Changes in event-related brain responses and habituation during child development – A systematic literature review

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HIGHLIGHTS

- With habituation, grade of neuronal maturity/integrity can be investigated from an early age.
- Behavioural studies are being increasingly complemented by neurophysiological measurements.
- Developmental changes in event-related brain responses should be considered.

ABSTRACT

Objective: This systematic review highlights the influence of developmental changes of the central nervous system on habituation assessment during child development. Therefore, studies on age dependant changes in event-related brain responses as well as studies on behavioural and neurophysiological habituation during child development are compiled and discussed.
Methods: Two PubMed searches with terms "(development evoked brain response (fetus OR neonate OR children) (electroencephalography OR magnetoencephalography))" and with terms "(psychology habituation (fetal OR neonate OR children) (human brain))" were performed to identify studies on developmental changes in event-related brain responses as well as habituation studies during child development.
Results: Both search results showed a wide diversity of subjects' ages, stimulation protocols and examined behaviour or components of event-related brain responses as well as a demand for more longitudinal study designs.
Conclusions: A conclusive statement about clear developmental trends in event-related brain responses or in neurophysiological habituation studies is difficult to draw. Future studies should implement longitudinal designs, combination of behavioural and neurophysiological habituation measurement and more complex habituation paradigms to assess several habituation criteria.
Significance: This review emphasizes that event-related brain responses underlie certain changes during child development which should be more considered in the context of neurophysiological habituation studies.

1. Introduction

1.1. Development of the human central nervous system (CNS)

When a human develops up from a fetus over childhood to adolescence, the brain undergoes continuous changes. During the third week after conception, the development of the human nervous system proceeds by expanding the neural plate – the origin of most of the neurons in the CNS. The development of the human CNS is characterized by cell proliferation, cell division, cell migration, cell aggregation, apoptosis and formation of networks (for a detailed

overview on intra-uterine anatomical brain development see (Pinel, 2003)). The development of white matter and the related progress of myelination begin before birth and persist, with area-specific differences, until adulthood (Lebel and Beaulieu, 2011; Lebel et al., 2008). The processes of CNS development are therefore not finished at birth but continue over the entire life span.

In earlier days, the development of the human brain, especially before birth, could be investigated only by post mortem studies. The invention of ultrasound observation of fetuses enabled the investigation of brain structure during the fetal period in vivo, as well as fetal inner organs and fetal movements. Moreover, as an indicator for stimulus perception and neuronal processing, fetal behavioural responses to external stimulation were evaluated by ultrasound. In most studies, the stimulation was acoustic or vibro-acoustic and applied outside of the maternal abdomen (Leader et al., 1982b; Bellieni et al., 2005; Shalev et al., 1989). However, despite providing important insight into brain development, behavioural studies could only indirectly explain brain functioning and were unable to directly illuminate functional brain processes. Thanks to technological advances, behavioural studies are now complemented by neurophysiological measurement methods.

Unlike behavioural observation, the neurophysiological measurement methods electroencephalography (EEG) and magnetoencephalography (MEG) meant that neuronal activity could be evaluated directly with a high spatial and temporal resolution. The first EEG recording of a human scalp was performed by Berger in 1911 (Berger, 1929). EEG measurements register changes in electrical neuronal activity on the scalp while MEG measurements register changes in the magnetic fields produced by neurophysiological activity. It should be noted that both methods are completely non-invasive. While in neonates both EEG and MEG are applicable, advances of the fetal magnetoencephalography (fMEG) technique allowed for neurophysiological measurement of event-related responses to auditory and visual stimulation already during the fetal period. In addition to fetal measurements, it is possible to measure event-related brain responses of neonates with fMEG devices. Both EEG and (f)MEG are suitable for measuring event-related responses in infants and children. However, depending on the age of the participants, the kind of stimulation and external conditions, each method has its advantages as well as its specific limitations. MEG devices tend to be more expensive and hence less available. Special MEG systems for children and fMEG devices are rarely accessible. One necessary prerequisite for the evaluation and interpretation of both behavioural and neurophysiological responses related to external stimulation is the functional development of the auditory and visual system. Prenatally, detection and discrimination of sounds is possible, and the development of sound localization, as well as improved sound source acuity and sound discrimination, occurs during the first years of life (Anbuhl et al., 2017). Shortly after the rapid anatomical maturation of the auditory system during the second trimester of pregnancy, the first studies evaluated auditory experiences in fetuses between the 25th and 30th week of gestational age (GA) (for review see (Moore and Linthicum, 2007)). Birnholz et al. detected first responses to vibroacoustic stimulation in fetuses between the 24th and 25th week GA by monitoring blink-startle reflexes ultrasonically (Birnholz and Benacerraf, 1983). Stable behavioural responses across the study group were observed at a GA of 28 weeks. Detection of different pure tone frequencies could be shown over the course of fetal development (Hepper and Shahidullah, 1994). First behavioural responses to 500 Hz tone stimuli in single subjects were detected at 19 weeks GA. At an age of 27 weeks GA, almost the whole sample of fetuses showed reactions to stimulation in the frequency range between 250 Hz and 500 Hz. The authors also ascertained that responses to higher frequencies of around 1000 Hz could be detected at 33 weeks GA,

whereas responses to 3000 Hz tones were not detected until 35 weeks GA (Hepper and Shahidullah, 1994). Other groups confirmed similar gestational ages for fetal responses to auditory stimulation (Querleu et al., 1988).

Visual stimulation in the prenatal period has, by comparison, been less well researched than auditory stimulation. It is important to note that not all parts of the visual system are mature before birth, but mature further during the first year of postnatal life. While scotopic vision (vision under low-light condition) becomes functional during the prenatal period between the 24th and 40th week GA, photopic vision (vision under well-lit conditions) requires the influence of direct light and is not functionally mature before birth (Graven and Browne, 2008). First brain responses to light flashes in the prenatal period have been detected as early as at the age of 28 weeks GA (Eswaran et al., 2004).

1.2. Auditory and visual event-related brain responses

Event-related brain responses show characteristic waveforms that consist of different components. The latter can be categorized into three types: exogenous components, endogenous components and motor components. Exogenous components, typically triggered by sensory stimuli, are modulated by characteristics of stimuli and occur in the first 150 ms after stimulus presentation. Unlike exogenous components, endogenous components are influenced by top-down-processes, consciousness and attention. This type of component is modulated by task relevant processes and is not entirely connected to the occurrence and physical aspects of a stimulus. The third category, motor components, emerges during preparation and execution of a motor response (Luck, 2005). Although in some cases the boundaries of these three categories are fluid, it is nevertheless a useful way of differentiating between event-related brain response components. The comparison of specific response components within participants of different age groups can therefore provide information about the development of distinct cognitive skills.

1.3. Habituation

The investigation of event-related responses facilitates the assessment of stimulus perception and processing by the direct examination of underlying neural correlates. The exploration of higher cognitive skills such as recognition or memory, however, requires complex stimulation paradigms. Habituation, as a form of basal learning competence, is one established concept for examining such higher cognitive processes. Habituation is commonly defined as "response decrement to repetitive stimulation" (Thompson and Spencer, 1966). However, alternative explanations for this process could be sensory adaptation or fatigue, defined as a state of decreased neuronal sensitivity as a result of constant stimulation (Carandini, 2000; Netser et al., 2011). To differentiate between these two possible sources of response decrement to repetitively presented stimulation, Thompson et al. developed criteria of habituation, which were later revised to provide ten characteristics of habituation by Rankin et al. (Supplementary Table S1) (Thompson and Spencer, 1966; Rankin et al., 2009).

In habituation studies, many different types of stimulation are applied. In addition to visual, tactile and auditory stimuli, combinations of two different sensory perceptions are used, e.g. vibroacoustic stimulation. The stimulation is selected on the characteristics and age of the participants and on the respective method of measuring habituation. In fetal studies, auditory stimulation is the predominant method. Visual stimulation is less feasible inside the maternal abdomen, even if stimulation with light flashes in fetal studies provides an additional possibility of stimulation. In neonates, visual and tactile stimuli gain importance in

addition to auditory stimulation (Adams and Courage, 1995; Lejeune et al., 2014).

Characteristics of stimuli (loudness, time of repetition, intervals between or modalities of presentation) may affect the processes of habituation as well as the internal condition of the subject under investigation (motivational aspects, state of behaviour, inner evaluation processes and current interests) (Butler, 1968; Barry, 2004; Ponce et al., 2011; Gatchel and Lang, 1974).

The most frequently investigated premises of habituation over the last decades were the characteristics *response decrement*, *stimulus specificity* and *dishabituation*. Many studies reported habituation merely by the occurrence of *response decrement* over repetitively presented stimulation (Clifton et al., 1968; Groome et al., 1995; Hepper et al., 2012). Other studies used two or more of the characteristics to differentiate between habituation and sensory fatigue: *stimulus specificity* and *dishabituation* (Marcus et al., 2012; Lejeune et al., 2014). *Stimulus specificity* is defined by response recovery to a new stimulus (deviant), which is inserted into an array of repetitively presented standard stimuli and which is often wrongly labelled as *dishabituation*. Leader et al. discussed the lack of distinctiveness between stimulus specificity and dishabituation as early as 1982 (Leader et al., 1982a). The term *dishabituation*, however, should be used to describe response recovery to the habituated standard stimulus itself once the deviant stimulus has been inserted (Rankin et al., 2009).

To distinguish habituation clearly from other phenomena that may cause a response decrement (for example sensory fatigue, refractoriness or adaptation), several of the criteria postulated by Rankin et al. should be investigated simultaneously (Berry and Meister, 1998; Perez-Gonzalez and Malmierca, 2014; Rankin et al., 2009). Already Thompson and Spencer suggested that the process of dishabituation should be used as a main indicator for real habituation (Thompson and Spencer, 1966). Rankin et al. propose in addition to test for stimulus specificity and frequency-dependent spontaneous recovery (Rankin et al., 2009). Both, dishabituation and stimulus specificity are therefore particularly suitable criteria to confirm habituation that can easily be integrated into habituation paradigms (Fig. 3).

To investigate habituation in humans, two different types of habituation paradigms are commonly used. In behavioural studies, stimulation is often repeated until response cessation, and habituation is quantified by the number of stimuli required before responses reach an asymptotic level (Kuhlman et al., 1988; Leader et al., 1982b). Alternatively, a predefined number of stimuli is presented and habituation is quantified by the amount of response decrement over this presented array (Sörös et al., 2001; Sheridan et al., 2008; Matuz et al., 2012). This method has the advantage of being less time consuming and is therefore often used in neurophysiological studies of infants and children.

Habituation is an established tool to investigate specific markers of behavioural and neurophysiological measures altered in disease states. Differences in habituation between patients and controls were found in migraine patients, in persons with autism spectrum disorder, with schizophrenia and with neurodegenerative disease (McDiarmid et al., 2017). For the field of neurodevelopmental research, habituation is particular well suitable because it can be applied without any specific behavioural response and is applicable over a wide age range. The recorded neurophysiological or behavioural correlates of habituation can be therefore used as markers for a healthy neurophysiological developmental process.

1.3.1. Behavioural habituation measurement

As early as 1963, Sokolov et al. described a decrement of the orienting reflex (a reaction to a novel or significant stimulus) which is characterized by three criteria: (1) nonspecificity with regard to the quality of the stimulus, (2) nonspecificity with regard to the

intensity of the stimulus and (3) selectivity of extinction of various properties of the stimulus with repeated presentation (Sokolov, 1963a). While the term "extinction" is comparable to "habituation", they used the term "disinhibition" similar to response recovery (Sokolov, 1963b). The first behavioural habituation studies were then published in the early 1980s (Schexnider et al., 1981; Leader et al., 1982b). To obtain higher objectivity in these trials, visual examination of a predefined behavioural response to a stimulus paradigm was often combined with videotaped recordings or other technology such as computer assisted recording programs, ultrasound monitoring of fetal behaviour, assessment of eye movements or fixation time (Groome et al., 1993; Groome et al., 1995; Leader et al., 1982b; Sommerville and Woodward, 2005). Moreover, implementation of special observer trainings, categorized documentation systems and calculation of inter-rater reliability are useful tools for minimizing observer effects that might influence data evaluation.

Reflexive action that is not controlled by conscious thoughts, such as the fetal startle response, is a behavioural component to assess habituation that is present in early fetal development. Its decrease is deemed a suitable marker for fetal habituation (Bellieni et al., 2005). The fetal startle response manifests itself not only by body movements but also by vegetative responses such as a change in heart rate (Buss et al., 2009; Sandman et al., 1997). A number of fetal studies therefore combine behavioural assessment and measurement of heart rate changes using ultrasound or transabdominal transducers (Groome et al., 1993; Leader et al., 1984). A further method of assessing habituation is to measure fixation time of participants to visual stimuli. In the past, gaze behaviour was mainly evaluated by observers. However, nowadays, eye-tracking-systems enable us to precisely and objectively record the direction and course of the subject's gaze (Streri and Pecheux, 1986).

Besides the reflexes, participants' conscious actions are an observable dependent variable in behavioural habituation studies. Tactile stimulation is a suitable method for examining habituation in neonates or premature infants and the duration of time that participants explore an object in their hands can be used as a marker for familiarization with its specific features (Lejeune et al., 2012; Sann and Streri, 2008; Lejeune et al., 2014; Streri and Pecheux, 1986).

1.3.2. Neurophysiological habituation measurement

As technology advanced, the behavioural concept of habituation was complemented by studies that analyse neurophysiological activity directly (Weber et al., 2016; Muenssinger et al., 2013c). Habituation, investigated with neurophysiological measurements, enables us to examine the underlying neuronal processes responsible for observable changes in behavioural habituation. In this context, amplitudes of event-related responses are used to detect habituation criteria analogous to behavioural responses (for details, see Section 2).

However, to date, most studies investigating habituation have been based on behavioural observations and only a small number of studies used neurophysiological measurement methods.

1.4. Objective

The aim of this review was to summarize results of habituation studies during child development with a focus on neurophysiological habituation measurements, based on the analysis of event-related brain responses.

Particularly during the first years of life, there is progressive development of the CNS (e.g. myelination, synaptic plasticity, formation of networks). These developmental changes cause changes in event-related responses (especially alterations in amplitude and

latency). As the investigation of event-related responses therefore allows to draw inferences in regard to the development of neural structures and/or neural functions, a general overview of studies on *"age-related changes in event-related brain responses"* is included. Here, the focus is on alterations in amplitude and latency linked to auditory and visual stimulation in the prenatal, postnatal and childhood period as the analysis of event-related brain responses is the most common technique for the investigation of neurophysiological habituation. We then performed a PubMed search on *"habituation studies during child development"* to analyse different methods of stimulation, response evaluation and the criteria used to differentiate between habituation and receptor fatigue. Finally, having drawn conclusions from the insights of both queries, we make recommendations for the evaluation of earlier studies and design of future trials.

2. Methods

This systematic review summarizes research data of studies investigating the development of event-related brain responses and habituation during childhood. For this purpose, relevant literature from the PubMed database was thoroughly reviewed in two independent searches. To summarize studies relating to *"age-related changes in event-related brain responses"*, a first search with certain terms "(development evoked brain response (fetus OR neonate OR children) (electroencephalography OR magnetoencephalography))" was performed. The term "evoked" was sought instead of "event-related" since use of the former has become more widespread in the last few decades. A second search with the terms "(psychology habituation (fetal OR neonate OR children) (human brain))" was used to identify *"habituation studies during child development"*.

Studies resulting from the search *"age-related changes in event-related brain responses"* were screened for the following inclusion criteria:

- Youngest age group <12 years
- Measurement of brain activity by EEG or (f)MEG
- Developmental processes within research question, including a comparison between at least two different age groups (cross-sectional or longitudinal)
- Healthy subjects or healthy control groups (except preterms)
- Original research articles

To enable a better comparison, it is generally established to label EEG components time-locked to a stimulus by the following definitions: "P" or "N" (P = positivity; N = negativity) combined with an integer number that approximately represents the mean latency of occurrence in milliseconds or the component number (for example "P100" or "P1"). Similarly, responses in (f)MEG studies are typically labelled with "M" followed by latency in ms or by component number (for example "M100", "M1"). Moreover, the respective amplitudes of event-related responses can be analysed. The typically described and frequently analysed components of a "Cortical Auditory Evoked Potential" (CAEP) include P1, followed by N1, P2 and N2 and P300 (Fig. 1). The typical "Cortical Visual Evoked Potential" (CVEP) shows components N1, P1, N2 and P300 (Fig. 2).

In neurophysiological habituation studies, characteristics of habituation can be observed by changes in amplitudes of event-related responses elicited by stimuli arranged in habituation paradigms (Muenssinger et al., 2013b). The observed components depend on the measurement method, the respective stimulation modality (auditory/visual/tactile) and the features of applied stimuli.
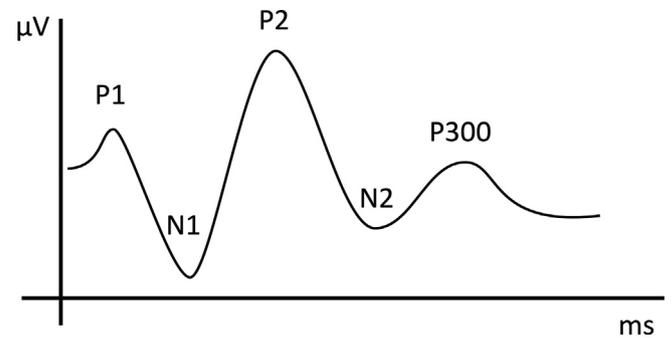
Fig. 1. Typical cortical auditory-evoked potential (CAEP) with the most prominent components P1, N1, P2, N2 and P300.
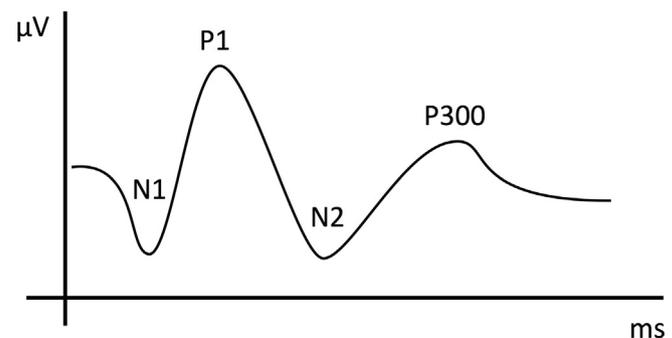
Fig. 2. Typical cortical visual-evoked potential (CVEP) with the most prominent components N1, P1, N2 and P300.

Studies resulting from the second search "*habituation studies during child development*" were screened for the following inclusion criteria:

- Youngest age group <12 years
- Healthy subjects or healthy control groups (except preterms)
- Repeated stimulation with evaluation of response characteristics
- Original research articles

Reference sections of studies that fulfilled inclusion criteria were also screened for further potentially relevant articles. Figs. 4 and 5 show the systematic literature review process. Characteristics, methods and results, as well as limitations and perspectives of exemplary studies, are summarized and discussed in the following sections.

3. Results and discussion

To simplify the overview of studies, age was grouped as depicted in Table 1 (Schneider and Lindenberger, 2012).

3.1. Age-related changes in event-related brain responses

In our first query, we searched for studies investigating event-related brain responses during child development. Table 2 shows a total of 85 studies that fulfilled the inclusion criteria for the first query. The number of participants varied between 10 and 586 with a median of 56. A longitudinal design (identified by "*") was chosen in 13 trials. A total of 72 studies recorded event-related responses by EEG and 12 studies by MEG or fMEG. One study used both EEG and MEG (Fig. 6).
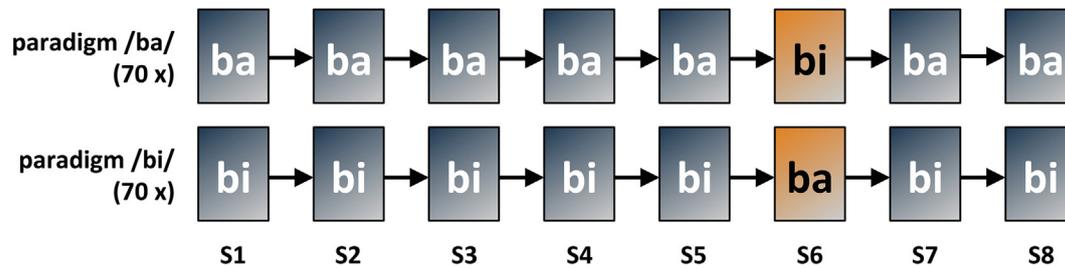
Fig. 3. Example for an auditory habituation paradigm. The paradigm enables testing for response decrement, stimulus specificity and dishabituation by presenting spoken syllables (Hartkopf et al., 2016).
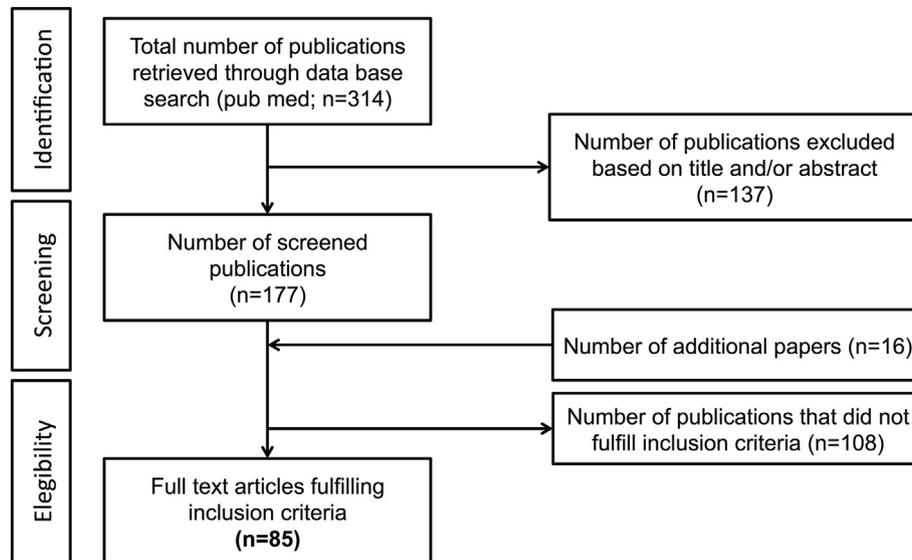
Fig. 4. Flow chart of literature review process and strategy of selection of relevant publications for search *"age-related changes in event-related brain responses"*.
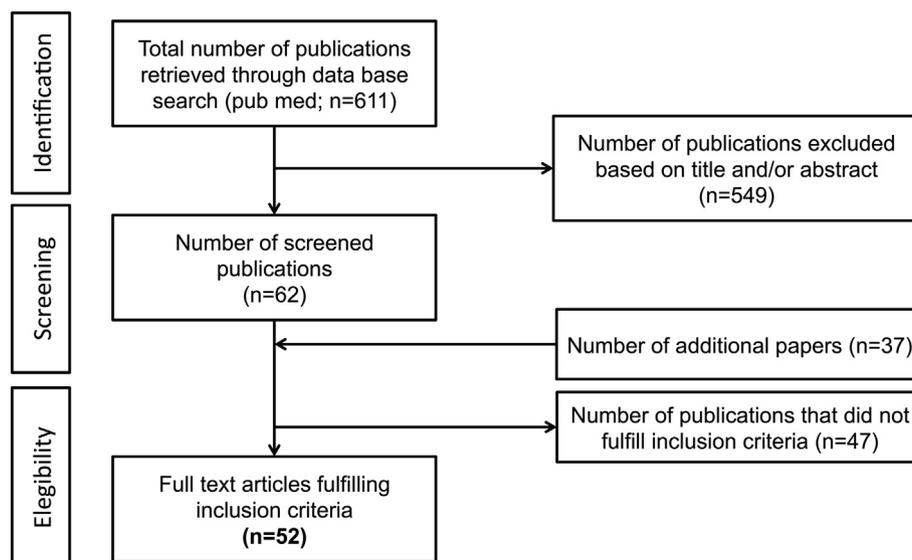
Fig. 5. Flow chart of literature review process and strategy of selection of relevant publications for search *"habituation studies during child development"*.

In one study, MEG was complemented with DTI (Diffusion Tensor Imaging), a non-invasive method for determining the anatomical connectivity of different brain regions by tracking white matter fibres, while another study used MRI alongside MEG to investigate the anatomical brain structure in more detail (Chen et al., 2010).

Changes in event-related brain responses during child development were shown in 73 of 85 studies. These changes may comprise different aspects of event-related brain responses. For example, an MEG-study using visual stimulation that compared children and adults (mean age 11 and 30 years respectively) showed a decrease

Table 1
Age-group classification of study populations.

Age category	Age in years	Developmental stage
1	<0	Fetal
2	0–2	Earliest childhood
3	2–6	Early childhood
4	6–12	Childhood (6–8: middle childhood; 9–12: late childhood)
5	12–18	Adolescence
6	>18	Adulthood

of latency and an increase of response amplitudes with increasing age (Chen et al., 2010). Although a majority of studies investigated age-related changes of event-related brain responses in 0–2 year old children, the changes appeared to persist up until late adolescence (Mahajan and McArthur, 2012). Importantly, fMEG studies demonstrated that developmental changes are already observable during the fetal period (Schneider et al., 2004; Eswaran et al., 2004).

For further investigation, we decided to focus on two component ranges: first, developmental changes in the exogenous components N1 (first negativity) and P1 (first positivity) and second, developmental changes in the later components P2, N2 and P300.

3.2. Age-related changes in primary exogenous event-related brain responses

3.2.1. Auditory P1

Seven studies using auditory stimulation investigated age-related changes in component P1 (Supplementary Table S2). Two studies showed that a typical P1 was not identifiable in very young participants. While one of these studies investigated preterm infants, and ascertained that the P1 component emerged between 37 and 38 weeks of gestational age, a second trial did not detect the component until an age of about 5 years (Weitzman et al., 1967; Lippe et al., 2009). However, different kinds of stimulation were used. The three studies analysing latency reported a decrease of latency with increasing age. Stimulation features such as inter-stimulus interval (ISI) and stimulus onset asynchrony (SOA) also have an influence on the latency and amplitude of the P1 component.

3.2.2. Auditory N1

Four studies investigated changes of the N1 component by comparing latencies and/or amplitudes between different age groups (Supplementary Table S3). However, these studies all differed with respect to the stimulation applied. Two studies showed an increase of the N1 amplitude. In one of these two trials, a go-/no-go task and a stop-signal-task were presented to children between seven and nine years of age, and the increase of amplitude was detectable only for auditory stop-signals in the parietal region (Johnstone et al., 2007). The second study showed an increased amplitude of evoked responses after presenting pure tones and syllables in children and adolescents aged between 10 and 18 years than in adults (Mahajan and McArthur, 2012). A further study, in which clicks were used to stimulate a younger group of children between 23 and 47 weeks of age, reported a decrease in latency (Weitzman et al., 1967). Sussman et al. investigated the influence of different kinds of pure tones with changing stimulation paradigm features (Sussman et al., 2008). Differences in amplitude and latency between age groups were, however, not statistically analysed and the N1 component, which was probably dependent on the stimulus rate, was visible in only a small number of the participants aged between 8 and 11 years.

The latency of the early auditory components P1 and N1 as exogenous components showed a tendency of becoming shorter as age increased. From the 11 studies that investigated either the auditory component N1 or P1, five studies confirmed this tendency by statistical analysis. Due to the fact that the focus was on changes in amplitudes, latency was not analysed in the other six studies. The phenomenon of a decrease of latency with age could be explained by the myelination of nerves that accelerates conduction (Pihko et al., 2009).

Findings were diverse with regard to the amplitudes of event-related responses. Most trials included participants of various age ranges, and almost all of the studies used different kinds of stimuli and stimulation paradigms. Given that age is associated with the degree of maturity of the CNS and that the applied stimulation impacts the elicited event-related responses, the lack of a developmental trend in amplitude heights of the compiled studies seems natural.

3.2.3. Visual N1

In all four studies, an age-dependent decrease in latency of the visual N1 was shown independent of the kind of stimulation and age of the participants (Supplementary Table S4). One of the studies also detected an increase in the amplitude of N1 with age; in the other trials there was no consistent age-related effect on the amplitude of N1. (Hirai et al., 2009; Lippe et al., 2007; Tremblay et al., 2014). In addition to stimulation type and age, the hemisphere under investigation seemed to have an influence on the amplitude and its potential developmental changes, thus contributing to the heterogeneous results.

3.2.4. Visual P1

Four out of eight studies observed a decrease in latency of the visual P1 with increasing age, while one showed only a partial decrease (Supplementary Table S5). An increase in amplitude was shown in only two studies, one of which did not perform a statistical test for significance. Five trials reported a decrease in amplitude as age increased. This observation was independent of stimulation conditions (all five studies applied different stimuli) and observable over various age groups. In three of these five studies, participants were six years of age and older, while very young participants (aged between 0 and 2 years) were investigated in the other two studies.

The type of visual stimulation varied in all five studies and an influence of stimulus complexity on the development of the component P1 can be excepted (Sokol and Jones, 1979). The diversity in age of the participants and the methodical differences of conditions mean that it is difficult to draw a firm conclusion with regard to the developmental changes observed in visual P1.

3.3. Age-related changes in primary endogenous event-related brain responses

3.3.1. Auditory P2

The four studies that investigated auditory P2 did not show consistent results with regard to age-related changes (Supplementary Table S6). P2 component appears to become more prominent during the first months of life and is influenced by the type of stimulation (Lippe et al., 2009). SOA levels of pure tones, as well as different conditions at a go-/no-go-task (response inhibition vs. response execution) affect the P2 (Sussman et al., 2008; Johnstone et al., 2007). Although amplitude of P2 was found to increase in one study stimulating with broadband noise, the P2 did not emerge until about the fifth year of life. Only one study carried out with premature infants registered a decrease in latency of P2 with increasing age within the first weeks after birth (Weitzman et al., 1967).

Table 2
Age-related changes in event-related brain responses. Columns represent number of subjects (N), method of event-related brain response evaluation, the respective age groups and whether or not a developmental trend could be observed. Asterisks (*) indicate studies that used a longitudinal design; EEG = electroencephalography; MEG = magnetoencephalography; DTI = diffusion tensor imaging; MRI = magnetic resonance imaging; PCA = principal component analysis; n.a. = not applicable.

Study	N	Method	Age fetal	Age 0–2	Age 2–6	Age 6–12	Age 12–18	Adults	Development trend	Kind of component investigated
(Agyei et al., 2016)*	20	EEG		x					yes	endogenous
(Anderson et al., 2015)	28	EEG		x					yes	exogenous (brainstem)
(Atchley et al., 2006)	29	EEG			x	x		x	yes	endogenous
(Babkirk et al., 2015)*	32	EEG			x	x			n.a. (prediction)	endogenous
(Brinkman and Stauder, 2007)	112	EEG			x	x		x	yes	exogenous
(Brinkman and Stauder, 2008)	122	EEG			x	x		x	yes	exogenous
(Brusini et al., 2016)	45	EEG			x			x	n.a.	endogenous
(Butler and Trainor, 2013)	60	EEG		x					yes	exogenous
(Byrne et al., 1999)	56	EEG			x	x	x		yes	endogenous
(Chan et al., 2015)	44	EEG				x		x	yes	exogenous/endogenous (NF, P1, N1)
(Chen et al., 2010)	80	MEG/MRI			x	x		x	yes	exogenous
(Chevalier et al., 2015)	64	EEG			x	x			yes	endogenous
(Cho et al., 2015)	188	EEG				x	x	x	yes	not relevant (frequency domain)
(Clery et al., 2012)	24	EEG				x	x	x	yes	exogenous
(Cody and Townsend, 1973)	179	EEG		x	x			x	no	exogenous/endogenous
(Cragg et al., 2009)	56	EEG				x			yes	endogenous
(Cummings et al., 2008)	28	EEG			x	x			yes	endogenous
(Davies et al., 2004a)	124	EEG			x	x		x	yes	endogenous
(Davies et al., 2004b)	153	EEG			x	x		x	yes	endogenous
(Eswaran et al., 2004)	12	fMEG	x						yes	endogenous
(Eswaran et al., 2005)	11	fMEG	x						n.a.	unclear
(Fabrizi et al., 2011)	46	EEG		x					yes	exogenous/endogenous
(Fox et al., 2010)	43	EEG				x	x	x	yes	exogenous
(Friedrich and Friederici, 2005)	113	EEG		x				x	yes	endogenous
(Fuchigami et al., 1993)	175	EEG			x	x	x	x	yes	endogenous
(Fuchigami et al., 2009)	99	EEG			x	x	x	x	yes	endogenous
(Fujioka et al., 2006)*	12	MEG		x	x				yes	exogenous/endogenous
(Gebuis et al., 2009)	51	EEG			x	x		x	yes	endogenous
(Gorga et al., 1989)	535	EEG			x	x			yes	exogenous
(Hadley et al., 2015)*	70	EEG		x	x				n.a. (training and follow up)	exogenous/endogenous
(He et al., 2015)	30	MEG			x			x	yes	exogenous/endogenous (M100, M170)
(Hirai et al., 2009)	60	EEG			x	x			yes	exogenous/endogenous
(Jansen-Osmann and Heil, 2007)	72	EEG			x	x		x	yes	endogenous
(Jeng et al., 2010)	18	EEG		x				x	no	not relevant (frequency domain)
(Johnstone et al., 2007)	24	EEG				x	x		yes	exogenous/endogenous
(Jonkman et al., 2003)	25	EEG				x		x	yes	endogenous
(Kihara et al., 2010)	178	EEG			x	x			yes	exogenous/endogenous
(Kimura et al., 2004)	24	MEG/EEG				x	x	x	yes	exogenous
(Kujawa et al., 2015)*	559	EEG			x	x			n.a.	endogenous
(Kushnerenko et al., 2001)	18	EEG		x				x	n.a.	endogenous
(Lamm and Lewis, 2010)	49	EEG				x	x	x	no	endogenous
(Lasky, 1984)	40	EEG		x				x	yes	exogenous
(Lauronen et al., 2006)	41	MEG		x				x	yes	exogenous
(Lee et al., 2012)	218	EEG		x	x	x		x	yes	exogenous
(Lippe et al., 2007)	79	EEG		x	x			x	yes	exogenous/endogenous
(Lippe et al., 2009)	40	EEG		x	x		x		yes	exogenous/endogenous
(Lo et al., 2013)	50	EEG			x	x			yes	endogenous
(Mahajan and McArthur, 2013)	100	EEG				x	x	x	yes	exogenous
(Marinovic et al., 2014)	66	EEG		x				x	yes	endogenous
(McIntosh et al., 2008)	79	EEG				x	x	x	yes (in PCA)	exogenous
(Mecklinger et al., 2011)	52	EEG				x		x	yes	endogenous
(Missana and Grossmann, 2015)	40	EEG		x					yes	not relevant (frequency domain)
(Missana et al., 2015)	40	EEG		x					yes	endogenous
(Muenssinger et al., 2013a)*	62	fMEG	x	x					n.a.	unclear
(Ojima et al., 2011)*	80	EEG				x	x	x	yes	endogenous
(Paquette et al., 2013)	40	EEG			x	x	x	x	yes	exogenous
(Pihko et al., 2009)	51	MEG		x	x	x		x	yes	exogenous
(Pincham et al., 2015)	60	EEG				x	x		yes	endogenous
(Putkinen et al., 2014a)	117	EEG				x	x		yes	endogenous
(Putkinen et al., 2014b)*	133	EEG				x	x		yes	endogenous
(Richards, 2000)	35	EEG		x					yes	exogenous
(Richardson et al., 2011)	77	EEG				x			no	exogenous/endogenous
(Roberts et al., 2009)	26	MEG, DTI				x	x		yes	exogenous

Table 2 (*continued*)

| Study	N	Method	Age fetal	Age 0–2	Age 2–6	Age 6–12	Age 12–18	Adults	Development trend	Kind of component investigated
(Rojas et al., 1998)	22	MEG				x	x		yes	exogenous
(Rojas-Benjumea et al., 2015)	176	EEG				x	x	x	yes	endogenous
(Rueda et al., 2004)	40	EEG			x			x	yes	exogenous/endogenous
(Santesso et al., 2006)	67	EEG			x			x	yes	endogenous
(Schipke et al., 2011)	87	EEG		x	x				yes	endogenous
(Schipke et al., 2012)	109	EEG		x	x	x		x	yes	endogenous
(Shafer et al., 2000)	78	EEG		x	x			x	yes	endogenous
(Skoe et al., 2015)	586	EEG	x	x	x	x	x	x	yes	exogenous (brainstem)
(Sussman et al., 2008)	61	EEG				x	x	x	yes	exogenous/endogenous
(Tremblay et al., 2014)	72	EEG		x					yes	exogenous/endogenous (N1)
(Uppal et al., 2016)	53	EEG			x	x			yes	exogenous/endogenous
(van den Boomen et al., 2014)	111	EEG				x	x		yes	exogenous/endogenous
(van der Meer et al., 2012)*	10	EEG		x					yes	endogenous
(Vanvooren et al., 2015)	67	EEG			x			x	yes	not relevant (frequency domain)
(Vuillier et al., 2016)	37	EEG				x		x	yes	endogenous
(Wakai et al., 2007)*	17	MEG		x					yes	endogenous
(Waxer and Morton, 2011a)	80	EEG			x	x		x	yes	exogenous/endogenous
(Weitzman et al., 1967)*	25	EEG		x					yes	exogenous/endogenous
(Yordanova and Kolev, 1996)	80	EEG				x		x	yes	not relevant (frequency domain)
(Yoshimura et al., 2014)*	20	MEG			x	x			yes	exogenous
(Yrttiaho et al., 2014)*	125	EEG		x					n.a.	endogenous
(Zemon et al., 1997)	40	EEG		x	x	x	x	x	yes	not relevant (frequency domain)
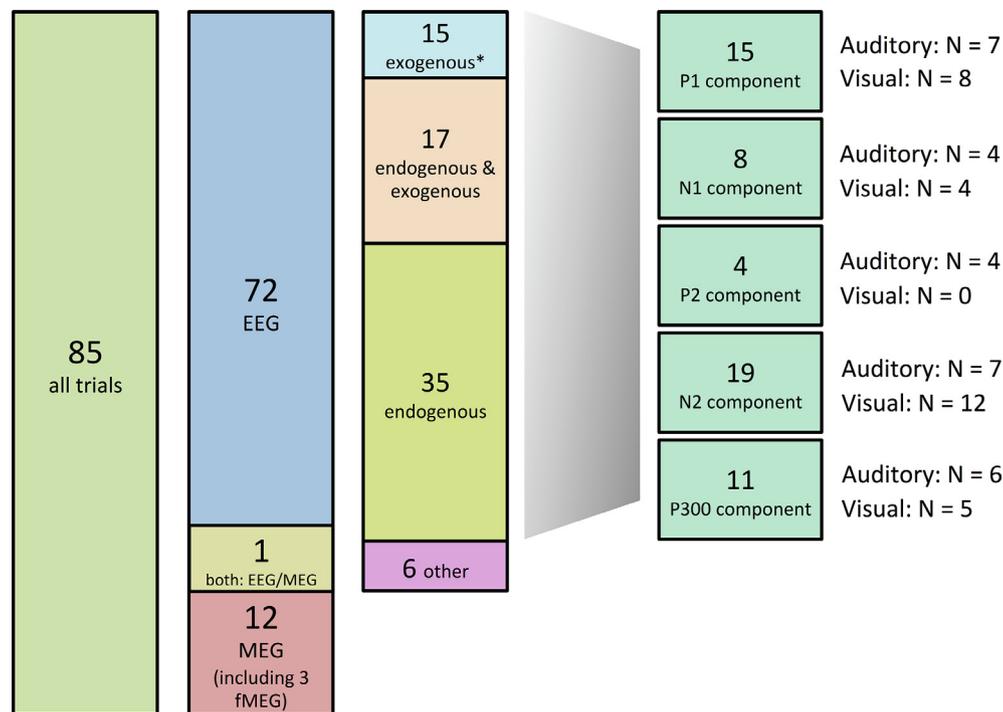
Fig. 6. Overview on studies from the search "*age-related changes in event-related brain responses*". Applied methods and the investigated components of the event-related responses are displayed. *including brain-stem responses.

3.3.2. Auditory N2

There is no consistency in age-dependent latency changes of N2 (Supplementary Table S7). Four of the seven studies investigating the N2 showed that the development of this component is dependent on the type of stimulus and the location of the electrodes. A decrease in latency was registered in one study only; all other studies found no consistent trend. Changes in amplitude are also heterogeneous. Two studies found no consistent changes, while two others reported that amplitude decreased as age increased.

3.3.3. Auditory P300

Development of auditory P300 was analysed in six trials (Supplementary Table S8). Albeit a decrease in latency with increasing age was found in three trials, two of these showed only a partial decrease, depending on what stimulation was applied. By contrast, one study showed an increase in latency. An increase in amplitude was observed in four studies, even though these changes depended on the kind of stimuli applied. The auditory P300 is supposed to represent higher cognitive processes related to working memory

such as context information, recognition or categorisation (Duncan et al., 2009). The development of this component is assumed to continue until at least adolescence.

3.3.4. Visual N2

The visual N2 was taken into consideration in twelve studies and was therefore the most frequently investigated component (Supplementary Table S9). An age-related decrease in latency was observed in six studies, however, in four of these trials the investigated age groups had a difference of at least six years. A decrease in latency of N2 with increasing age therefore seems to occur relatively slowly (Luck and Kappenman, 2011).

Although an increase of amplitude was established in four studies, one did not report a statistical test for significance (Waxer and Morton, 2011b). A further six studies registered a decline or no change of amplitude. It is, therefore, not possible to draw any conclusions about developmental changes in amplitude of the visual N2 component.

3.3.5. Visual P300

Visual P300 component was analysed in five studies (Supplementary Table S10). The majority of the studies that investigated P300 used go-/no-go or novel-target detection stimulation paradigm. One study, which used a congruency/incongruency task as its stimulus, observed a decrease in latency with age (Rueda et al., 2004). An increase in amplitude was detected in another study that investigated novelty processing by presenting faces and patterns (Kihara et al., 2010). None of the other trials showed consistent results for either a decrease in latency or/and an increase in amplitude for the visual event-related P300 component. The visual P300 is presumably influenced by memory and attention processes (Polich, 2007). The low number of studies and the inconsistent results do not permit us to make any valid conclusion with regard to developmental trends of the P300. Furthermore, the complex and diverse stimulation paradigms complicated the comparison and conclusions from these results.

3.4. Habituation studies during child development

In our second quest, we searched for studies that evaluated habituation during child development. Table 3 summarizes a total of 52 studies and shows the methods applied, type of stimulation and types of habituation criteria tested (Supplementary Table S1).

3.4.1. Participants

A total of 15 of the habituation studies were fetal studies, while 27 studies investigated habituation in infants aged between 0 and 2 years and a further 4 studies examined both fetuses and infants aged between 0 and 2 years. In all, 46 of the 52 trials investigated participants between fetal age and 24 months, thus supporting the particular suitability of habituation for the examination of early learning capability and – directly with measurement of brain activity or indirectly by behavioural analysis – for drawing conclusions about the function of the developing CNS.

3.4.2. Stimulation

Most studies used visual or auditory stimulation (14 visual stimulation, 21 auditory or vibroacoustic stimulation). Tactile/ vibrotactile stimulation (passive as well as active) was applied in 11 trials, one of which also combined tactile stimulation with visual stimulation. Six studies applied a combination of visual stimulation and auditory stimulation. In addition to response decrement following repeated stimulation, which was analysed in all of the studies, 26 trials also analysed stimulus specificity. The criterion of response decrement was found to be fulfilled in 35 of the trials, and partially fulfilled in 13 of the studies.

Twenty-eight of the studies tested for two criteria (response decrement & stimulus specificity, response decrement & dishabituation or response decrement & spontaneous recovery). Of these, 12 reported that both criteria were fulfilled. Habituation paradigms, which allow the investigation of three or more habituation criteria, were used in only 5 trials. In a tactile habituation study, Marcus et al. ascertained that premature infants already show response decrement, stimulus specificity and dishabituation to a wooden object (Marcus et al., 2012). The authors concluded that premature infants already display developed skills of memorization, discrimination and recognition to tactile explored objects. In a fetal behavioural habituation study, Leader et al. investigated 40 fetuses with vibrotactile stimulation and found evidence of habituation and dishabituation (Leader et al., 1982a). The paradigm design would even have been suitable to test for stimulus specificity, but this step was not performed since the data had not been analysed for this purpose.

3.4.3. Neurophysiological habituation studies

Of all the studies that fulfilled the inclusion criteria, habituation was analysed by direct visual observation of behavioural responses (including videotaped recordings and observation by ultrasound) in 38 studies. Eight studies evaluated changes in heart rate partly in combination with other response types such as respiration or behavioural observation. The neurophysiological activity was directly measured during the habituation procedure to examine habituation criteria in only 8 studies (Table 4).

The first habituation study we identified that used a neuroimaging method was published in the early 1990s and recorded event-related brain responses in children by EEG (McIsaac and Polich, 1992). Beside MEG or fMEG, EEG is still the most widely used neurophysiological approach in habituation studies. Besides its feasibility, the applied method depends on the aims of a study and the respective trial design. EEG, which is feasible in children and adults, is suitable not only for the measurement of temporal dynamics of event-related brain responses but also for examining spatial information by comparing signals at different electrodes. In the search, three EEG studies were found to investigate habituation in children. The study populations of these three studies varied between preterm infants, babies, children and adolescents and investigated habituation in different components of the event-related brain responses, depending on the kind of stimulation and the research question. To compare habituation in 10 infants of approximately 6 months of age with that of a group of 10 young adults, McIsacc et al. chose a paradigm that uses single tones presented in sequences (McIsaac and Polich, 1992). The component P300 was found to have a similar morphology in both groups, but peaked earlier and with lower amplitudes in infants than in adults, indicating a developmental effect. Interindividual differences in P300 were more pronounced in infants. There was no significant response decrement to repeated stimulation in either the group of infants or within young adults. The authors therefore suggested that the kind of stimulation (a passive stimulation paradigm) and the related attention processes inhibited response decline. However, the small sample size limited the generalisability of these results.

Kropp et al. used an auditory two-stimulus reaction time go/no-go task to examine habituation in migraine and healthy participants (Kropp et al., 1999). The early component of contingent negative variation (called iCNV) following the reaction to the go-stimulus was investigated. Response decrement in healthy children was not shown, whereas healthy adults habituated to the stimulation.

The third EEG-study, conducted by Weber et al., examined habituation in 17 healthy preterm infants and 16 term infants with an auditory oddball-paradigm (Weber et al., 2016). The mismatch

Table 3

Habituation studies during child development. Columns represent number of subjects (N), method and objective of response evaluation, method of stimulation, the habituation criteria used and the respective age groups. EEG = electroencephalography; MEG = magnetoencephalography; fMEG = fetal magnetoencephalography; EMG = electromyography; EKG = electrocardiogram. (Y) = habituation criterion was met; (P) = habituation criterion was partially met; (X) = habituation criterion was not met; (n.a.) = not applicable.

Study	N	Method	Objective	Stimulation	Tested habituation criteria	Age fetal	Age 0–2	Age 2–6	Age 6–12	Age 12–18	Adults
(Adams and Courage, 1995)	140	visual observation	behavioural/fixation time	visual	response decrement (Y), stimulus specificity (Y)		x				
(Adams et al., 1991)	40	visual observation	behavioural/fixation time	visual	response decrement (Y), stimulus specificity (P)		x				
(Bellieni et al., 2005)	22	ultrasound	fetal movement	vibro- acoustic	response decrement (Y)	x					
(Clifton et al., 1968)	100	polygraph	heartrate, respiration	auditory	response decrement (P)		x				
(Colombo et al., 2004)	70	EKG	changes in heart rate	visual	response decrement (Y), stimulus specificity (n.a.)		x				
(Fiser and Aslin, 2002)	24	visual observation	behavioural/fixation time	visual/auditory	response decrement (Y), stimulus specificity (P)		x				
(Groome et al., 1993)	90	ultrasound	behavioural	vibro- acoustic	response decrement (Y)	x					
(Groome et al., 1995)	56	ultrasound	behavioural/heartrate	vibro- acoustic	response decrement (Y)	x					
(Hartkopf et al., 2016)*	58	fMEG	brain activity	auditory	response decrement (X), stimulus specificity (P), dishabituation (X)	x	x				
(Hepper et al., 2012)	78	ultra-sound	behavioural	auditory	response decrement (Y)	x					
(Horst et al., 2005)	78	visual observation (videotaped)	behavioural	visual/auditory	response decrement (P), stimulus specificity		x				
(Kirkham et al., 2007)	96	visual observation	behavioural	visual	response decrement (P), stimulus specificity (P)		x				
(Kropp et al., 1999)	320	EEG	brain activity	auditory	response decrement (X)				x	x	x
(Kuhlman et al., 1988)	174	ultrasound	behavioural	vibro- acoustic	response decrement (P)	x					
(Laucht et al., 1994)	226	visual observation	behavioural/fixation time	visual	response decrement (Y), stimulus specificity (Y)			x	x		
(Leader et al., 1982a)	67	ultrasound	fetal movement	vibro- acoustic	response decrement (Y)	x					
(Leader et al., 1982b)	185	ultrasound	behavioural, maternal observation	vibro- acoustic	response decrement (Y)	x					
(Leader et al., 1984)	167	ultrasound	behavioural, heartrate, maternal observation	vibro- tactile	response decrement (Y)	x					
(Lejeune et al., 2010)	24	visual observation	behavioural	tactile	response decrement (Y), stimulus specificity (Y)		x				
(Lejeune et al., 2012)	24	visual observation	behavioural	tactile	response decrement (Y), stimulus specificity (Y)		x				
(Lejeune et al., 2014)	40	visual observation	behavioural	tactile	response decrement (Y), stimulus specificity (Y), dishabituation (P)		x				
(Madison et al., 1986)	39	ultrasound	behavioural, heartrate	vibro- tactile	response decrement (Y)	x					
(Marcus et al., 2012)	48	visual observation (videotaped)	behavioural	tactile	response decrement (Y) stimulus specificity (Y), dishabituation (Y)		x				
(Matuz et al., 2012)*	63	fMEG	brain activity	visual/auditory	response decrement (P), stimulus specificity (P)	x	x				
(McIsaac and Polich, 1992)	20	EEG	brain activity	auditory	response decrement (X)				x		x
(Millar et al., 1991)	42	visual observation	behavioural/fixation time	visual	response decrement (P), stimulus specificity (P)		x	x			
(Milligan et al., 1970)	37	polygraph	behavioural/heart rate	tactile/sensation of falling	response decrement (Y), spontaneous recovery (P)		x				
(Molina et al., 2015)	64	visual observation/measurement of hand pressure	behavioural/grasp time/hand pressure frequency	tactile	response decrement (Y), stimulus specificity (P)		x				
(Morokuma et al., 2004)	26	ultrasound	behavioural	vibro- acoustic	response decrement (P)	x					

Table 3 (*continued*)

Study	N	Method	Objective	Stimulation	Tested habituation criteria	Age fetal	Age 0–2	Age 2–6	Age 6–12	Age 12–18	Adults
(Morokuma et al., 2008)	21	ultrasound	heartrate characteristics	auditory	response decrement (Y), stimulus specificity (Y)	x					
(Muenssinger et al., 2013b)	62	fMEG	brain activity	auditory	response decrement (P), stimulus specificity (Y), dishabituation (X)	x	x				
(Muenssinger et al., 2013c)	51	MEG	brain activity	auditory	response decrement (X), stimulus specificity (X), dishabituation (X)				x		x
(Oakes et al., 2009)	60	visual observation	behavioural	visual	response decrement (P), stimulus specificity (Y)		x				
(Ornitz et al., 1993)	72	EMG	muscle activity	auditory	response decrement (Y)			x			x
(Perone et al., 2008)	41	visual observation	behavioural	visual/auditory	response decrement (Y), stimulus specificity (Y)		x				
(Pons et al., 2012)	144	visual observation	behavioural	auditory/visual	response decrement (Y), stimulus specificity (P)		x				
(Potter et al., 2000)	50	visual observation	behavioural/head turning	auditory	response decrement (P), stimulus specificity (P)		x				
(Sandman et al., 1997)	84	transabdominal transducers	fetal heart rate	visual	response decrement (Y), dishabituation (Y)	x					
(Sann and Streri, 2008)	24	visual observation	behavioural	tactile	response decrement (Y), stimulus specificity (P)		x				
(Schexnider et al., 1981)	20	visual observation	behavioural/fixation time	visual	response decrement (Y), stimulus specificity (Y)		x				
(Shalev et al., 1989)	103	ultrasound	behavioural	auditory	response decrement (Y)	x					
(Sheridan et al., 2008)*	37	fMEG	brain activity	visual	response decrement (P)	x	x				
(Sinyaya et al., 1992)	72	bipolar electrodes	galvanic skin response	auditory/visual	response decrement (Y)			x			x
(Slater et al., 1984)	52	visual observation	behavioural	visual	response decrement (Y), stimulus specificity (Y)		x				
(Slater et al., 1988)	16	visual observation	behavioural/fixation time	visual	response decrement (Y), stimulus specificity (Y)		x				
(Sommerville and Woodward, 2005)	80	visual observation	behavioural/fixation time	visual	response decrement (P), stimulus specificity (P)		x				
(Sommerville et al., 2005)	30	visual observation	behavioural/fixation time	visual	response decrement (P), stimulus specificity (P)		x				
(Streri and Pecheux, 1986)	64	visual observation	behavioural	Tactile/visual	response decrement (Y), stimulus specificity (Y)		x				
(Streri et al., 2008)	72	visual observation	behavioural	tactile	response decrement (Y), stimulus specificity (P)		x				
(van Heteren et al., 2000)	19	ultrasound	behavioural	vibro- acoustic	response decrement (Y)	x					
(van Heteren et al., 2001)	37	ultrasound	behavioural	vibro- acoustic	response decrement (Y)	x					
(Weber et al., 2016)	33	EEG	brain activity	auditory	response decrement (Y), stimulus specificity (Y)		x				

Table 4
Neurophysiological habituation studies.

Study	Method	Investigated component	Kind of stimulation	Tested habituation criteria and results (fetuses and infants only)	Study population
(Hartkopf et al., 2016)*	fMEG	auditory event-related response	auditory (syllables)	response decrement (X), stimulus specificity (P), dishabituation (X)	30 fetuses (GA: 28–39 weeks), 28 infants (age: 0–3 months)
(Kropp et al., 1999)	EEG	contingent negative variation (CNV)	auditory (two-stimulus reaction time go/no-go task)	response decrement (X)	86 children (age: 8–14 years), 27 youths (age: 15–19 years), 207 adults
(Matuz et al., 2012)*	fMEG	visual event-related response	visual /auditory (light-flashes with tone)	response decrement (P), stimulus specificity (P)	40 fetuses (GA: 30–38 weeks), 26 newborns (age: 6–35 days)
(McIsaac and Polich, 1992)	EEG	P300	auditory (blocks consisting of 10-tone sequences)	response decrement (X)	10 infants (mean age: 6.6 months, SD = 0.49), 10 adults (mean age: 19.8 years, SD = 0.98)
(Muenssinger et al., 2013b)	fMEG	auditory event-related response	auditory (pure tones)	response decrement (P), stimulus specificity (Y), dishabituation (X)	41 fetuses (GA: 30–39 weeks), 22 newborns or babies (age: 6–89 days)
(Muenssinger et al., 2013c)	MEG	M1 component	auditory (tones)	response decrement (P), stimulus specificity (X), dishabituation (X)	29 children (mean age: 9.69 years, SD = 0.47), 14 adults (mean age: 29.29, SD = 3.47)
(Sheridan et al., 2008)*	fMEG	visual event-related response	visual (light flashes)	response decrement (P)	25 fetuses (GA: 29–37 weeks), 12 newborns (age: 6–22 days)
(Weber et al., 2016)	EEG	mismatch negativity (MMN)	auditory (passive oddball paradigm)	response decrement (P), stimulus specificity (P)	17 healthy preterm infants (mean GA: 27.4 weeks, range 25.0–31.3), 16 term infants (mean GA: 40.3 weeks, range 37.9–41.7)

negativity (MMN) component in both groups was investigated at the term-equivalent age of approximately 40.8 weeks of GA. The MMN is assumed to reflect a pre-attentive cognitive discrimination capacity. No significant differences in MMN amplitude and latency between preterm and term infants were found. However, response decrement and stimulus specificity were found in both groups. It is also interesting to note that the authors were able to show a positive correlation between habituation and the scores of a developmental follow-up assessment at approximately 20 months of age in both preterm and term infants.

While the above studies examined endogenous components and MMN, the remaining five developmental related habituation studies analysed exogenous components of event-related brain responses. One research question in the neurophysiological habituation field addressed whether exogenous components, also referred as early components, actually show habituation or if a response decline is potentially caused by adaptation phenomena like refractoriness processes or sensory fatigue (Barry et al., 1992; Verbaten et al., 1986; Budd et al., 1998). However, there is evidence that habituation occurs also in early components, like N1/P1. In adults, for example, habituation of visual N1 was shown. By using a long, varying ISI, refractoriness could be excluded as reason for response decline, since the length of the ISI exceeded the refractory time (Verbaten et al., 1986). It should be mentioned that the variation of the length of the ISI influences the amplitudes of event-related responses and is in general a factor known to influence neurophysiological habituation (Pereira et al., 2014; Miltner et al., 1991). The length of the ISI can modulate how fast habituation occurs and how long the effects persist (Fruhstorfer et al., 1970; Gatchel, 1975; Davis, 1970). Habituation of auditory N1 was moreover shown by Woods and Elmasian, presenting speech sounds and tones (Woods and Elmasian, 1986). Here, the long ISI-condition (1000 ms duration) should be long enough to enable recovery of N1 (Cowper-Smith et al., 2013). The applied paradigm allowed testing for stimulus specificity that was shown additionally to response decrement. The authors examined habituation of N1 by comparing amplitudes of responses and stimulus-

specificity across stimulation blocks. This procedure served as a further criterion to exclude adaptation, as the time interval between blocks is usually longer than the ISI.

An MEG-study by Muenssinger et al. examined auditory habituation of component M1 in a sample of 29 children and 14 adults (Muenssinger et al., 2013c). The habituation paradigm consisted of five equal tones, with an inserted different tone followed by two tones as previously, to allow assessment of response decrement, stimulus specificity and dishabituation following the recommendations of Rankin et al. (2009). Response decrement caused by sensory adaption or neuronal fatigue is implausible using this approach, if several habituation criteria are met. In the group of children, none of the three tested habituation criteria within-trains could be confirmed and only response decrement across the stimulation blocks was found. By comparison, the adult group showed response decrement and stimulus specificity within-blocks. Rankin et al. describe stimulus specificity next to frequency-dependent spontaneous recovery as an appropriate marker to prove for habituation (see Supplementary Table S1) (Rankin et al., 2009). The study by Muenssinger et al. also suggested that developmental changes occur in habituation processes across different age groups, as supported by the diverse results in children and adults.

Four neurophysiological habituation studies measured event-related responses with fMEG, where the first detectable peak is examined. This can be interpreted as early component. Sheridan et al. presented repeated trains of four light flashes to 25 fetuses and 12 newborns (Sheridan et al., 2008). In the group of neonates, all infants with detectable event-related responses (9 out of 12) showed a decline in amplitude from the first to the last flash of light. About a third of the fetuses showed detectable event-related response components with a decrement after the first stimulus. The ISI between the stimuli in a block with two seconds should enable recovery of the measured component, however, there is little knowledge about the recovery time of event-related components in fetuses. The second fMEG visual habituation study of Matuz et al. used an advanced version of the light flash paradigm

of the recent study by Matuz et al. (2012) and Sheridan et al. (2008). In the light flash paradigm, a burst tone was also implemented to allow the examination of stimulus specificity. Moreover, two different conditions of inter-train-interval (ITI) duration were implemented to exclude sensory fatigue. In neonates, under the long ITI condition, both response decrement and stimulus specificity could be shown. However, in fetuses, the response rates to the visual stimuli were at a similarly low level as in the study of Sheridan et al. and habituation was not demonstrated consistently (Sheridan et al., 2008). Muenssinger et al. conducted an fMEG study for fetuses and neonates with an auditory habituation paradigm consisting of eight pure tones with one inserted deviant in place of the sixths tone similar to the paradigm as depicted in Fig. 3 (Muenssinger et al., 2013b). The paradigm allowed investigation of response decrement, stimulus specificity and dishabituation. A significant response decrement between the second and the last tone was detected in fetuses, and stimulus specificity was present in both fetuses and neonates. Dishabituation was found neither in fetuses nor in neonates. In a further fMEG study, an auditory habituation paradigm (Fig. 3) consisting of syllables was presented to fetuses and neonates (Hartkopf et al., 2016). Stimulus specificity was demonstrated in neonates only; neither response decrement nor dishabituation could be shown in either age group.

Generally, in future research of neurophysiological habituation studies, the impact of adaptation phenomena on response decrement should be consequently excluded by testing for stimulus specificity and dishabituation. Furthermore, the influence of the ISI should be investigated systematically in this context, with a differentiation of early and late components during child development.

3.4.4. Longitudinal studies

Habituation is widely accepted as a suitable tool for the investigation of the development of early cognitive skills (for example cognitive encoding, information processing skills, discrimination and memory; for a review, see (Kavsek and Bornstein, 2010). Longitudinal designs are particularly suitable for investigating development, for example the timing of specific cognitive changes during childhood. None of the eight neurophysiological habituation studies used the same stimulation paradigm to compare changes in neural correlates from more than two time-points during child development. Further studies should seek to bridge this gap, even if longitudinal research is more time-consuming than cross-sectional studies.

4. Conclusion

In this review, we aimed to collect and describe studies investigating habituation in the context of developmental processes in growing children with an emphasis on neurophysiological habituation measurements, based on the analysis of event-related brain responses.

Age-related changes of event-related brain responses themselves are linked to an increasing maturity of the sensory organs and the central nervous system and, indeed, a large number of the reviewed studies reported age-related changes in components of event-related responses (Birbaumer and Schmidt, 2006). However, the developmental changes observed were not consistent. Although general trends such as a decrease in latency and an increase in amplitude, which can reflect structural or functional maturation processes of the CNS (e.g. increasing myelination or formation of neural networks) are presumed to exist particularly in exogenous components, it is challenging to confirm this on the

basis of the studies included in our review. The diversity in methods, selected age groups, chosen stimulation paradigms and investigated components, drastically restricts the comparability of the results.

To facilitate better comparability, the studies were divided according to specific methodical characteristics: a) the kind of investigated component(s) (exogenous versus endogenous components) and b) the stimulus modality (auditory versus visual). In addition, the separate components of the typical CAEP and CVEP were taken into consideration. However, even this differentiated overview did not lead to a generally valid statement about developmental trends in components of event-related brain responses.

Nearly all of the included studies used different stimuli/stimulation paradigms, investigated participants in different age groups and analysed their data on the basis of various methods. Besides the age of participants – and hence the state of maturity of the CNS – changes in event-related brain responses are strongly related to different types of stimulation. Fuchigami et al., for example, showed that response latencies decreased more rapidly with increasing age for complex stimuli than for simple tones (Fuchigami et al., 2009). Moreover, further attributes of the stimuli such as novelty, the emotional context or spatial motion impacted characteristics of event-related brain responses during development (Kihara et al., 2010; Mecklinger et al., 2011; Lamm and Lewis, 2010; van der Meer et al., 2012). This wide range of different study designs and methods limits the interpretation of developmental trends of event-related brain responses or their components and does not endorse a general trend in developmental changes of latency and amplitude during childhood.

Habituation, a basic form of learning, which is manifest very early in development, is a concept to assess cognitive function. It can be measured by two main approaches: the observation of behavioural changes and neurophysiological measurements of event-related brain responses, which enable for a direct evaluation of brain developmental processes. Components of event-related responses measured by EEG and (f)MEG/MEG seem to be suitable for investigating changes in habituation during child development. Studies with fetuses demonstrated that brain responses to auditory and visual stimulation are already measurable during the third trimester of pregnancy, meaning that it is possible to investigate event-related brain responses from an early stage of development. It should be mentioned that fMEG as measuring method has some limitations, for example a low signal-to-noise ratio or the sensitivity to environmental artefacts. The stimuli should meet certain criteria so that they can be perceived by the fetus through tissue layers and amniotic fluid. Therefore, visual light stimuli need to be in a defined range of wavelenghts and auditory stimulation in a certain range of frequency to ensure a satisfactory transferability (Preissl et al., 2004; Sheridan et al., 2010). Most of the habituation studies examining changes in latency and amplitude of event-related responses or their particular components in different age groups found differences that were possibly related to age-dependent stimulus processing. However, it is still difficult to rule out whether other variables, such as the type and the context of the applied stimuli, the examined brain region and the selection of the analysed components impact the results. Unlike behavioural habituation studies, the number of neurophysiological habituation studies remains low.

To rule out sensory fatigue as the driving mechanism for response decrement, habituation studies should use at least three of the postulated habituation criteria: "response decrement", "stimulus specificity" and "dishabituation". Despite the fact that these criteria can be easily implemented in most habituation paradigms, only very few of the included studies used all them. A large number of studies that do not examine these criteria thus lose

quality, as it is not possible to draw clear conclusions about habituation as a driving mechanism for response decrement. This should be also taken into account in future habituation studies.

Despite the large number of studies investigating event-related brain responses and habituation in early development, it is currently not possible to make any conclusive statements about developmental trends. This is mainly due to the fact that stimulation protocols are very diverse. More consistent stimulation paradigms are needed to replicate findings and to better compare different study populations. An interesting issue would also be the combination of behavioural and neurophysiological habituation assessment in order to compare results of both approaches directly with each other. Ultimately, more trials with longitudinal designs are needed to provide clearer information about maturational changes of event-related responses during the process of growing up.

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Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

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