lai, Casanova, & Desarkar, 2016). Further, the perception of thirst and the perception of the onset of illnesses were found to be reduced in autism (Fiene & Brownlow, 2015). But on the other hand, there are indications that the recall of more sensory details is accompanied by the recollection of earlier life events in autism (please see *study 1*; Zamoscik et al., 2016). Increasing memory competence plays an important role in the learning and study habits during

life and might also help in interventions and everyday interactions with autistic individuals.

For depression, first hints on the role of sensory sensitivity were found as remitted depressed individuals with diminished body perception showed higher levels of rumination and depression (Zamoscik, 2016; Zamoscik et al., 2015). Mindfulness trainings and meditation are often used to reduce depressive symptoms (Khoury, Knauper, Schlosser, Carriere, & Chiesa, 2017). Importantly, primarily standardized meditation trainings require attending to respiration and body sensations which was also underscored by the work “mindfulness starts with the body” (Kerr et al., 2013). This also emphasizes an association of sensory perception, body perception in this case, and respiration respectively respiration control.

Surprisingly, even though these findings indicate a major role of sensory sensitivity especially body perception ability and respiration, it is often neglected in research and theories. For example, sensory features were not introduced as relevant in autism until 2013 (APA, 2013). For depression, sensory sensitivity is not a part of diagnostics and mainly also not included in therapy. In addition to the relevance for diagnostics, a targeted modulation of sensory influences and training to increase body perception ability could be an additional tool to support the treatment of patients or even be used in prevention programs, e.g. for mood disorders in healthy populations. However, this neglect of aspects regarding sensory processing in clinical psychology and psychiatry might be in part due to a lack of appropriate instruments to measure sensory sensitivity. Therefore, as a part of the present research program, a standardized self-report questionnaire, the sensory inventory, for sensory sensitivity was developed (Zamoscik et al., 2017) and applied to the investigation of different clinical groups.

The main aims of the analyses presented in this short middle section are first to understand the characteristics of sensory sensitivity in mental disorders like autism and depression measured with the newly developed questionnaire, and second to further elucidate the relation of body perception as a part of sensory sensitivity and respiration in remitted depression. Respiration patterns in remitted depression are then focused on in the second study.

3.2 Methods

These analyses were performed in line with the Declaration of Helsinki and written informed consent was obtained from all participants. Self-report questionnaire data assessing sensory sensitivity were available from a large sample consisting of 3 groups: 1) 1257 healthy individuals, 2) 30 individuals with professional ICD diagnosis of autism, most of them diagnosed with the Autism Diagnostic Observation Schedule (Lord et al., 1989), 3) 86 individuals with remitted depression according to DSM IV, assessed with the Structured Clinical Interview for DSM (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997). About 1000 of the healthy participants filled in the sensory inventory (SI) online, so no formal diagnoses could be given or excluded, and inclusion of participants into the healthy group is based on self-reports. Please see table 2 for a more detailed sample description.

Table 2: Sample characteristics

	Control	*Remitted depression*	*Autism*
n	1257	86	30
Mean age ± SD [years]	33 ± 15	39 ± 11*	35 ± 9
% male	31	31	37
Mean education ± SD [years]	15 ± 5	13 ± 3*	14 ± 4
Remitted depression	-	86	3
Autism	-	-	30
AD(H)D	-	-	5
PTSD	-	-	2
Tourette Syndrome	1	-	1
Migraine	3	-	-
Epilepsy	2	-	1

AD(H)D: attention deficit (hyperactivity) disorder
PTSD: post-traumatic stress disorder
*indicates significant ($p < 0.05$) differences between control and diagnostic group tested for age and education (*t*-tests) and sex (Chi^2 test)

Remitted depressed participants originated mainly from two studies using a sad mood induction paradigm with personal negative life events inside an fMRI scanner. For 73 individuals (no significant differences in mean age, sex and education compared to the complete remitted depressed sample), respiration parameters from two sad mood induction phases were available (please see *study 2* for in- and exclusion criteria, the description of the fMRI sad mood induction paradigm and respiration analyses; for fMRI paradigm see also Zamoscik et al., 2014). For a subsample of 53 additional respiration data of two resting state phases and for

another subsample of 20 data of a 6-months follow up on symptomatology was available.

The multidimensional construct of sensory sensitivity was assessed using a questionnaire, the sensory inventory (SI), which was recently developed (Zamoscik et al., 2017). Since it is a short instrument it can easily be integrated in a clinical or research environment and good test characteristics could be demonstrated (Zamoscik et al., 2017). The SI consists of 34 items in a 6-factorial structure (body perception, smell/taste, temperature/pain, sensory seeking/touch, multiple input, hearing/sight) of which the two subscales body perception ability and smell/taste explain the most variance in the overall score, emphasizing the importance of especially of these two aspects for humans. The present analyses focus mainly on body perception ability as this might be a connection to respiration.

Respiration pattern variability (RPV) was analyzed by means of autocorrelation and coefficient of variance of respiration rate and expiratory pause duration. Further, Welch's power spectral density estimates were calculated for spectral analyses resulting in two parameters, the maximum peak frequency/main respiration rate and the number of frequency bins above 10% cutoff of maximum peak. For further details of respiration analyses please see also *study 2*.

ANCOVAS with sex and age as covariates were conducted to test differences between groups in regard to sensory sensitivity (body perception and a sum score including the five SI subscales smell/taste, temperature/pain, sensory seeking/touch, multiple input, hearing/sight). Further, leave one out classifications with the SI body perception subscale for remitted depression and autism (for autism: additional classification with SI body perception together with the above mentioned SI sum score) were executed to be able to show the potential of sensory features detecting differences in mental disorders based on sensory features only. To investigate the relationship between depressive symptomatology and body perception, the SI body perception score was correlated to a depressive symptom parameter consisting of the z standardized sum score of Montgomery and Asperg Depression Rating Scale (MADRS, interviewer rated; Montgomery & Asberg, 1979) and Beck Depression Inventory II revised (BDI II, self-rated; Beck, Steer, & Brown, 1996). Further, body perception was related to this depression score assessed six months later (T2) to get an impression of the influence of body perception on mental health.

The subsample of participants with remitted depression was used to relate body perception to depression symptoms and RPV parameters in which also correlations of body perception and RPV parameters of the first sad mood induction phase and the first resting state phase were conducted.
In an exploratory ANOVA (n=20), remitted depressed individuals with meditation experience (n=12) were compared to those without in regard to body perception. Statistical analyses were conducted with IBM SPSS 22 (SPSS Inc., Chicago, Illinois, USA) and effect sizes were calculated with G*Power 3.1.2 (Faul, Erdfelder, Lang, & Buchner, 2007).

3.3 Results

Autistic individuals compared to controls have higher sensory sensitivity (sum score: $F(3,1278)=92.31$, $p<.001$, $f=0.27$). Additionally, autistic individuals reported lower body perception ability ($F(3,1278)=113.46$, $p<.001$, $f=0.30$). Body perception was also lower in remitted depressed individuals compared to controls ($F(3,1334)=4.61$, $p=.032$, $f=0.05$) and sensory sensitivity was a bit higher but differed not significantly from controls (sum score: $F(3,1334)=2.49$, $p=.115$, $f=0.04$). Displaying body perception scores together with the sum score of the remaining five subscales of the SI (smell/taste, temperature/pain, sensory seeking/touch, multiple input, hearing/sight) one can see an interesting picture for autistic and remitted depressed individuals (figure 3) to whom *study 2* relates. Further, in a leave one out classification with the body perception subscale, remitted depressed individuals and healthy controls were 58% correctly classified into the original groups (sensitivity: 52%, specificity: 58%), in autism even 84% were correctly classified (sensitivity: 73%, specificity: 84%; together with the SI sum score sensitivity: 87%, specificity: 92%).

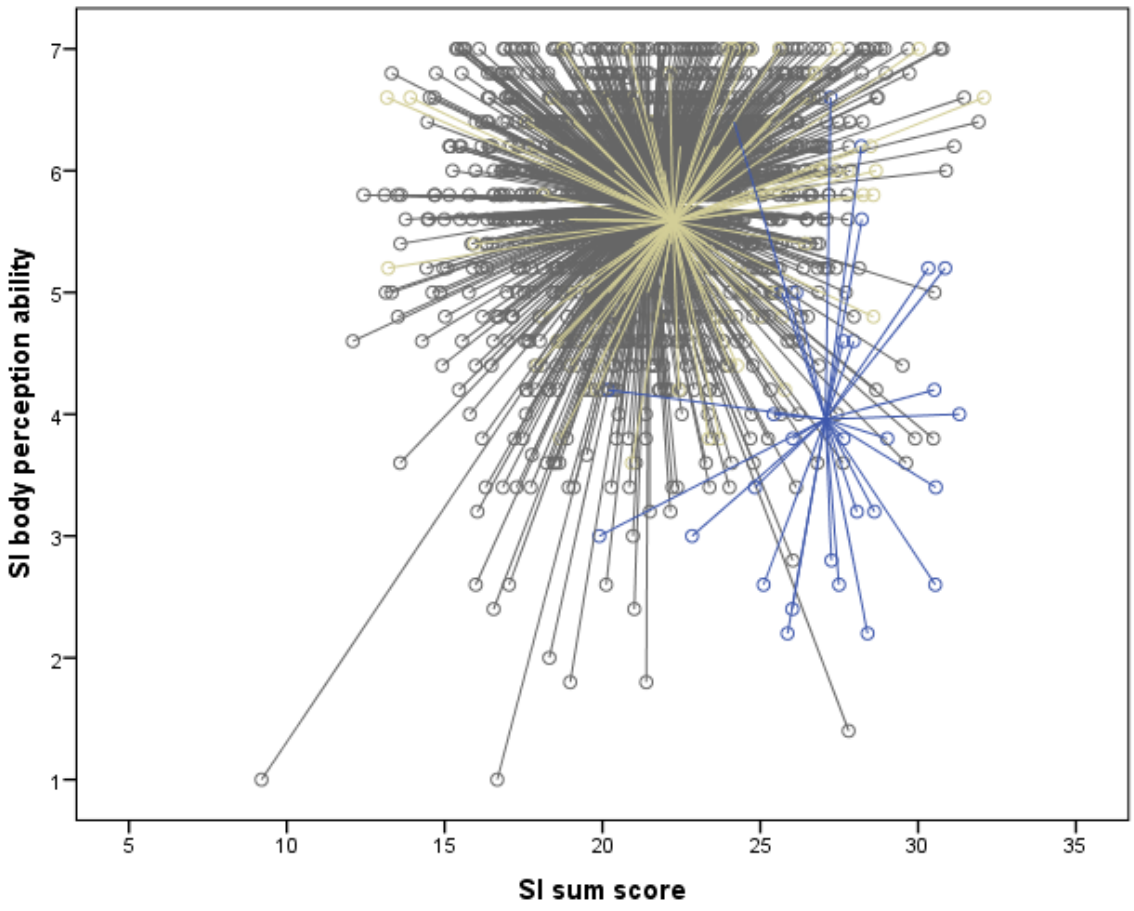

Figure 3: Overview of the differences in sensory sensitivity (body perception and the sum score including the 5 subscales: smell/taste, temperature/pain, sensory seeking/touch, multiple input, hearing/sight) in healthy individuals (n=1257), individuals with remitted depression (n=86), and autism (n=30); lines pointing to group centroid

In formerly depressed individuals, higher body perception was not related to lower baseline depression symptoms (T1 sum score BDI II / MADRS: $r(73)=-.10$, $p=.211$) but to lower depression scores after six months (T2 sum score BDI II / MADRS: $r(20)=-.43$, $p=.029$).

During a resting state, in remitted depressed individuals a negative correlation of body perception and main respiration frequency was found ($r(53)=-.28$, $p=.022$). In addition, during sad mood induction higher body perception ability was related to a more regular respiration pattern ($r(73)=.21$, $p=.035$). Furthermore, in an exploratory analysis, a strong but not significant effect of higher body perception ability in

formerly depressed participants with meditation experience compared to those without was found ($F(1,20)=3.48$, $p=.079$, $f=0.44$).

3.4 Discussion

The aims of the presented analyses were to further describe sensory sensitivity in mental disorders and relate sensory sensitivity to respiration pattern variability with the possible link of body perception ability. The results fit nicely into the picture of the importance of sensory sensitivity including body perception as a significant factor in respiratory regulation for mental disorders.

For autism, one can see the impact of the sensory system not only in *study 1* (Zamoscik et al., 2016) but also in the findings that sensory sensitivity is significantly higher and body perception lower in autism compared with controls. Additionally, sensory sensitivity can be used to correctly classify individuals with and without autism in 92% of the cases with the SI, a self-report questionnaire needing about 9 minutes to fill in. Including sensory features in the diagnosis of autism was overdue.

Sensory sensitivity in remitted depression was a bit higher but did not significantly differ from controls. Classification of participants with remitted depression only with body perception scores was slightly above chance with 58% correct classifications. According to hints from literature and reports by depressed patients, it might be the case that in acutely depressed patients this classification is better. Interestingly, also in the remitted depression group body perception scores were significantly lower compared to controls. This replicates the finding of decreased body perception ability in self-reported mental disorders (Zamoscik et al., 2017) and underscores the idea that this might be a widespread vulnerability mechanism with varying intensities for different mental disorders. These are first hints that classification of individuals with mental problems based on sensory sensitivity, including body perception as an important factor, may be possible. These very promising results require verification in independent samples.

Knowledge about sensory sensitivity including body perception could also achieve greater acceptance, compliance, efficacy and satisfaction in interventions of patients when they experience that more important factors of their problems are included. This would be further important for their everyday life when including sensory

alterations in coping strategies or even relatives may attribute altered behavior to sensory variations.

Interestingly, body perception was related to depressive symptoms more strongly after six months which might be a hint that body perception influences a trait factor which then leads to a worse outcome if body perception is lower. In addition, respiration was also related to body perception ability. During a resting state, remitted depressed participants with higher body perception ability showed lower respiration frequencies which is considered as more relaxed and healthy (Modesti, Ferrari, Bazzini, & Boddi, 2015). Besides, during sad mood, respiration was more regular with higher body perception ability reflecting also a more relaxed and healthy respiration pattern. Both results are in line with the idea of body perception exerting influence on respiration during rest as well as during negative emotional challenge of sad mood induction. Therefore, increasing body perception or having a stronger body focus during emotional challenge might be a promising coping strategy especially for remitted depressed individuals. A further hint derived from the exploratory analysis of meditation experience among former patients with depression showing higher body perception ability in those individuals compared to non-meditators. This effect is not significant maybe due to a lack of power as the sample is very small. Indeed, the finding that mindful breathing influences body perception (Kerr et al., 2013) hints to the same association found here. It would be very interesting if this holds true in larger samples. In addition, the items referring to the subscale body perception in the SI are not focused on respiration directly which might reduce effects.

Importantly, body perception and control and with that respiration control seem to be a significant factor in stress related responses especially for individuals with remitted depression as they seem to have less respiration control especially during the emotional challenge of sad life events. More generally, it is of fundamental relevance for survival particularly in stressful and of course also life threatening situations. In this day and age, as we live in a safer environment, one might understand this relation more intuitively when looking at certain activities such as diving or firefighting, in which respiration control is a crucial competency (Donovan & McConnell, 1999; Tetzlaff et al., 2008). Importantly, together with first hints from the literature (Meyer, Matthes, Kusche, & Maurer, 2012) it seems that people may be able to increase their body perception ability with training, but larger systematic intervention studies are lacking to proof this. Therefore, alongside meditation, trainings focusing on

respiration and body perception may be helpful in different circumstances and seem also to be central during stress and in mental disorders. Although no respiration data is available for autistic individuals, the reduced body perception found for autism might hint to beneficial effects of respiration training also for autistic individuals.

A limitation of these analyses is that there could be an underlying personality trait which explains both, higher body perception ability as well as the more regular respiration. Small effects of personality related to body perception ability were found for extraversion and negatively for neuroticism (Zamoscik et al., 2017). As neuroticism is related to depressive symptoms (Ono et al., 2017) this relationship is not surprising. Further, people with a better body image, which is presumably influenced by body perception (Zopf, Contini, Fowler, Mondraty, & Williams, 2016), may be more satisfied with their body and therefore also appear more extraverted (Allen & Walter, 2016). Moreover, unwanted sensations of the body are less perceived when attention is directed more externally (Banos et al., 2016). Therefore, small effects of personality are also not surprising. Further studies are needed to deepen our knowledge of the role of body perception ability on respiration.

On a neural level, the default mode network is considered the basic network involved in self-referential processes (Whitfield-Gabrieli et al., 2011). Interestingly, and in line with the considerations above, there are clues that meditation training (often including respiration foci) also reduces DMN connectivity (Taylor et al., 2013) whereas increased DMN activity and connectivity was linked to depression (Berman et al., 2011; M. D. Greicius et al., 2007; Li et al., 2012; Sheline et al., 2009; Sheline et al., 2010; Zamoscik et al., 2014). In *study 2* it was focused if increased DMN connectivity is related to increased respiration pattern variability in remitted depressed individuals and if RPV is further related to worse outcome. Several RPV parameters were analyzed to determine which of them are most relevant, so future interventions can be designed and adapted based on these findings.

4 *STUDY 2* – Respiration pattern variability and related default mode network connectivity are altered in remitted depression

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4.1 Abstract

Background - Studies with healthy participants and patients with respiratory diseases suggest a relation between respiration and mood. The aim of the present analyses was to investigate whether emotionally challenged remitted depressed participants show higher respiration pattern variability (RPV) and whether this is related to mood, clinical outcome and increased default mode network connectivity.

Methods - To challenge participants, sad mood was induced with keywords of personal negative life events in individuals with remitted depression (rMDD, *n*=30) and matched healthy controls (HC, *n*=30) during fMRI. Respiration was measured by means of a built-in respiration belt. Additionally, questionnaires, a daily life assessment of mood and a 3 years follow-up were applied. For replication, we analysed RPV in an independent sample of 53 rMDD who underwent the same fMRI paradigm.

Results - In both samples rMDD showed greater variability in respiration patterns, with e.g. shorter respiratory pauses, higher variability in pause duration, higher main respiration frequency and lower expiration to inspiration ratio. Higher RPV was related to lower daily life mood and predicted higher depression scores as well as relapses during a 3 year follow-up period. Furthermore, in rMDD compared to HC higher main respiration frequency exhibited a more positive association with connectivity of the posterior cingulate cortex and the right parahippocampal gyrus.

Conclusions - The results suggest a relation between RPV, mood and depression on the behavioural and neural level. Based on our findings, we propose interventions focusing on respiration to be a promising additional tool in the treatment of depression.

4.2 Introduction

The basic meaning of the Greek word ψυχή / psyche is life in the sense of ‘breath of life’ or soul derived from ψύχω (breath, blow). The relationship between breath and mind is also central to the spiritual beliefs in several Asian countries, in which respiration is seen as origin and essence of life and soul, named for example atman,

prana, lung and qi. Considering the emphasis many cultures put on the role of respiration for human life not solely in terms of survival but also with respect to mental processes, investigating the biological connection between respiration and mental processes becomes a necessity.

Accordingly, research has recently begun to focus on this. So far, a small number of studies with healthy individuals have demonstrated an influence of emotion induction on what we summarizingly term respiration pattern variability (RPV). For example, Rainville and colleagues found a significant increase of the standard deviation of the respiration period during sadness induction (Rainville et al., 2006). Vlemincx and coworkers report an increase of respiration variability during negative and high arousing emotions (Vlemincx et al., 2015). In another study, they observed a more variable and less flexible respiration pattern during worry induction compared to a mindfulness condition (Vlemincx et al., 2013).

The connection between irregular respiration and mood has also been investigated in patients with respiratory disorders such as chronic obstructive pulmonary disease (COPD) and asthma. In a sample of more than 1000 patients with COPD, 72% reported elevated depressive symptoms, 38% suffered from a clinical depression (Kunik et al., 2005). Another study also found increased prevalence of depressive symptoms among patients with COPD, asthma, and asthmatic bronchitis (44-67%), and revealed an association between psychopathology and severity of pulmonary obstruction (Asnaashari et al., 2012). Interestingly, the prevalence of depressive symptoms in chronic respiratory diseases is strikingly higher compared to patients with other chronic diseases such as type-II diabetes (18%; Ali et al., 2006) or during the first year after a myocardial infarction (25%; Spijkerman et al., 2005). These findings suggest a close connection between respiration irregularity and sad mood. In addition, trainings for COPD patients aiming at respiratory rehabilitation have been proposed to result in improvements of depressive symptoms (Fan & Meek, 2014), potentially not only via an overall increase in well-being.

Given the influence of negative emotions and related cognitions, particularly sadness and worry on respiration variability in healthy individuals, we would assume that depression as a disease often characterized by chronic sadness is associated with increased variability of respiration patterns, too. Research on the connection between respiratory diseases and depression, substantiates this hypothesis. However, so far

there is no research on the relation between RPV and depression. We not only expect increased RPV in depression, but also that interindividual differences in RPV might be related to alterations in connectivity as observed in depressed patients, particularly with an increased default mode network (DMN) connectivity (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015).

It is well established that brain network connectivity measured with functional magnetic resonance imaging (fMRI) in general, and particularly DMN connectivity is related not only to neural and mental but also to physiological processes like respiration (Birn et al., 2006), heart rate (Chang, Cunningham, & Glover, 2009) and heart rate variability (Chang et al., 2013). At the same time, there is clear evidence that the covariation of the blood oxygenation level dependent contrast cannot be exclusively attributed to physiological noise but is still observable after correcting for physiological artefacts (Birn, 2012). Furthermore, there is increasing evidence for a large overlap between networks identified by functional covariations and structurally defined brain networks (Marrelec, Messe, Giron, & Rudrauf, 2016) excluding the interpretation of large-scale brain networks as exclusively reflecting physiological noise. Alterations of resting state networks have been observed in different mental disorders (M. Greicius, 2008; Woodward & Cascio, 2015). For example, we have recently shown an increase of DMN connectivity to the parahippocampal gyri in formerly depressed individuals during sad mood induction (Zamoscik et al., 2014). In this study, we used the imagination of personal negative autobiographical events to induce sad mood. Consistently, Masoaka and colleagues found a relation between the retrieval of autobiographical memory, respiration pattern and the activation of the parahippocampal gyrus (Masaoka, Sugiyama, Katayama, Kashiwagi, & Homma, 2012). Several other brain regions have also been related to respiration related processes. Recently, in mice it was found that a small group of neurons of the preBötzinger complex, a group of brainstem interneurons involved in the generation of respiration rhythms, was linked to locus coeruleus which may connect the respiration rhythm to functions such as arousal, attention, memory, olfactory processing and emotions (Yackle et al., 2017). Furthermore, in humans, posterior cingulate cortex deactivation (Brannan et al., 2001) and insula activation (Evans et al., 2002) have been associated with dyspnea-related unpleasantness, whereas dyspnea relief was related to activation in the superior and middle temporal cortices (Peiffer, Costes, Herve, & Garcia-Larrea, 2008). Even the mere anticipation of

dyspnea seems to activate brain areas involved in dyspnea perception, and emotion-related areas such as the insula which might reflect anticipatory unpleasantness or even fear, and boost maladaptive health behaviors in patients with respiratory abnormalities (Stoeckel, Esser, Gamer, Buchel, & von Leupoldt, 2016). Interestingly, the insula was also found to be related to interoceptive and bodily self-awareness and sense of body ownership (Karnath, Baier, & Nagele, 2005; Tsakiris, Hesse, Boy, Haggard, & Fink, 2007) which might also be associated with respiration patterns.

Originally based on the clinical observations during scanning that the respiration of remitted depressed participants showed visually detectable differences compared to healthy controls and further literature research the hypothesis of altered respiration with higher variability and respiration rate in rMDD was derived. The present analyses were conducted to investigate RPV and its relation to DMN connectivity in remitted depressed individuals and matched healthy controls. We used the data of our established paradigm of sad mood induction via personal negative life events to pose an emotional challenge in which differences in RPV can be expected. In addition, since heart rate variability (HRV) is related to respiration, reduced in depression (Kemp et al., 2010) and also impacts resting state connectivity (Chang et al., 2013), we tested for the relation between HRV and RPV as we expect RPV to be an important independent somatic factor. We aimed to investigate whether higher RPV is associated with depression, how this effect predicts worse outcome in terms of symptom course and relapse, and whether RPV is related to alterations in DMN connectivity.

4.3 Methods

4.3.1 Participants

For the analyses we used two independent samples. Participants of the main sample (S1) were 30 remitted depressed participants (rMDD) with at least two previous major depressive episodes (*n*=28) or a previous chronic major depressive episode of at least two years (*n*=2), and 30 healthy controls (HC), who were individually matched to the rMDD participants by age, sex, and education level. All rMDD participants had to be in a state of partial or full remission, id est, did not fulfill the criteria of a major depressive episode for at least the previous two months. One rMDD currently fulfilled

also criteria for agoraphobia and another participant for social phobia. Participants were recruited using online and newspaper call outs. Sample S1 initially included 64 individuals, however, four cases (2 rMDD, 2 HC) were excluded from analyses due to altered physiological parameters (1 rMDD: temporal atrophy; 1 HC: pituitary gland adenoma) or missing triggers in the physiology files. The second independent sample (S2) comprised 53 rMDD participants with at least two previous major depressive episodes fulfilling the same inclusion criteria as S1, and was used to replicate our findings on RPV parameters. Two of the S2 participants fulfilled the criteria for generalized anxiety disorder and ten for partial remitted comorbid disorders: four for social phobia, four for agoraphobia, and two for specific phobias. Six cases were excluded from analyses due to altered physiological parameters (1 falx meningioma which had impact on normalization, 1 thrombosis diagnosis after inclusion, 1 heterotopia of grey matter, 1 white matter lesions) or missing triggers in the physiology files. For a detailed samples description see table 3.

Exclusion criteria for all groups were bipolar and psychotic disorders, substance dependence, current substance abuse, current obsessive-compulsive, posttraumatic stress, and eating disorders as well as contraindications for the fMRI (including hypertension, heart diseases and surgeries and other severe illnesses). For S2, current psychotherapy was also an exclusion criterion. Psychopathology-related in- and exclusion criteria were assessed by a trained clinical psychologist with the Structured Clinical Interview for DSM-IV axis I (SCID; Wittchen et al., 1997).

The study was approved by the local ethics committee of the University of Heidelberg and conformed to the Declaration of Helsinki. All participants gave written informed consent.

Table 3: Descriptive and psychometric variables of both samples at T1; main sample S1 additionally at follow up 3 years later (T2); independent sample S2 for replication

	mean ± SD			*p value (Cohens d)*
	HC S1	**rMDD S1**	**rMDD S2**	**HC S1 - rMDD S1**
n	30	30	53	
sex: female/male (%)	21/9 (70/30)	20/10 (67/33)	35/18 (66/34)	.781[a]
age [years]	44.53 ± 8.01	45.00 ± 7.90	38.21 ± 10.62	.821[b] (0.06)
education: CSE, high school diploma, A levels (%)	3/8/19 (10/27/63)	4/7/19 (13/23/63)	6/10/37 (11/19/70)	.901[a]
age of illness onset [years]	-	23.10 ± 11.16	23.34± 14.88	-
number of depressive episodes	-	3.83 ± 1.95	4.25 ± 1.95	-
average length of previous depressive episodes [weeks]	-	54.32 ± 67.37	35.15 ± 45.84	-
time since remission [weeks]	-	208.73 ± 185.64	152.66 ± 163.98	-
previous inpatient treatment (%)	-	73	40	-
current psychotropic medication (%)[c]	-	27	17	-
current psychotherapy (%)	-	37	-	-
BDI II T1	3.47 ± 4.06	9.93 ± 8.28	6.78 ± 9.08	<.001[b] (0.99)
MADRS T1	1.37 ± 2.40	5.80 ± 5.20	3.52 ± 4.53	<.001[b] (1.09)
dep-score T1 (z)	-0.45 ± 0.48	0.50 ± 1.10	-0.06 ± 0.84	<.001[b] (1.12)
dep-score T2 (z)	-0.21 ± 0.70	-0.04 ± 0.89	-	.453[b] (0.21)
SOFAS T2	89.87 ± 6.00	77.11 ± 14.37	-	<.001[b] (1.56)
MDE T1 – T2 (%)	1 (3)	13 (43)	-	-
daily life mood T1	4.70 ± 1.18	3.91 ± 1.01	-	.008[b] (0.72)

[a] Chi^2 test
[b] two sample *t*-test
[c] selective serotonin reuptake inhibitors (SSRIs): n = 6
serotonin-norepinephrine reuptake inhibitors (SNRIs): n = 6
noradrenergic and specific serotonergic antidepressant (NaSSA): n = 3
tricyclic antidepressants (TCAs): n = 1
norepinephrine-dopamine reuptake inhibitors (NDRA): n = 1
Lithium: n = 2
atypical antipsychotic medication: n = 2
melatonin: n = 1
n = 5 participants with multiple prescriptions

CSE: Certificate of Secondary Education, 8 years
BDI II: Beck Depression Inventory Revised, self-rated
MADRS: Montgomery and Asberg Depression Rating Scale, rated by a trained clinical psychologist
dep-score: z standardized depression sum score of the BDI II and MADRS scores
SOFAS: Social and Occupational Functioning Assessment Scale, rated by a trained clinical psychologist
MDE: major depressive episode
-: no data available or not tested
%: might not add to 100% as rounded values are used to display

4.3.2 Interview, questionnaire-based, and daily life measures

At baseline (T1), depressive symptoms during the previous two weeks were assessed with the self-rated Beck Depression Inventory II-Revised (BDI II; Beck et al., 1996) and the Montgomery and Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) rated by a clinical psychologist. The mean of z-standardized sum scores of the BDI II and MADRS was calculated and used for subsequent analyses (Huffziger et al., 2013).

Daily life mood was measured using ambulatory assessment (Trull & Ebner-Priemer, 2013; Wilhelm & Schoebi, 2007), conducted over two consecutive weekdays with ten pseudorandomized assessments per day using personal digital assistants (Palm Tungsten E2, Palm Inc.). At each subjective assessment, indicated by a beep, participants rated momentary mood (Huffziger et al., 2013). For the present analyses, scores were aggregated per person over the two days.

For the main sample after 3 years (T2) a follow-up on depressive symptoms was conducted and the Social and Occupational Functioning Assessment Scale (SOFAS; Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000) was assessed by a clinical psychologist. Six participants dropped out between T1 and T2 (1 rMDD, 5 HC).

4.3.3 Analyses of respiration pattern variability (RPV)

Respiration was measured during MRI at a sampling rate of 50 Hz using a respiration belt (PMU Wireless Physio Control, Siemens Healthineers, Erlangen, Germany) around the upper abdomen below the chest and analyzed with in-house MATLAB scripts (The MathWorks Inc., Natick, USA). Data, representing respiration as a change in amplitude over the time course of the experiment, were smoothed using a 50^{th} order one-dimensional median filter, and normalized to mean 0 with variance 1000.

The typical respiration rate (RR) for a healthy adult would be one respiration every 4 to 5 seconds (.2 - .25 Hz). Therefore, to not miss any respirations, we took record of all maximum peaks with a minimal distance of 70 samples, corresponding to one respiration every 1.4 seconds, which had to have a minimal peak prominence of 1/3 of the total data variance to count as a respiration. Additionally, we identified all minimal turning points which protruded with at least 1/100 of the total data variance, which are used for pause detection.

For our analysis we determined for each subject a set of respiration parameters, related to the concepts of expirations, pause duration (PD) between expiration and inspiration, and respiration frequency. The expiration was defined as starting at each maximum peak and ending at the lowest local minimum before the next maximum peak. Correspondingly, inspiration was defined as the time between the lowest minimum and the next maximum peak. Since we expected irregular respiration

patterns to manifest also with abnormalities in the exhaling part of the respiration cycle, we calculated the expiration-to-inspiration ratio.

Respiration patterns are not always as regular as a simple cosine function, and often pauses between respiration cycles occur, therefore we determined the length of pauses between inspiration cycles. For this, we calculated the slope of the respiration curve at a window size of 5 samples with a cutoff of 2. Clusters of minimum peaks were used to determine coarse temporal markers for a provisional pause onset, which was then recursively extended into both directions based on the slope parameters to determine pause onset and offset.

For spectral analysis, we calculated Welch's power spectral density estimate using Hamming windows with a 50% overlap to transform the data from the time to the frequency domain. We expected regular respiration to be reflected in a power spectrum with one dominant maximum frequency peak, whereas irregular respiration would result in a broader distribution of power over several frequency bins. To probe this, we counted the number of frequency bins with a cutoff greater than 10% of the maximum frequency power.

In addition, we calculated coefficient of variance (CV; standard deviation divided by mean) and autocorrelation[1] (AR) of two respiration parameters: mean respiration rate and mean pause duration. Additional parameters calculated were maximum peak frequency of the spectral analysis and number of frequency bins above the cutoff. The maximum peak frequency can be seen as main respiration frequency which we think is an important additional feature to describe respiration variability. To take expiration related problems into account, expiration to inspiration ratio was calculated.

4.3.4 Heart rate variability (HRV)

We used four HRV parameters: mean size of all beat intervals (mNNI [ms]), standard deviation of all beat intervals (SDNN [ms]), percentage of consecutive beat intervals which differ more than 50ms (pNN50 [%]), and the root mean square of the successive differences (RMSSD [ms]).

[1] AR(A,B) = cov(A,B)/(std(A)*std(B)), with A = breath(1:n-1), and B = breath(2:n)

4.3.5 Statistics

Statistical analyses for all analyses not including fMRI were performed with IBM SPSS22 (SPSS Inc., Chicago, Illinois, USA). We conducted Chi square and two sample *t*-tests for the analyses of sample parameters (see table 3) and ANCOVAS (covariates sex and age) and correlations for the RPV (RR, RR AR, RR CV, PD, PD AR, PD CV, EIR, maximum peak frequency, number of frequency bins above threshold) and HRV (mNNI, SDNN, pNN50, RMSSD) parameters. For prediction of outcome (T2 depression score, T2 SOFAS, T1-T2 relapse) we used regression analyses. To include baseline depression scores in the longitudinal analyses, stepwise regressions were applied. For relapse prediction logistic regression analyses using maximum likelihood estimation and Wald and Hosmer-Lemeshow-tests were conducted. Effect sizes were calculated with G*Power 3.1.2 (Faul et al., 2007).

4.3.6 Functional Magnetic Resonance Imaging (fMRI) session

The fMRI experiment was conducted using scanner built-in goggles and the Presentation software package (version 18.1; www.neurobs.com) for stimulus presentation. Scanning was carried out within two weeks after the SCID interview and the ambulatory assessment. The complete experimental procedure comprised six phases of 4.5 minutes each: two resting states, two sad mood inductions, one rumination phase, and one distraction phase (the order of the rumination and distraction phases was counterbalanced across participants). In this paper we reanalyzed the fMRI data of our previous study with a new research question. A more detailed description of the study design can be found in Zamoscik et al. (2014). In the present analyses we focus on the first sad mood induction phase as we expected sad mood induction via personal negative life events to pose a greater emotional challenge for rMDD and the first sad mood induction phase is not influenced by other phases. Sad mood was induced with three negative life events which were individually assessed for every participant immediately before the fMRI session started and were later presented consecutively in the scanner via a keyword (each for 1.5 minutes). In parallel, participants listened to instrumental background music

(parts of Adagio in g-minor by Albinoni). None of the participants fell asleep during the session.

4.3.7 FMRI data acquisition and analyses

6x180 T2* weighted EPI images (TR = 1.5 s, α = 80°, TE = 28 ms, using parallel imaging with GRAPPA with iPAT=2) with 24 slices (slice thickness 4 mm, voxel size 3x3x4 mm^3, FOV 192 mm^2) were recorded with a 3 T Trio TIM Scanner with a 12 channel head coil (Siemens Healthineers, Erlangen, Germany). Further, we collected high-resolution 3-dimensional T1 weighted anatomical images (MPRAGE; TR = 2.3 s, α = 9°, TE = 3.03 ms) with 192 slices (slice thickness 1 mm, voxel size 1×1×1 mm^3, FOV 256 mm^2). In addition, heart rate and respiration rate were sampled at 50Hz with the scanner built-in equipment (PMU Wireless Physio Control, Siemens Healthineers, Erlangen, Germany). The first twenty images of each phase were discarded. Data were corrected for physiological artefacts using the Aztec software tool (van Buuren et al., 2009) including a high-pass filter of 1/512Hz. Importantly, this correction removes direct first-order effects of respiration and heart beat from the fMRI time series. Detrimental effects of small head movements were corrected by wavelet despiking using the BrainWavelet toolbox (Patel et al., 2014). Preprocessing included segmentation of the MPRAGE and registration to the SPM8 TPM templates, coregistration of the functional images to the individual MPRAGE, motion correction, slice time correction (13th slice as reference), normalization of the functional images with normalization parameters derived during MPRAGE segmentation, and smoothing with a 9 mm Gaussian kernel. fMRI preprocessing and statistics were conducted with SPM8 v5236 (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom). Seed region for first level functional connectivity analyses was the posterior cingulate cortex (PCC; 10 mm sphere around MNI coordinates -7, -45, 24) as the main posterior part of the DMN (Berman et al., 2011). First level general linear models included the seed region time course, six movement parameters, cerebro spinal fluid and white matter signals, and a constant. PCC connectivity maps were then used as input for second level analyses. To test for the relationship of respiration parameters with PCC connectivity we conducted independent regression analyses within each group for parameters that showed at least a medium effect size of the difference between HC and rMDD and was related

to clinical parameters. Second level general linear models included the respective respiration regressor, age and sex as covariates, and a constant. Additionally, we tested for group differences in the relationship between individual respiration parameters and PCC connectivity by a moderated multiple regression approach (Jaccard & Turrisi, 2003). In other words, a moderated multiple regression analysis was used to test for group x respiration parameters interaction effects on PCC connectivity. These models included the respective respiration parameter, group dummy variables for each group, interaction terms between group and respiration, age and sex as covariates, and a constant. To assess group differences, contrasts between the interaction terms were applied and tested for significance. In all imaging analyses we used either a whole-brain threshold of $p<0.05$, FWE corr., or, when this threshold was not reached, a ROI analysis in the parahippocampal gyri, which we found in our previous analysis of the sample to be relevant during sad mood induction in depression (Zamoscik et al., 2014) and which was recently replicated (Renner et al., 2017).

4.4 Results

4.4.1 Respiration pattern variability (RPV)

Healthy controls and formerly depressed individuals differed significantly in their respiration patterns (table 4). To provide an impression of these altered patterns, figure 4 displays exemplary respiration time courses and corresponding frequency analyses from one HC (upper panel) and one rMDD participant (lower panel).

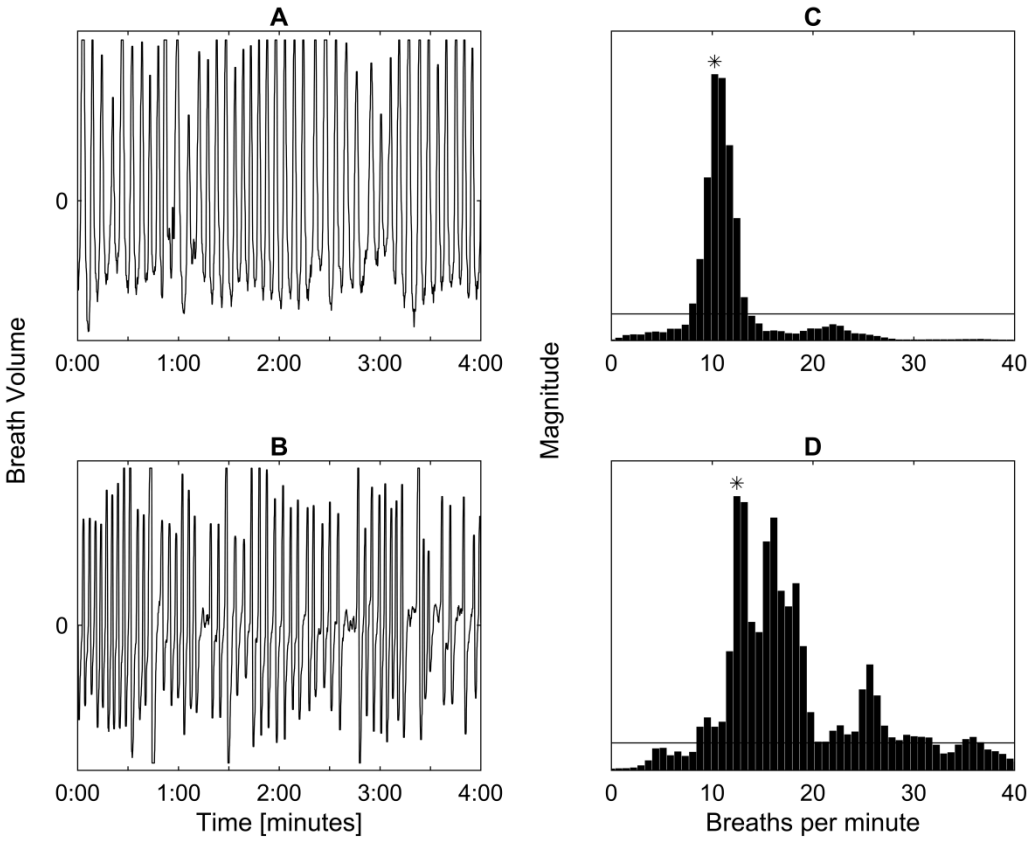


Figure 4: Exemplary four minutes respiration recordings (left) and corresponding Welch's power spectral density estimates (right) during sad mood induction of a healthy (upper panel, A+C) and a remitted depressed individual (lower panel, B+D); recordings normalized to mean 0 with variance 1000; *: maximum peak frequency, line: threshold 10% of the maximum frequency power

The two groups differed significantly in several RPV parameters with the variance of the respiratory pause duration showing the largest effect size. Furthermore, for the comparison with the second clinical sample only the maximum peak frequency differed significantly between both rMDD groups. For this parameter we tested also the difference of S2 rMDD compared to S1 HC which was also significantly different. Importantly, RPV parameters were not significantly related to sad mood after sad mood induction (see supplemental material). For additional details see table 4.

Table 4: Respiration parameters during sad mood induction in both samples with statistics from ANCOVAs (covariates sex and age)

	mean ± SD			*p value (f value)*	
	HC S1	**rMDD S1**	**rMDD S2**	**HC S1-rMDD S1**	**rMDD S1-rMDD S2**
Respiration rate [/min]	16.08 ± 3.76	15.35 ± 3.49	16.41 ± 4.28	.880 (.11)	.128 (.27)
RR AR	.19 ± .17	.19 ± .21	.12 ± .21	.588 (.19)	.392 (.20)
RR CV	.21 ± .10	.28 ± .10	.24 ± .11	.030 (.41)	.078 (.30)
Pause duration [s]	.77 ± .43	.71 ± .23	.77 ± .27	.104 (.34)	.328 (.21)
PD AR	.05 ± .13	.06 ± .17	.03 ± .12	.498 (.21)	.376 (.20)
PD CV	.58 ± .26	.81 ± .21	.75 ± .31	.002 (.55)	.121 (.27)
EIR	.81 ± .26	.71 ± .30	.67 ± .22	.015 (.45)	.770 (.12)
Max peak frequency	14.50 ± 4.12	15.83 ± 4.68	15.15 ± 5.37	.136 (.32)	.017 (.37) [.012 (.38) to HC S1]
Number of frequency bins above threshold	16.73 ± 10.11	27.63 ± 18.45	23.30 ± 21.54	.026 (.42)	.159 (.26)

AR: autocorrelation, CV: coefficient of variance
RR: respiration rate, PD: pause duration
EIR: expiration to inspiration ratio

Further analyses were conducted on those RPV parameters which showed at least a medium effect size for the difference between HC and rMDD (RR CV, PD CV, EIR, maximum peak frequency, number of frequency bins above threshold).

4.4.2 RPV related to heart rate variability (HRV)

In healthy controls, none of the RPV parameters were correlated with HRV parameters. In formerly depressed participants, respiration rate CV and pause duration CV were negatively correlated with SDNN (r=-.47, p=.009; r=-.42 p=.021) and EIR was negatively correlated with mNNI (r=-.38, p=.037) and with RMSSD (r=-.39, p=.033).

4.4.3 RPV related to mood parameters and prediction of 3 years outcome

In healthy controls, higher maximum peak frequency was associated with lower daily life mood (r=-.37, p=.045). In rMDD, higher RR CV and PD CV were associated with higher depression scores (RR CV: r=.36, p=.048; PD CV: r=.50, p=.005) and with lower daily life mood (RR CV: r=-.43, p=.020; PD CV: r=-.44, p=.017, fig. 5).

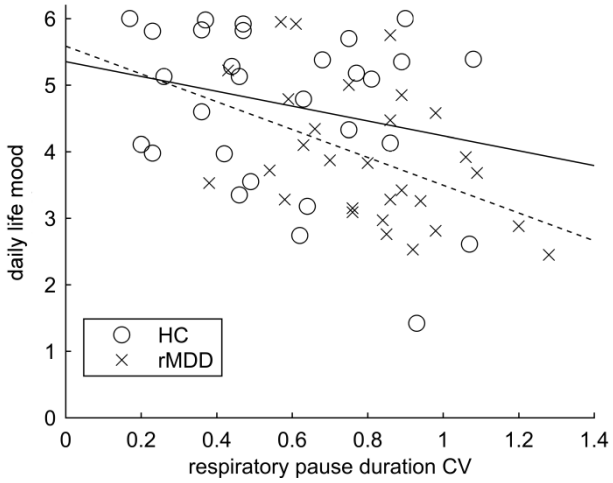


Figure 5: Higher respiratory pause duration coefficient of variance (CV) in relation to lower daily life mood (rated on a scale from 0/not at all to 6/very much; two consecutive weekdays with ten assessments per day, scores aggregated over both days) in remitted depressed participants (rMDD, dashed line) and matched healthy controls (HC, solid line)

Furthermore, RPV parameters predicted outcome 3 years later. In rMDD, T2 depression scores were predicted by T1 PD CV (F=10.76; R^2=0.41, *B*=2.62, *SE*=0.62, *p*<.001; T1 depression scores excluded in stepwise regression). Higher T1 EIR predicted higher T2 SOFAS scores in HC (F=5.32; R^2=0.20, *B*=10.51, *SE*=4.56, *p*=.031) whereas in rMDD higher T2 SOFAS scores were predicted by lower T1 PD CV (F=5.38; R^2=0.18, *B*=-28.17, *SE*=12.15, *p*=.029). Relapse of rMDD between T1 and T2 was predicted by T1 RR CV (Chi^2=5.23; Nagelkerke R^2=0.23, *B*=9.69, *SE*=4.86, *p*=.046; Hosmer-Lemeshow-test *p*=0.362).

The pattern of results stayed the same after excluding all participants with current medication with only small changes in *p*-values (and effect sizes) presumably due to smaller sample size (see supplemental material). The only results which seemed to have changed after exclusion was that lower rMDD T2 depression scores and higher T2 SOFAS scores were not predicted by lower T1 PD CV (*p*=.180; *p*=.214) which might be an effect of reduced variance in T2 scores after exclusion of medicated participants.

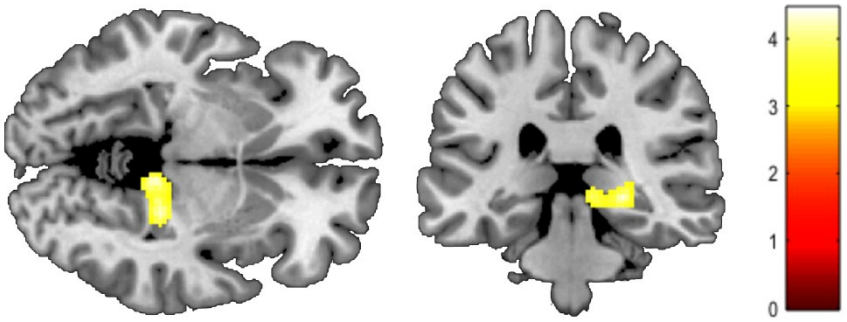
We did not correct for all conducted tests.

For fMRI analyses we used those RPV parameters showing associations with mood parameters or outcome prediction (RR CV, PD CV, EIR, maximum peak frequency).

4.4.4 RPV related to DMN connectivity

A whole-brain significant effect at a threshold of $p<.05$ FWE corrected was found for the maximum peak frequency in HC. Lower maximum peak frequency was associated with significantly increased connectivity of the PCC to the right insula, the right middle temporal gyrus as well as the left middle/superior temporal gyrus. No significant cluster was found in rMDD. To test for significant group differences in the association between the maximum peak frequency and PCC connectivity (i.e. the group x peak frequency interaction effect on connectivity) we applied a moderated multiple regression model. ROI analysis in the parahippocampal gyrus revealed right PCC - parahippocampal gyrus connectivity being significantly higher associated with maximum peak frequency in rMDD. At an exploratory threshold of $p<.001_{unc.}$ this cluster consisted of 269 voxels and was divided into two peaks (peak t_1=4.45 and peak t_2=4.27), with the second being located within the hippocampus (fig. 6). As we did not have a hypothesis for this region we did not test this with a ROI analysis.

The pattern of the fMRI results also stayed the same when including medication as a covariate, as well as when excluding all medicated participants (see supplemental material).



	anatomical region	MNI			cluster size	peak *t*
		x	y	z		
HC pos	ns					
HC neg	left middle / superior temporal gyrus	-56	-6	2	6	6.46
	right middle temporal gyrus	46	-8	-10	1	6.89
	right insula	40	6	2	1	6.40
rMDD pos	ns					
rMDD neg	ns					
group interaction						
MDD>HC	right parahippocampal gyrus	22	-36	-6	1	3.68
	right parahippocampal gyrus	24	-34	-8	1	3.63
HC>MDD	ns					

Figure 6: Higher association of PCC - right parahippocampal gyrus connectivity with maximum peak respiration frequency during the sad mood induction phase in the depression group (rMDD, n=30) contrasted to the control group (HC, n=30). For display purposes only: whole-brain main effect $p_{unc.}$<.001, k=10 voxels, bar indicates *t*-values; table comprises corrected statistics for relationship of maximum peak respiration frequency to PCC connectivity *p*<.05 FWE corrected, group interaction ROI analyses *p*<.05 FWE corrected, ns: no significant clusters

4.5 Discussion

To study the relation between respiration pattern variability (RPV) during sad mood induction, depression and their neural underpinnings, we investigated a sample of remitted depressed individuals (rMDD) together with a matched sample of healthy controls (HC) in regard to RPV, different clinical parameters like depression scores and daily life mood, and alterations in default mode network (DMN) connectivity with fMRI. We further assessed an independent replication sample of rMDD individuals with respect to their RPV patterns.

Our results suggest an association between RPV, mood and depression on the behavioral but also on a neural level in HC and to a greater extent in rMDD. Further, the results show that RPV parameters may even be used to predict depressive symptoms, global functioning and relapse over periods as long as 3 years.

Healthy and formerly depressed individuals showed clearly different respiration patterns. Especially respiratory expiration pause duration and expiration to inspiration ratio (EIR) exhibited prominent differences between the groups. Both could be an indicator that rMDD show maladaptive expiration behavior. It seems that the altered respiration pattern consists amongst others of an incomplete expiration part of the respiration cycle and shorter expiration pauses. The importance of the expiration phase during sad mood induction for emotional well-being is also reflected by the fact that in HC EIR predicted global functioning after 3 years. Therefore, it can be concluded that RPV is also an important factor in healthy populations.

The maximum peak frequency might be seen as main respiration rate in relation to other frequencies which derived from frequency analyses. As the main respiration frequency was higher in rMDD this might be a hint to higher emotional strain in those participants during sad mood induction. The finding that higher main respiration frequency was also associated with lower daily life mood in HC is also consistent with this interpretation as one might experience lower daily life mood with more negative emotional challenge. Furthermore, the higher number of bins above threshold in frequency analyses gives an additional hint to a more irregular respiration behavior in rMDD, as it indicates a tendency away from one dominant breathing frequency towards a more widespread distribution of breathing frequencies, i.e. greater variability. Higher RPV was associated with higher depression scores and lower daily life mood in rMDD. This implies that higher RPV is maladaptive and related to unpleasant outcome. These findings also fit to higher depression rates among somatic respiration disorders (Asnaashari et al., 2012; Kunik et al., 2005).

The second independent rMDD sample showed similar RPV parameters compared to the other rMDD group. Only the maximum peak frequency was significantly lower. Importantly, it was still significantly higher than in the HC group which, in combination with the depression scores and other respiration and symptom related scores, indicates that the second rMDD group might be, in clinical terms, an intermediate group between the healthy group and the rMDD group from our first study. Therefore,

we conclude that RPV parameter results could be replicated in the independent second sample.

Another informative aspect of the present study is the possible relation of the respiration pattern and HRV. Higher HRV is seen as adaptive and healthy and lower HRV is related to depression and sad mood (Hamilton & Alloy, 2016). An important HRV parameter, the respiratory sinus arrhythmia, is related to respiration. It reflects the increase of the heart rate during inspiration and its decrease during expiration as an expression of parasympathetic activity. Two studies on healthy participants used controlled breathing tasks to investigate the influence of inspiratory/expiratory time ratio on HRV. Whereas one study found larger respiratory sinus arrhythmia in trials with short inspiration and long expiration compared to trials with long inspiration and short expiration (Strauss-Blasche et al., 2000), the other study found no association between respiration patterns and HRV parameters (Klintworth, Ajtay, Paljunite, Szabados, & Hejjel, 2012). Interestingly, altered respiratory sinus arrhythmia was found to be related to relapse in adolescents with depression (Kovacs et al., 2016) which might be a hint of respiration related factors to be a vulnerability mechanism in depression. As we found only few associations between RPV and HRV in rMDD and none in HC we assume that RPV represents a different aspect than HRV does. Furthermore, our results show that in those cases in which HRV was related to RPV in rMDD, the parameters were negatively correlated. This completely fits the hypothesis as we see high RPV maladaptive and related to worse outcome.

Remarkably, RPV parameters predicted clinical outcomes 3 years later. Pause duration CV in rMDD explained 41% of the variance of the depression scores 3 years later. The predictive value of pause duration CV was even higher than that of baseline depression scores. In addition, PD CV could predict global functioning in rMDD and the expiration to inspiration ratio predicted global functioning in HC. Further, RR CV which was predictive for relapse in rMDD was not related to the number of depressive episodes ($r=.08$, $p=.695$). These results suggest that respiration behaviour during sad mood induction represents a phenotype that may not only be related to the present emotional state but also to the general ability of the individual to cope with critical life events. Therefore, increased RPV could be a vulnerability factor for major depressive episodes as it was proposed for adverse cognitive styles like rumination (Figueroa et al., 2015). The role of RPV as a vulnerability mechanism is also supported by the fact that not only in rMDD but also

in HC daily life function and well-being seems to be related to RPV. Therefore, respiration might be an important target in future interventions or prevention programs.

Of note, posterior cingulate cortex (PCC) connectivity to several brain regions was significantly associated with respiration parameters even after correction of the fMRI time series for physiological effects. This highlights the importance of RPV also on a neural level. Our analyses in the HC identified the insula and the temporal gyri to be significantly stronger connected to the PCC with lower maximum peak frequency. These brain areas have been described to be involved in interoceptive awareness, bodily self-awareness and sense of body ownership and might further be related to unpleasant feelings during respiration (Karnath et al., 2005; Stoeckel et al., 2016; Tsakiris et al., 2007). However, the insula was also found activated during passive listening to music (Brown, Martinez, & Parsons, 2004) and therefore different respiration while listening to atmospheric music could be related to this finding as well. As we identified a cluster located more in the posterior part of the insula, our finding might be more related to bodily-self-awareness and body ownership as those concepts were found to be related to the presence of and activity in the posterior insula (Karnath et al., 2005; Tsakiris et al., 2007). Furthermore, the more positive association of main respiration frequency with connectivity of the PCC to the parahippocampal gyrus in rMDD compared to HC adds to our previous findings of a neural ‘scar’ of higher PCC - parahippocampal connectivity in the same sample (Zamoscik et al., 2014) and further suggests that such connectivity might be maladaptive and related to worse outcome in depression. Therefore, it can be assumed that RPV may also be indicative of neural processes during the experience of sad mood, which are both related to the course of the disorder.

A limitation of the study is that we did not correct for all conducted tests. However, to limit the number of conducted tests we restricted subsequent analyses to those variables showing at least a medium effect size and relations to our variables of interest.

The fMRI analyses are based on a reanalysis of the data in Zamoscik et al. (2014), with a few more subjects included and an updated SPM8 processing pipeline. We had to choose this data set for our analyses because the follow-up study did not include healthy control participants, and thus a comparison between groups would

not have been possible. However, the analysis targets a completely different research question, which is complementary to the results reported in Zamoscik et al. (2014) and thus does not lead to circular reasoning. It is also important to note that we used a relatively large anatomical mask of the parahippocampal gyri rather than a functional mask for regional analyses, which minimizes double-dipping. In addition, Renner et al. (2017) found similar effects in the parahippocampal gyri which can be seen as replication of our findings in 2014 and emphasizes the use of the parahippocampal gyri as ROI. A potential source of artifacts are cerebro-spinal fluid pulsations (Strik, Klose, Erb, Strik, & Grodd, 2002), which are known to be related to respiration (S. Yamada et al., 2013; Yildiz et al., 2017). We corrected the data for physiological signals prior to connectivity analyses and used the CSF signal as a nuisance variable in all first level analyses, but it is unclear whether this adequately controls for the putative effect of CSF pulsations. In the future it will be an important task to better understand the relevance of such artifacts in fMRI analyses and how they are best controlled for.

Further, we did not check for depressive episodes in relatives of our control group participants. This would be interesting to check in future studies as higher risk healthy controls might show slightly altered breathing as well which would hint towards a genetic contribution on respiration patterns. In the current analyses however, possibly included higher risk HC would reduce our effects rather than accentuating them. A further limitation of the present analyses is that they are based on data acquired with a simple setup with only one respiration belt that prohibited including e.g. variations in respiratory volume which would make it also easier to find pauses more accurately. However, already this limited setup provided sufficient information to detect the reported associations. Future directions should include two respiration belts to allow a more complete look on RPV. In addition, it would be very informative to also apply the present paradigm to a sample of acutely depressed participants. We expect those to have even higher variability in respiration patterns compared to remitted individuals presumably already during a resting state whereas remitted individuals might ‘need’ triggers like emotional challenge to show the reported alterations in respiration. Our results emphasize the use of respiration based interventions as an additional tool in the treatment of depression and maybe also other stress related disorders.

4.6 Supplemental material

Table S1: RPV – sad mood after sad mood induction (r-values, all n.s. at p<.05)

	HC S1	**rMDD S1**
RR CV	.03	.14
PD CV	.10	.15
EIR	.12	-.03
maximum peak frequency	.01	.15
number of frequency bins above threshold	.26	.13

Table S2: RPV – HRV (r-values, most n.s. at p<.05, sig. in bold)

	HC S1				**rMDD S1**			
	mNNI	*SDNN*	*pNN50*	*RMSSD*	*mNNI*	*SDNN*	*pNN50*	*RMSSD*
RR CV	-.24	-.13	.07	-.24	.02	**-.47**	.17	-.01
PD CV	.07	.11	-.13	.07	-.03	**-.42**	.22	-.06
EIR	-.12	-.06	-.21	-.12	**-.38**	-.11	.22	**-.39**
maximum peak frequency	-.35	-.20	.19	-.34	-.13	-.16	-.02	-.14
number of frequency bins above threshold	.00	-.06	.10	-.01	-.34	.13	.23	-.33

Table S3: RPV – T1 depression scores, daily mood (r-values, sig. at p<.05 in bold)

	HC S1		**rMDD S1**	
	T1 depression score	*Daily mood*	*T1 depression score*	*Daily mood*
RR CV	.24	-.12	**.36**	**-.43**
PD CV	.16	-.25	**.50**	**-.44**
EIR	-.07	.15	-.16	.10
maximum peak frequency	.14	**-.37**	-.04	-.06
number of frequency bins above threshold	.12	.04	.25	-.15

Table S4: Prediction: T2 depression score, T2 SOFAS, T1-T2 relapse (p-values; ex: excluded in stepwise regression with T1 depression scores)

	HC S1		**rMDD S1**		
	T2 depression score	*T2 SOFAS*	*T2 depression score*	*T2 SOFAS*	*T1-T2 relapse*
RR CV	.693	.718	.495	.183	.046
PD CV	.959	.754	<.001	.029	.063
EIR	.045 (ex)	.031	.108	.673	.518

maximum peak frequency	.919	.552	.271	.668	.517
number of frequency bins above threshold	.460	.556	.343	.164	.474

Results for the sample without rMDD participants who took medication

Table S5: RPV parameters (p-values)

	HC S1-rMDD S1	**rMDD S1-rMDD S2**
Respiration rate [/min]	.966	.100
RR AR	.410	.702
RR CV	.084	.019
Pause duration [s]	.094	.124
PD AR	.458	.310
PD CV	.022	.021
EIR	.091	.309
Max peak frequency	.069	.005
Number of frequency bins above threshold	.042	.061

Table S6: RPV – sad mood after sad mood induction (r-values, all n.s. at p<.05)

RR CV	.26
PD CV	.19
EIR	-.13
maximum peak frequency	.21
number of frequency bins above threshold	.16

Table S7: RPV – HRV (r-values, most n.s. at p<.05, sig. in bold)

	mNNI	*SDNN*	*pNN50*	*RMSSD*
RR CV	-.09	**-.50**	.20	-.13
PD CV	-.01	-.41	.29	-.05
EIR	**-.49**	-.17	.26	**-.50**
maximum peak frequency	-.14	-.16	.04	-.16
number of frequency bins above threshold	-.20	.11	.23	-.19

Table S8: RPV – T1 depression scores, daily mood (r-values, sig. at p<.05 in bold)

	T1 depression score	*Daily mood*
RR CV	.36	**-.44**
PD CV	**.60**	**-.43**
EIR	-.13	.13

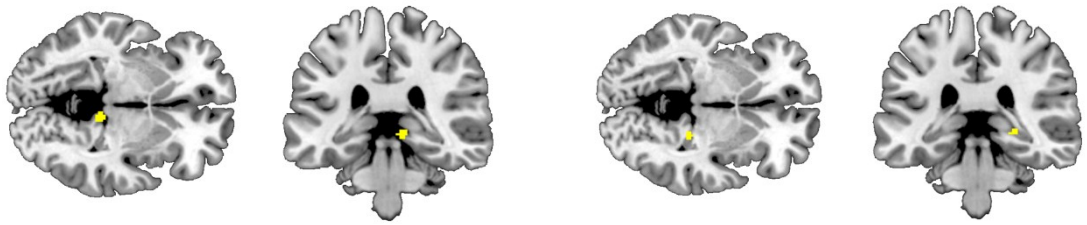
maximum peak frequency	.00	-.09
number of frequency bins above threshold	**.41**	-.27

Table S9: Prediction: T2 depression score, T2 SOFAS, T1-T2 relapse (p-values)

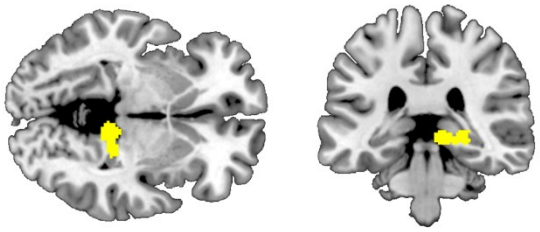
	T2 depression score	*T2 SOFAS*	*T1-T2 relapse*
RR CV	.234	.118	.038
PD CV	.180	.214	.046
EIR	.262	.774	.102
maximum peak frequency	.957	.667	.886
number of frequency bins above threshold	.428	.543	.197

fMRI

The pattern of the MRI results also stayed the same when including medication as a covariate, as well as when excluding all medicated participants. For MNI 22, -36, -6: Currently medicated excluded (big cluster divided into two smaller ones): n.s. *t*=2.91



Medication as dummy covariate: n.s. *t*=3.34



But those participants who were medicated on average were more severely affected showing more inpatient treatments (F=6.55, *p*=.016, f=.48) and a medium but non-significant effect for higher depression z scores (.62 vs. .16 possibly additionally influenced by medication; F=1.58, *p*=.221, f=.25). Taking medication and depression severity is confounded.

5 GENERAL DISCUSSION

The primary aim of the research program reported in this thesis was to advance the understanding of two basic biological features in human behavior, sensory sensitivity and respiration pattern variability, their interrelation and their relationship to mental disorders. This discussion will further point out, how both features might assist in the further improvement of interventions, but also with their role as potential vulnerability mechanisms.

Two main studies were conducted including autistic, remitted depressed and healthy participants and in addition supplementary analyses with independent samples were described that relate both features together. The studies were exemplarily conducted with autism and depression as autism is related to sensory alterations (Brauns, 2002; Hilton et al., 2010; Markram & Markram, 2010) and depression to altered respiration (Asnaashari et al., 2012; Ellis et al., 2016; Kovacs et al., 2016; Kunik et al., 2005) and both to body perception (DuBois et al., 2016; Fiene & Brownlow, 2015; Zamoscik, 2016).

The results show higher sensory sensitivity in autistic individuals and a relation of sensory features to increased memory for autobiographical events. Additionally, sensory sensitivity scores can be used to classify autistic individuals from controls with 92% accuracy. These findings point to the high relevance of sensory features in autism and affirm their inclusion in the 5th edition of the DSM diagnostic criteria for autism (APA, 2013). In the second study with remitted depressed participants during sad mood induction with personal negative life events, higher respiration pattern variability (RPV) could be shown which was related to worse outcome. Furthermore, higher respiration frequency was related to increased default mode network (DMN) connectivity in remitted depressed participants, and higher RPV to lower body perception ability. This suggests a deep embedding of RPV and associated alterations into features relevant for depression as increased DMN was also shown to be related to depressive symptoms and worse outcome (Zamoscik et al., 2014).

Both, sensory sensitivity and RPV, might be broader domains relevant in mental health which would be also in line with the Research Domain Criteria (RDoC) approach (Insel et al., 2010) studying the integration of many levels of information to better understand basic dimensions of functioning underlying human behavior. For example, body perception was found to be lower in autistic and formerly depressed

individuals compared to controls, indicating a greater prevalence of this sensory alteration.

5.1 Sensory sensitivity and RPV in autism and depression

The results, consistent with and extending findings from the literature, point to the high importance of sensory sensitivity in autism and to the significant influence of respiration on depression even with regard to relapse prediction. In detail, autistic individuals remembered earlier events of their childhood containing more sensory details with more different senses involved compared with matched non-autistic individuals in which visual details were directly related to memories of an earlier time point of childhood. Differences in sensory involvement between autistic and non-autistic people could be an explanation for the autistic individuals remembering earlier events. Since they show marked responses to sensory stimulation (Asperger, 1944; Baranek et al., 2006; Leekam et al., 2007), memory processing with initially increased attention to and perception of sensory details in autistic individuals might be enhanced, which would amplify richness and facilitate retrieval of those memories using sensory pathways. The results support these assumptions and are also in line with the hyper-perception described in the intense world theory of autism proposed by Markram and Markram (Markram & Markram, 2010) and with the increased attention to fine detail (Jolliffe & Baron-Cohen, 1997), leading autistic individuals to better remember details of a situation rather than the whole picture. Therefore, more precise knowledge of sensory alterations might improve learning interventions in autism by comprising sensory based memory competency. This competency could further be used to help autistic individuals to better cope by at least partly shifting their focus also on positive aspects of multi-sensory experiences, otherwise frequently perceived as negative. Further supporting findings in regard to sensory sensitivity were found in the independent sample of autistic individuals in which they were more prone to experience low body perception and high sensory sensitivity. It was possible to classify autistic from non-autistic individuals 92% correctly with sensory features only. The sensitivity of commonly used diagnostic instruments for autism is not larger. Of course, this is not to say that sensory sensitivity should be used as standalone feature or concept for diagnosis, but underscores its potential support. Also for everyday interactions it might be supportive and may change those

interactions positively when altered sensory processing is respected as being part of autistic cognition and feeling.

Of note, body perception was reduced in autism and remitted depression, possibly pointing to a broader connection of this aspect of sensory sensitivity to mental health in general maybe also via respiration control. Body perception ability seems to be linked to respiration which is not surprising as naturally physical activity is related to both, body perception (Gesell, Scott, & Barkin, 2010) and respiration (Smejkal, Vavra, Bartakova, Kryl, & Palecek, 1989) both of which can be influenced by humans. The present analyses showed that greater body perception ability seem to be associated with a more regular and slower breathing pattern, whereas lower body perception ability was associated with lower mood and depression. This supports the hypothesis that body perception ability might have impact on respiratory regulation alongside physiological aspects like the partial pressure of carbon dioxide.

Several biomolecular influences on respiration (carbon dioxide) and sensory sensitivity (e.g. pheromones) were described, interestingly one molecule appears to be associated to both features, namely tryptophan. It seems to be related to alterations in ventilation and reported distress during respiratory challenge (Colasanti et al., 2011; Kent et al., 1996), and further to sensory sensitivity with regard to pain and body perception (Dalkner et al., 2017; Martin et al., 2017). Therefore, in addition to sensory processes as biological factor, the tryptophan/serotonin metabolism could be one of the underlying biomolecular connections between respiration and mental disorders like depression since both have been associated with it (Colasanti et al., 2011; Kaluzna-Czaplinska et al., 2017; Kent et al., 1996). This fits also well in the picture as the serotonin system is relevant for various mental disorders (Kaluzna-Czaplinska et al., 2017). As mentioned above, besides respiration the serotonin metabolism seems also be related to pain (Martin et al., 2017) and body perception, like problems with the evaluation of hunger, as tryptophan availability is related to food craving (Dalkner et al., 2017). Further, the dampening of intestinal inflammation with tryptophan was shown (Etienne-Mesmin, Chassaing, & Gewirtz, 2017) which might also further explain the connection of depression and bowel diseases (Nikolaus et al., 2017). These connections might possibly be influenced by a genetic factor, the tryptophan hydroxylase 1 polymorphism which was also found to be related to depression (Mushtaq et al., 2016). Additionally, findings from rats suggest a relation of tryptophan availability, pain perception and stress (Kelly & Franklin, 1985). In

healthy individuals, an association of tryptophan and stress was also found. Higher tryptophan availability attenuated the cortisol response in acute stress (Firk & Markus, 2009), which links the serotonin metabolism to the hypothalamic–pituitary–adrenal axis. Further hints to the relation to stress in this context are preliminary results from the reported remitted depressed sample in which salivary cortisol levels point to a reduced cortisol awakening response associated with higher respiration frequency and variability. Interestingly, very recently an influence of diaphragmic breathing (a mind-body practice) on cortisol levels was reported (Ma et al., 2017). This would 'close the circle' linking body perception, respiration and stress together, but further analyses and research are necessary to verify these associations. Although no respiration data is available for autistic individuals, the reduced body perception and high stress and cortisol levels found for autism might hint to beneficial effects of respiration training also for autistic individuals.

Respiration was shown to be highly associated with depression but seems also of importance in the healthy population as RPV was linked to global functioning. In remitted depressed participants, depression scores were higher with higher RPV and higher respiration rate. This is in accordance with the view that a more regular, slow, and deep breathing is healthy (Modesti et al., 2015). Fitting this idea, irregular respiration was related to lower daily life mood and predictive for reduced global functioning and higher relapse risk within three years. These findings are also in line with higher depression rates among somatic respiration disorders (Asnaashari et al., 2012; Kunik et al., 2005), repeatedly described as alterations in expiration (Topalovic et al., 2015). Just as in depression, one main problem seems to be the expiration part of the respiration cycle as several related alterations, including altered expiration to inspiration ratio, were found. When looking on anxiety disorders this makes sense as also hyperventilation, which often arises during great anxiety and panic attacks, is a problem of expiration. Carbon dioxide, which is important for the respiratory drive, is lower during hyperventilation due to fast expiration and with that hypocapnia and respiratory alkalosis (because CO_2 is acidic in solution) might follow, which also causes cerebral vasoconstriction leading to cerebral hypoxia and thus could also influence mental processes. In accordance, under uncomfortable breathing reduced cognitive ability was found in healthy participants (Nierat et al., 2016). Before this vicious circle manifests, slow expiration and in general better respiration control should be used which is a method people with this problem can learn (DeGuire,

Gevirtz, Hawkinson, & Dixon, 1996; Meuret, Ritz, Wilhelm, & Roth, 2005). Respiration control can thus serve as a substitute treatment for rebreathing into bags to increase carbon dioxide levels. Both strategies should also lead to normal brain oxygen levels and related cognitive function.

A further relation of respiration and the brain is the connectivity of the default mode network and the parahippocampal gyri. This was shown to be related to more depressive episodes and relapse prediction in remitted depressed individuals (Zamoscik et al., 2014) and was further associated to respiration. Higher respiration rate was linked to a more positive association of the posterior cingulate cortex and the right parahippocampus in remitted depressed participants even after correcting the data for respiration and heart rate parameters. Of note, it was shown that DMN connectivity might be reduced by mindfulness-based training, particularly the connections to the parahippocampal gyri during rest (Taylor et al., 2013) which were identified to be involved in mood, altered respiration and higher relapse risk in depression. Interestingly, increased gray matter volume in the parahippocampal gyri was found in meditators (Leung et al., 2012), whereas the cortex was thinner in this area in late life depressive patients who did not respond to psychotherapy (Mackin et al., 2012). Together with the findings of Zamoscik et al. (2014) in remitted depression and the replication thereof by Renner et al. (2017) in acute depression, it stands to reason that the parahippocampal gyri are an important brain area involved in depression. As suggested earlier (Zamoscik et al., 2014) the connection of the DMN and the parahippocampal gyri might reflect a kind of neural ‘scar’ which is related to the course of the disorder as it was increased with the number of previous major depressive episodes and was predictive for worse outcome. These new respiration related findings for the same brain region add important information to the underlying mechanism. The positive impact of deep breath meditation or respiration focused trainings on depression can be hypothesised to be at least partly regulated via this pathway. Future studies focusing on this question could test for reduced connectivity also during emotional challenge or stress after respiration based trainings and with that try to demonstrate a further biological alteration in depression which could be a potential focus for evidence based interventions.

5.2 Sensory sensitivity and RPV as markers for mental health?

Several findings hint to an important role of sensory sensitivity for autism and respiration pattern variability for depression, and a relationship of both features with each other and with other mental health problems. These features are associated with relapse prediction and social functioning (Hilton et al., 2010). Also, sensory overstimulation and related situations are more likely perceived as traumatic stress leading to worse outcome (Haruvi-Lamdan et al., 2017). Thus, it seems feasible that both aspects might not only be contributing to the aforementioned disorder or condition, but instead constitute vulnerability mechanisms. These vulnerability mechanisms might have an increased influence in stressful and challenging situations as several associations with stress, the hypothalamic–pituitary–adrenal axis, and the serotonin metabolism were found as well. Considering that everybody experiences stressful events and most if not all mental disorders are somehow connected to stress (C. C. Conway, Starr, Espejo, Brennan, & Hammen, 2016), and particularly with regard to the findings of the impact of sensory sensitivity and respiration in various disorders, one might hypothesize that sensory sensitivity and RPV are concepts important in mental health in general, fitting the new approach of the RDoC describing functional domains rather that specific disorders. Derived from several hints in the literature, accounts from relatives and patients, and the reported findings a scheme to embed both features into a broader concept was derived (see figure 7) in which sensory sensitivity and respiration have several connections to each other and further to other features relevant in mental health like depression symptoms. The sensory feature body perception which also includes the evaluation of hunger and illness seems to be reversely connected to other sensory features. That is why it is considered separately. Sensory sensitivity seems to have an influence on stress responses and therefore also on altered social behavior, atypical reactions and further well-being. Body perception is in addition associated with respiration and social behavior when e.g. not reporting an illness appropriately, which both again influence well-being. Respiration patterns seem to be connected to DMN connectivity and depression symptoms. As mentioned before, further connections to the serotonin metabolism are also likely. In the proposed scheme the focus lies mainly on problems produced by increased sensory sensitivity, lower body perception ability and higher RPV and interventions reducing those problems.

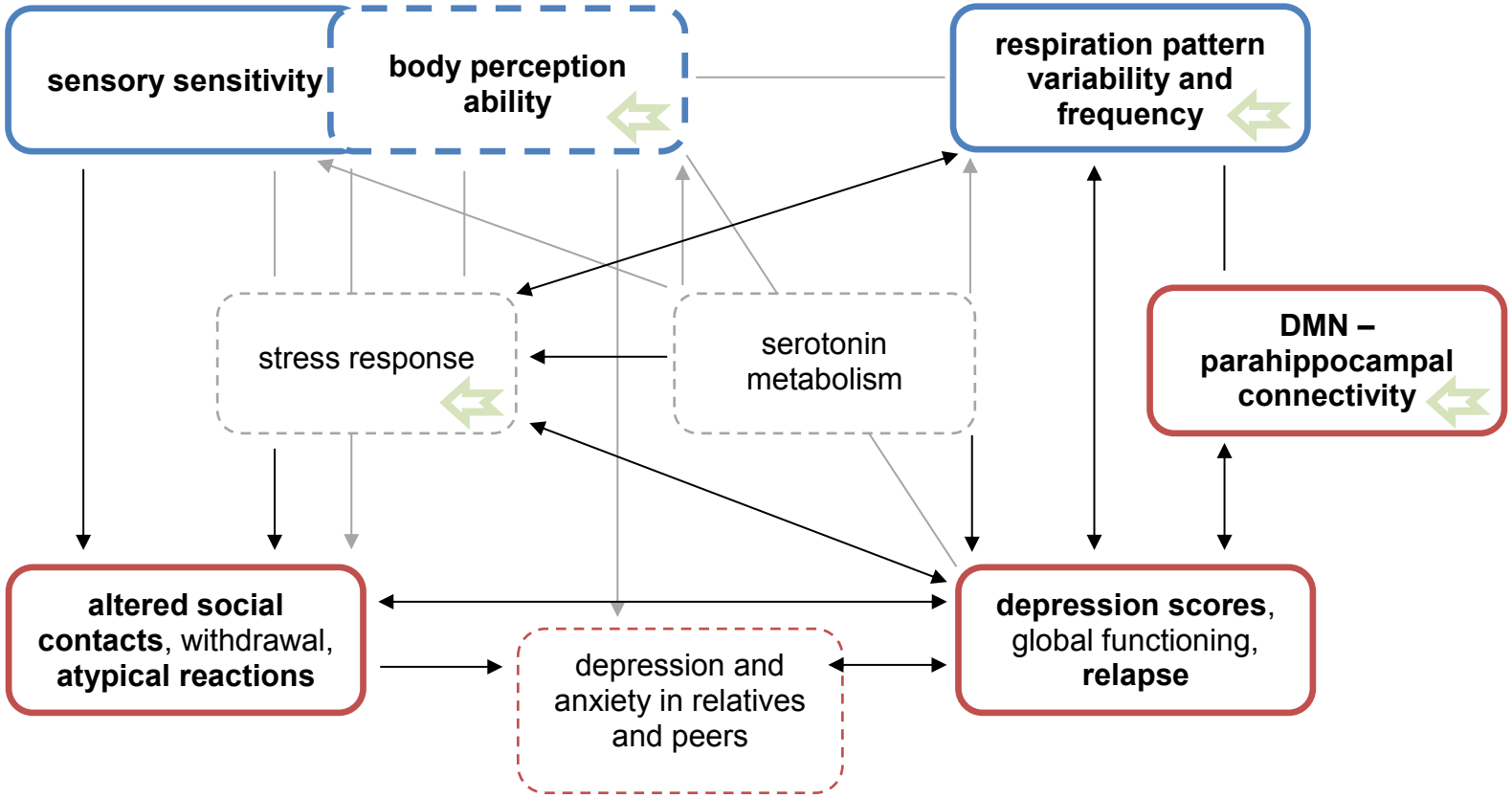


Figure 7: Schematic overview on sensory sensitivity and respiration pattern variability (RPV) alterations, related problems, possible interactions and selected further connections, and intervention pathways (arrows show possible influence of respiration training); DMN: default mode network; black arrows show evidence based connections (several supporting findings), grey lines show possible connections (few findings or reports), some connections are likely bidirectional

Of course, on the other side, strengths deriving from e.g. higher sensory sensitivity, for example in memory, which could be used in learning interventions or day-to-day interactions should not be forgotten. In addition to patients and healthcare professionals, relatives and caregivers could be taught that these connections of sensory sensitivity or respiration might be influencing a wider range of symptoms but also could be a point of intervention and good prospects. Affected persons can learn coping strategies in regard to personal sensory alterations, learn to relax and distract, and focus additionally on positive aspects of their personal sensory sensitivity.

To include the new concepts in interventions or daily life coping one has to know where the alterations might be. Respiration can be measured via several devices like respiration belts, whereas sensory sensitivity can be assessed e.g. with the sensory inventory (SI). Thereby, personally reported alterations in sensory sensitivity can be included in coping strategies. Sensory sensitivity can further be used to better understand atypical reactions, altered social contacts or withdrawal and might help relatives and caregivers to attribute untypical behavior. This might help in coping with the situation, increase well-being, and reduce anxiety related to the well-being of the affected person. Further, the knowledge of possibly lower body perception can be included in the estimation of pain and illness in (maybe lacking or incomplete) reports and therefore improve medical assistance when needed or used to develop and try special training techniques to improve body perception ability. In addition, there might be a use of sensory sensitivity in evaluating and monitoring prodromal and residual symptoms helping for example in reducing relapse risk, but data is lacking so far. Altered respiration parameters could be used for a respiration focused training intervention which might impact symptoms and alterations in mental health. Of course, achieving lower RPV and lower respiration frequency would then be the main focus but interestingly there are several hints for possible additional positive effects like increase of body perception ability, lower DMN – parahippocampal connectivity, and the assistance in learning to relax in and to cope better with stress and overwhelming situations.

5.3 Limitations

One limitation is that there are no data available on respiration and the DMN in autism although the strongly reduced body perception found for autism might hint to both aspects being important in autistic individuals as well and beyond the finding that depression is a common problem in autism.

Further, some connections proposed in the scheme are based only on few findings and reports. Studies addressing these connections are necessary and very important to demonstrate whether those associations are present or not. The same is true for the directions of associations as some aspects could only be proposed as connected without a clear direction. Further, several associations are likely bidirectional but data to prove this are lacking.

An additional important point to address in future studies is that the current analyses did not directly include levels of fear and anxiety but the stress response. Fear and anxiety might influence the found connections to some extent and therefore possibly constitute a further aspect influencing the presented and proposed connections in excess of stress.

Samples of individuals at high risk for depression, acutely depressed participants and other mental disorders are necessary to be able to test the view of sensory sensitivity and RPV as important concepts in mental health in general and not only in autism and depression. In addition, variations in both features with the course of disorders have to be evaluated in detail to obtain data whether the use of them in monitoring disorders would be beneficial and reasonable as adjuvant instrument for mental disorders or in prevention programs.

5.4 Future directions

For the measurement of sensory sensitivity the sensory inventory (SI) is now available. This is a good and reliable instrument for the integration of this concept in research and clinical practice. Further, it can be tested for various disorders with regard to prodromal symptoms whether alterations might be related to the onset or course of mental disorders. This might help in the recognition of problems at a very early stage and thus have the possibility to start interventions early. In addition, it

may be used as an additional fast and cost effective tool to differentiate between disorders that commonly share various symptoms (e.g. autism and ADHD). Also residual symptoms might be caught by the SI and therefore the knowledge might help to reduce reoccurrence or relapse risk if additional focused help is possible which might help to alter interventions and everyday interactions with respect to variations in sensory sensitivity. This might increase e.g. effectivity of interventions but also mood in affected individuals, as she or he might feel more accepted and involved. Further, it might also help relatives and caregivers to better understand possible atypical reactions and with that possibly reduce negative feelings of relatives.

With regard to respiration, first promising results for respiration focused trainings were recently shown for individuals who survived the earth quake in Japan 2013 and practiced a mainly respiration-based mediation which lead to more positive feelings, less fatigue, and less depressive symptoms (Iwakuma, Oshita, Yamamoto, & Urushibara-Miyachi, 2017). In addition, a pilot study showed positive effects of such a meditation on depressive symptoms in patients with depression who did not adequately respond to medication (A. Sharma, Barrett, Cucchiara, Gooneratne, & Thase, 2017). Thus, examining the effects of a standardized respiration focused training without a meditation component could be a next step in which a deeper understanding of the associations of respiration and depression might help to adapt and improve intervention strategies.

And finally, a research program which brings the two main concepts of this thesis, sensory sensitivity and respiration pattern variability, even closer together would be very interesting. Analyses should not only include the behavioral level (like body posture measurements for analyzing the relation to respiration), but could range from genetic (like alterations in genetic variations of the tryptophan and cortisol metabolisms) and epigenetic (like stress effects on epigenetic markers of the aforementioned metabolisms) via neural (like influence of fear and anxiety related brain areas like thalamus or insula; volumetry to compare brain regions like the PHG in respiration training vs. no training) up to other biological features (like tryptophan levels in the blood as well as levels of other substances related to these concepts like vitamin D or specific bacteria or protozoa etc. like *toxoplasma sp.*).

6 SUMMARY

Sensory perception and respiration are two core features fundamental for human life, behavior and well-being. We are only able to live when we breathe and to understand the world when we perceive stimuli from it which we then interpret. Both features vary between individuals and between situations, for example during emotional challenges, and are likely relevant for mental health. Initial evidence suggests that body perception and respiration are coupled, but systematic research about their relationship and their association with mental disorders is currently lacking.

The presented work aims at advancing the understanding of sensory sensitivity and respiration pattern variability with regard to mental disorders and proposes biological mechanisms linking both together. Based on the results of two studies, one with autistic and one with remitted depressed participants, and supplemental analyses of a large independent sample these relationships are addressed.

In a sample of autistic individuals, sensory sensitivity was assessed with the sensory inventory, a newly developed standardized questionnaire on sensory sensitivity in which higher sensory sensitivity in autistic individuals was found. Scores of the inventory could further be used to discriminate autistic individuals with a sensitivity of 92% correctly from controls. In another sample more sensory content of memories was found to be related to increased memory for autobiographical events, pointing to a high relevance of sensory features in autism. In the second study, remitted depressed participants underwent a sad mood induction functional magnetic resonance imaging paradigm with negative autobiographical events as cues and were also assessed with the sensory inventory. In the remitted depressed participants higher respiration pattern variability during sad mood was found which was associated with lower body perception ability, worse outcome and relapse, and increased default mode network connectivity in comparison to healthy controls, demonstrating the importance of both concepts and their relationship in depression. Furthermore, in autistic and formerly depressed participants body perception was lower in comparison to controls, suggesting a broader distribution of this sensory alteration in mental disorders.

These relationships of sensory features as well as respiration and associated alterations with the intensity and course of mental disorders might also highlight important concepts for the development of future sensory and respiration-based

interventions. Sensory aided trainings for everyday activities and interactions could be helpful to better memorize learned content. Respiration focused training could be a promising additional tool as it might not only influence respiration directly but also body perception, default mode connectivity and could be helpful for coping with stress and relaxing in general. Taken together, the present thesis might stimulate an increased attention of body related processes like sensory sensitivity and respiration pattern variability in the investigation of causes and treatments of mental disorders.

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8 PUBLICATIONS

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Bähner, F., Demanuele, C., Schweiger, J., Gerchen, M.F., Zamoscik, V., Ueltzhöffer, K., Hahn, T., Meyer, P., Flor, H., Durstewitz, D., Tost, H., Kirsch, P., Plichta, M.M., & Meyer-Lindenberg, A. (2015). Hippocampal Dorsolateral Prefrontal Coupling as a Species-Conserved Cognitive Mechanism: A Human Translational Imaging Study. *Neuropsychopharmacology 40 (7):* 1674-81.

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