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INFANT BRAIN FUNCTION AFTER FETAL EXPOSURE TO NEUROACTIVE DRUGS

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ACADEMIC DISSERTATION

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Science is organized knowledge.
Wisdom is organized life.

(Immanuel Kant)

ABSTRACT

Background: *In utero* exposure to antiepileptic drugs (AEDs) or to serotonin reuptake inhibitors (SRIs) is associated with structural and functional teratogenesis. The aim of this thesis was to investigate whether prenatal SRI or AED exposure changes newborn brain activity. In addition, we wanted to evaluate the effects of prenatal AED exposure on visual attention and emotion-related attention in infancy and to characterize functional connectivity in healthy term newborns.

Material and Methods: A prospective cohort of infants with *in utero* AED exposure (n=56) and similar cohort with *in utero* SRI exposure (n=22) were compared to infants without drug exposure (n=67). Background information, exposure data, pregnancy outcome, neuropsychological evaluation of the mothers (AED), mood and anxiety of mothers (SRI), and neurological status of the infants were assessed at neonatal age and at 7 months-of-age. Electroencephalography (EEG) was used to evaluate newborn cortical function and an eye-tracking-based test to assess the infants' visual attention and orienting to faces.

Results: Neurological assessment showed subtle abnormalities in both the AED- and the SRI-exposed newborns. Early language abilities were impaired at 7 month-of-age in infants with *in utero* carbamazepine, oxcarbazepine, and valproate exposure. The general speed of visuospatial orienting or attentional bias for faces did not differ between AED-exposed and control infants.

Computational EEG analyses demonstrated several differences between the exposed and control newborns. AED-exposed newborns had lower amplitudes at multiple frequencies, higher interhemispheric synchrony in frontal versus posterior parts of the brain, more even distribution of interhemispheric interval durations, and fewer frontal alpha bouts of typical duration. In the SRI-exposed newborns, interhemispheric connectivity was reduced, cross-frequency integration was lower, and frontal activity at low-frequency oscillations was reduced. These effects were unrelated to maternal depression or anxiety. In unexposed newborns, functional connectivity was shown to vary significantly between vigilance states and to mature rapidly after normal birth.

Conclusions: The results suggest that prenatal AED and SRI treatment may change newborn brain function and affect early neonatal neurologic status. In addition, AED exposure may impair verbal abilities in a way that can be detected already in infancy. Early development of visual attention as well as orienting and face perception were spared after *in utero* AED exposure.

Results in the newborn connectivity study support the view that emerging functional connectivity exhibits fundamental differences between sleep states during the neonatal period. The findings suggest that interference in the development of an activity-dependent network may be a possible mechanism to explain the link from prenatal AED and SRI exposure to later adverse functional effects.

Keywords: Pregnancy, Epilepsy, Depression, EEG, AED, SRI, Eye-tracking, Newborn, Connectivity

TIIVISTELMÄ

Tausta: Sikiöaikainen altistuminen antiepileptiselle lääkitykselle (AED) ja serotoniinin takaisinotonestäjälääkitykselle (SRI) aiheuttaa rakenteellisia ja toiminnallisia kehityshäiriöitä. Tämän väitöskirjatyön tavoitteena oli tutkia, aiheuttaako sikiöaikainen altistuminen näille lääkkeille muutoksia vastasyntyneiden aivojen toiminnassa. Lisäksi halusimme arvioida AED altistuksen vaikutuksia visuaalisen tarkkaavuuden suuntaamiseen imeväisiässä ja arvioida aivojen eri osien välistä yhteistoimintaa (konnektiivisuutta) terveillä vastasyntyneillä.

Menetelmät: Tutkimukseemme osallistui 56 sikiöaikana AED- ja 22 SRI-lääkkeille altistunutta imeväistä sekä 67 verrokkia. Keräsimme prospektiivisesti tausta-, altistumis-, synnytys- ja vastasyntyneisyyskauden sairauskertomustiedot. Lisäksi äideille tehtiin neuropsykologinen (AED) ja psykiatrinen (SRI) tutkimus. Lastenneurologi tutki lapset sekä vastasyntyneenä että 7 kk iässä käyttäen strukturoituja menetelmiä. Vastasyntyneen aivojen toimintaa arvioitiin elektroenkefalografian (EEG) avulla ja imeväisikäisen visuospatiaalista tarkkaavuutta ja tarkkaavuuden suuntaamista eri tunnetiloja ilmentäviin kasvoihin mitattiin silmänliikekameratekniikkaan perustuvalla menetelmällä.

Tulokset: Neurologisessa arviossa todettiin vähäisiä eroja AED ja SRI lääkkeille altistuneissa vastasyntyneissä verrattuna verrokkilapsiin. Varhaisten kielellisten taitojen todettiin olevan heikommat karbamatsepiinille, okskarbatsepiinille ja valproaatille sikiöaikana altistuneilla lapsilla 7 kk iässä. Visuospatiaalisen tarkkaavuuden suuuntaamisnopeudessa ei todettu eroa AED altistuneiden ja verrokkilasten välillä.

Tietokonepohjaiset EEG analyysit toivat esille useita muutoksia altistuneiden ja altistumattomien vastasyntyneiden aivosähkötoiminnassa. AED lääkkeille altistuneiden vastasyntyneiden sähköisen toiminnan voimakkuus oli matalampaa useilla taajuuksilla, aivopuoliskojen välinen synkronia oli korostuneempaa etuosissa kuin takaosissa, purskeiden välinen aika ei eronnut aivojen etu-ja takaosien välillä ja etuosissa oli vähemmän tyypillisen pituisia alphataajuisia jaksoja. SRI-lääkkeille altistuneiden vastasyntyneiden eri aivoalueiden yhteistoiminta ja aivokuoren paikallinen synkronoituminen oli heikompaa. Lisäksi aivojen etuosien aktiivisuus matalilla taajuuksilla oli alhaisempaa kuin verrokkilapsilla eivätkä nämä muutokset liittyneet äitien masennukseen tai ahdistuneisuuteen. Verrokkilapsilla tutkittuna aivojen eri osien välinen yhteistoiminta erosi merkittävästi eri vireystilojen välillä ja kypsyi nopeasti ajan myötä.

Päätelmät: Tulosten perusteella on pääteltävissä, että sikiöaikainen altistuminen epilepsia- tai SRI-lääkitykselle näkyy vastasyntyneen aivojen toiminnassa ja kliinisessä neurologisessa arviossa. Lisäksi AED lääkitys saattaa heikentää kielellisiä taitoja imeväisiässä tavalla, joka on todettavissa jo 7 kk iässä. Toisaalta AED-lääkitys ei näytä vaikuttavan heikentävästi varhaiseen visuospatiaaliseen tarkkaavuuteen tai kasvojen tunnistamiskykyyn. Aivojen konnektiivisuuden muutokset vastasyntyneen ensiviikkoina vahvistavat ajatusta siitä, että vireystila ja aivojen kypsyminen vaikuttavat merkittävästi varhaiseen konnektiviteettiin. Löydösten perusteella voidaan ajatella, että aivojen varhaisen verkostoitumisen häiriintyminen saattaisi olla yksi mekanismi, jolla AED ja SRI lääkealtistuksen myöhemmin esille tulevat haittavaikutukset syntyvät.

Avainsanat: Raskaus, epilepsia, masennus, EEG, AED, SRI, silmänliikekamera, vastasyntynyt, konnektiviteetti

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in roman numerals in the text:

I. Videman M, Tokariev A, Stjerna S, Roivainen R, Gaily E, Vanhatalo S. Effects of prenatal antiepileptic drug exposure on newborn brain activity. Epilepsia. 2016 Feb;57(2):252-63.

II. Videman M, Stjerna S, Roivainen R, Nybo T, Vanhatalo S, Gaily E, Leppänen JM. Evidence for spared visual attention in 7-month-old infants with prenatal exposure to antiepileptic drugs. Epilepsy & Behavior. 2016 Oct 11 [Epub ahead of print]

III. Videman M, Tokariev A, Saikkonen H, Stjerna S, Heiskala H, Mantere O, Vanhatalo S. Newborn Brain Function is Affected by Fetal Exposure to Maternal Serotonin Reuptake Inhibitors. Cerebral Cortex. 2016 June 8 [Epub ahead of print]

IV. Tokariev A, Videman M, Palva JM, Vanhatalo S. Functional Brain Connectivity Develops Rapidly Around Term Age and Changes Between Vigilance States in the Human Newborn. Cerebral Cortex. 2015. Sep 23 [Epub ahead of print]

The publications are referred to in the text by their roman numerals.

Author's contribution to the studies included to the Thesis

Study I: The author conducted all the clinical examinations of the newborns, reviewed the visually and rated EEG data, analyzed visual EEG and clinical data, and wrote the manuscript together with AT and SV.

Study II: The author conducted all the clinical and developmental assessments of the 7 month old infants, analysed clinical, developmental and eye-tracker data, and wrote the manuscript together with JL and EG.

Study III: The author conducted all the clinical examinations of the newborns, visual reviewings and ratings of EEG data, performed all data analyses, and wrote the manuscript with OM and SV.

Study IV: The author did the visual review of the EEG data, extracted and rated the vigilance state epochs, and contributed to the manuscript.

ABBREVIATIONS

AAC	Amplitude-amplitude correlations
AED	Antiepileptic drug
aEEG	Amplitude-integrated electroencephalogram
AMPA	Alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid
AS	Active sleep
ASD	Autism spectrum disorder
ASI	Activation synchrony index
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BSID	Bayley Scales of Infant Development
BZD	Benzodiazepine
CA	Conceptional age
CBZ	Carbamazepine
CNS	Central nervous system
EDF	European data format
EEG	Electroencephalogram
ESM	Ethosuximide
FA	Frontal alpha
fMRI	Functional MRI
GA	Gestational age
GABA	Gamma-aminobutyric acid
GBP	Gabapentin
HINE	Hammersmith infant neurological examination
HNNE	Hammersmith neonatal neurological examination
HPA	Hypothalamic-pituitary-adrenal
HUH	Helsinki University Hospital
IBI	Interburst interval
LAC	Lacosamide
LEV	Levetiracetam
LTG	Lamotrigine
MCM	Major congenital malformation
MDD	Major depression disorder
MEG	Magnetoencephalogram
MRI	Magnetic resonance imaging
OXC	Oxcarbazepine
PAC	Phase-amplitude correlations
PB	Phenobarbital
PGB	Pregabalin
PHT	Phenytoin
PLV	Phase locking value
PPC	Phase-phase correlations

PWE	Pregnant women with epilepsy
QS	Quiet sleep
SAT	Spontaneous activity transients
SD	Standard deviation
SERT	Serotonin transporter
SRI	Serotonin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SV2A	Synaptic vesicle protein
TMS	Transcranial magnetic stimulation
TPM	Topiramate
TT	Temporal theta
VPA	Valproic acid

Metrics

ms	Millisecond
Hz	Herz
°	Unit of angle

1 INTRODUCTION

One of the miracles in life is the birth of a human being. How precisely and accurately a newborn is built, from beautiful tiny fingers and toes to already highly functional senses, can only be admired (Partanen et al., 2013; Clark-Gambelunghe and Clark, 2015). Even more, the amazing development continues postnatally as we see the infant's abilities expand during the first years of life. The development of human central nervous system (CNS), in particular, requires a substantial time period to mature, due to its anatomically and morphologically sophisticated structure, but even more so because of its highly complex functionality (Gogtay et al., 2004). The development of higher neurocognitive functions is particularly dependent on interaction, i.e. connectivity between different regions of the CNS.

The complexity and long duration of CNS development makes it highly vulnerable to adverse environmental effects. Numerous genetic, epigenetic and environmental factors control CNS development, some of them being favorable and others unfavorable (Andersen, 2003; Graignic-Philippe et al., 2014).

One of the factors that may affect fetal brain development, and thus influence the subsequent steps in neurodevelopment, is the exposure of a fetus *in utero* to maternal medications. Two chronic diseases that require regular medication during pregnancy are epilepsy and depression (Bennett et al., 2004; Viinikainen et al., 2006). In Europe, approximately 6 million people have a diagnosis of epilepsy (Baulac et al., 2015), and the life-time prevalence of major depressive episodes is 13-16% (Volkert et al., 2013). Both of these conditions are treated with medications that cross the placenta (Rampono et al., 2009; Harden, 2014) and the blood-brain barrier (Halliday et al., 2012; Booth and Kim, 2014).

There is an accumulating body of knowledge on the obstetric and both structural and cognitive teratogenic effects of antiepileptic (Borthen, 2015; Inoyama and Meador, 2015; Tomson et al., 2015c) and antidepressant drugs (Hanley and Oberlander, 2014; Hanley et al., 2015; Kepser and Homberg, 2015; Man et al., 2015). Due to confounding pre- and postnatal circumstances, it is often difficult, if not impossible, to distinguish the impacts of individual factors. Evaluation immediately after, or very soon after, prenatal exposure reduces the impact of postnatal factors, though fails to eliminate this problem altogether.

As neonatal EEG reflects both prenatal and postnatal experiences, it can be used as one possible technique to reveal the underlying mechanisms of the adverse developmental consequences of prenatal drug exposures and, furthermore, act as a potential biomarker of later cognitive development. Novel quantifiable computational methods of EEG analyses have been developed during recent years (Tokariev et al., 2012; Räsänen et al., 2013; Tokariev et al., 2016; Vanhatalo et al., 2005b). These advancements have made the highly detailed EEG assessment of functional cortical activity possible, including analyses of functional connectivity (Minlebaev et al., 2007; Tokariev et al., 2012; Colonnese and Khazipov, 2010; Engel et al., 2013).

The aim of this thesis was to evaluate whether prenatal antidepressive or antiepileptic drug exposure changes newborn brain activity. As such, this study sought to elucidate the possible underlying mechanisms for the adverse neurocognitive and behavioral consequences of these drugs. The effects of prenatal AED exposure on visual attention and emotion-related attention in infancy were evaluated. In addition, functional connectivity changes between vigilance states and maturation during the early weeks of postnatal life were investigated. Altogether, the creation of non-invasive and objective quantitative methods was sought to detect cognitive developmental deviations already in infancy.

2 REVIEW OF THE LITERATURE

2.1 DEVELOPING BRAIN

2.1.1 STRUCTURAL AND FUNCTIONAL DEVELOPMENT

In humans, the development of the CNS begins during the first gestational weeks and, predominantly, terminates in young adulthood. Development of the CNS can be considered from two perspectives: structural and functional.

Structural development. The major morphological features of CNS development comprise a multiplex cascade from neurulation, i.e. transformation of the neural plate to neural tube, to configuration of greatly convoluted cerebral and cerebellar hemispheres, brainstem, spinal cord, and peripheral nervous system. In tandem, from the gestational age (GA) of 12 weeks onward, major histological changes take place in the form of radial migration of immature neurons, followed by organizational differentiation and myelination from the GA of 24 weeks onward. These phenomena occur mostly simultaneously. The first trimester of pregnancy is characterized by the formation of the main structures, the second and the third trimesters by the expansion of the weight and surface area of the hemispheres due to rapid increase in the length and complexity of dendrites and axons, synaptogenesis and apoptosis, i.e. programmed cell death (Aicardi, 2009).

Functional development. In terms of function, CNS development can be roughly divided into cortical specialization and connectivity maturation. Our knowledge was based earlier on animal studies and post mortem investigations. The methodological advances like the development of magnetic resonance imaging (MRI), electroencephalogram (EEG), magnetoencephalogram (MEG), and functional MRI (fMRI) have enhanced our ability to image human fetal brain, and at the same time they have expanded our understanding of normal and abnormal brain development (Studholme, 2015). Furthermore, these advances have made it possible to relate the maturation of cerebral structures to neurodevelopment and behavior (Dubois et al., 2014).

Later neurocognitive development depends greatly on how well different parts of the central nervous system co-operate and connect with each other. This co-operation takes place in different levels: between adjacent neurons via synapses, locally between nearby-located neurons, and between neurons or groups of neurons situated further apart creating functional neural circuits. The strength of synaptic signals is constantly modified by sensory input and

experience. This adaptation process is called synaptic plasticity, which is believed to modulate higher-order brain tasks, like social cognition, emotional learning, and memory (Lesch and Waider, 2012). Neurotransmitters are essential endogenous messengers that facilitate signal transmission from one neuron to another across synapses. The capacity to synthesize and degrade neurotransmitters emerge already early in embryogenesis even before synapses are formed (Thompson et al., 2009). Both histological (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2010) and functional MRI studies (Smyser et al., 2010) have shown evidence of fetal brain-wide networks, including subplate and thalamocortical connectivity during late prenatal life.

Prior studies have shown that by term age, all major fiber systems are in place (Qiu et al., 2015). During infancy, dendritic arborization, synaptogenesis, myelinization, apoptosis, and neurotransmitter development continue intensely (Scher et al., 2005; Gilmore et al., 2007; Provenzale et al., 2007). Fetal and infant brain has enormous capacity for functional adaptivity that is widely sensory driven (Anderson and Thomason, 2013). It seems that during early postnatal life, locally-dense communication dominates over long-distance connections, within and across the two cerebral hemispheres (Qiu et al., 2015). Furthermore, regional cerebral brain changes are asynchronous, i.e. sensory-motor regions develop early with rapid pace, whereas associative regions develop later and slowly over decades (Dubois et al., 2014).

2.1.2 POTENTIAL DISRUPTIONS

The consequences of adverse events during fetal development depend on the event itself and on the time of occurrence. In general, it is regarded that malformations arise during the first trimester, and neurocognitive or behavioral problems, so-called functional teratogenesis, are due to adverse influences during the later parts of pregnancy.

Neurodevelopmental changes are associated with various environmental factors like maternal stress, prenatal infections, inflammation, or prenatal drug exposures, assuming that these factors operate during the developmental windows of susceptibility (Adams Waldorf and McAdams, 2013; Zhao et al., 2013; Grandjean and Landrigan, 2014; Bale, 2015; Hagberg et al., 2015). Development is further confounded by epigenetic modification, i.e. altered gene expression by environmental influences without involving a change in DNA sequence (Bale, 2015). Furthermore, neuropsychiatric disorders with cognitive, emotional, and behavioral deficits are recognized to at least partly arise from developmental origins very early in prenatal life (Beardslee et al., 2011; Bale, 2015).

Overall, CNS development, including the prenatal time period, represents the highest level of plasticity, representing both opportunity and vulnerability (Gao et al., 2016). Research on the developing human brain during the remarkably plastic time of fetal development has major significance for both preclinical and clinical practice (Anderson and Thomason, 2013). Abnormalities originating in this period will affect consequent neural network patterns and growth (Tau and Peterson, 2010). Therefore, it is crucial to acquire better understanding of this sensitive period of fetal brain development and the embedded risks, to allow either avoidance of these adverse factors as well as possible, or at least to facilitate early interventions.

One of the prenatal hazards is fetal exposure to maternal medication. Two widely used groups of these medications include antiepileptic drugs and anti-depressants (Bennett et al., 2004; Viinikainen et al., 2006). Both of these groups of medications have pharmacological qualities that allow adverse CNS effects: they cross both the placenta (Harden et al., 2009; Rampono et al., 2009) and the blood-brain barrier (Halliday et al., 2012; Booth and Kim, 2014).

2.2 ANTIEPILEPTIC DRUGS

The efficacy of antiepileptic drugs (AEDs) is, to some degree, specific for epilepsy types and syndromes. Thus, the selection of medication is not random and should be based on the diagnosis of epilepsy syndrome (or type) and etiology. Until 1993, the choice of AEDs was limited to seven or eight major substances. Since then, 16 new AEDs have been approved for use in epilepsy (Abou-Khalil, 2016).

The mechanisms of action of the AEDs are diverse. The main mechanisms of action are explained in the recent paper from Abou-Khalil (Abou-Khalil, 2016): sodium channel blocking which reduces high frequency neuronal firing (e.g. PHT, CBZ, OXC, LTG and LAC), gamma-aminobutyric acid (GABA)-A receptor binding which prolongs or increases the opening of chloride channels (PB, BNZ), calcium channel binding (GBP, PGB, ESM), synaptic vesicle protein SV2A binding which decreases neurotransmitter release (levetiracetam), GABA transaminase inhibition (vigabatrin), and AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid) receptor antagonism (perampanel). Some AEDs have multiple mechanisms of action, like valproic acid, topiramate, felbamate, and zonisamide. Furthermore, lamotrigine and rufinamide, although providing sodium channel blocking as the main mechanism of action, are likely to have other antiepileptic mechanisms as well (Abou-Khalil, 2016).

2.2.1 ANTIEPILEPTIC DRUGS AND PREGNANCY

Approximately 0.5% of pregnant women have epilepsy (Viinikainen et al., 2007). Pregnancy is associated with a number of physiological, endocrine, and psychological changes, which may lower seizure threshold (Patel and Pennell, 2016). Most women with epilepsy need antiepileptic drug (AED) treatment during pregnancy as seizures can harm both the mother and the fetus.

Harmful effects of *maternal seizures* have been demonstrated both in animal (Cossa et al., 2016) and in human (Chen et al., 2009; Edey et al., 2014; Sveberg et al., 2015) studies. Cossa and co-workers (Cossa et al., 2016) investigated the impact of seizures during pregnancy in rodents with epilepsy but without AED medication. The authors suggested that the adverse consequences of seizures may be associated with ischemia and/or maternal stress and they may cause fetal suffering, intrauterine growth delay, altered protein synthesis, changes in the expression of apoptotic proteins and long-term disturbances in brain function. Maternal and fetal hypoxia and acidosis (Yerby, 2000) as well as alterations in electrolytes, blood pressure, heart rate, and oxygenation (Hiilesmaa et al., 1985; Sveberg et al., 2015) have been observed in human studies after generalized tonic-clonic seizures. Occurrence of more than one generalized tonic-clonic seizure during pregnancy has been associated with a five-times higher risk of preterm labor and reduced birth weight in boys (Rauchenzauner et al., 2011).

The results have been inconsistent regarding whether maternal seizures affect neurocognitive functioning of offspring (Inoyama and Meador, 2015). In some studies (Adab et al., 2004; Vinten et al., 2005), the occurrence of five or more maternal tonic-clonic seizures during pregnancy has been associated with lower verbal IQ in the offspring. In contrast, other studies (Shallcross et al., 2014; Shallcross et al., 2011) have described no association of maternal seizures with lower verbal IQ of the exposed children at 2 years-of-age. Instead, seizures were associated with lower abilities in language comprehension, gross motor skills, personal and social skills, hand and eye coordination, and performance skills at the age of 3 to 4.5 years-of-age of the offspring. The same children were later re-examined: Prenatal seizure load was no longer associated with measured cognitive abilities of the AED-exposed children or with need for additional educational support at 6 years-of-age (Baker et al., 2015).

The most commonly used AEDs cross the placenta in clinically relevant amounts (Harden et al., 2009). The AEDs prescribed to women of childbearing age have changed over the last two decades: the prescriptions of carbamazepine, phenytoin, and valproate for pregnant women have decreased while the prescriptions of lamotrigine, topiramate, and levetiracetam have increased (Ackers et al., 2009; Vajda et al., 2010). The most often used

medications among pregnant women in the UK in 2005, and in Australia in 2007, were lamotrigine, carbamazepine, and valproate (Ackers et al., 2009; Vajda et al., 2010) although the use of valproate has probably decreased since due to recommendations described in the following chapters. The changing practices make it difficult to obtain up-to-date data on the presently used AEDs because long follow-up times are needed for documenting functional teratogenicity.

2.2.2 ANTIEPILEPTIC DRUGS, OBSTETRIC RISKS, AND PERINATAL OUTCOME

Diagnosis of epilepsy and exposure to AEDs during pregnancy have been associated with an increased risk for adverse obstetric outcome, like premature induction of labor, caesarean section, increase in hypertensive disorders, and post-partum hemorrhage (Borthen, 2015; MacDonald et al., 2015; Viale et al., 2015). Adverse perinatal outcomes such as low birth weight, smallness for gestational age, low Apgar scores, small head circumference, respiratory problems, and admission to neonatal care, have been documented in several other studies as well (Pennell et al., 2012; Artama et al., 2013; Kilic et al., 2014; Patel and Pennell, 2016).

Vilae and co-workers (Viale et al., 2015) took into account the *impact of AED* on the obstetric outcome in their meta-analysis and compared women with epilepsy with AED medication to women with epilepsy but no AED medication. The AED-exposed group had increased risk for post-partum hemorrhage, induction of labor, fetal growth restriction, and admission to a neonatal intensive care unit. No increased risk was noted for fetal or neonatal mortality.

To evaluate the *impact of epilepsy* on perinatal outcome, Artama et al. (Artama et al., 2013) analyzed 4867 infants, including live births and stillbirths, and compared women with epilepsy and AED medication to women with epilepsy without medication and to women without epilepsy. Women with epilepsy on AED had an increased risk for treatment in a neonatal care unit, for preterm labor, and for low birth weight when compared to women with epilepsy not taking AED (Artama et al., 2013; Farmen et al., 2015). Furthermore, it seems that there may be an increased risk for maternal complications with the use of lamotrigine and carbamazepine (Borthen, 2015).

2.2.3 ANTIEPILEPTIC DRUGS AND DEVELOPING BRAIN

The first information on the teratogenicity of drugs arose in the 1960s and the research in the field has since spread to comprise AEDs as well as other drugs. At first, the main interest in AEDs was major congenital malformations (MCM), but in the 1990s the neurocognitive and behavioural consequences were drawn into the focus of investigations as well (Inoyama and Meador, 2015). As the discontinuation of the use of antiepileptic drugs during pregnancy is not advisable, AEDs have been investigated intensely.

The *effects of maternal epilepsy* type or etiology as a confounding factor are difficult to determine as they often go hand in hand with the choice of medication. Few studies have researched the relationship between maternal epilepsy type and outcome of the offspring. Holmes et al. (2000) revealed this issue by comparing cognitive abilities of children with or without maternal epilepsy and excluding those children who had prenatal AED exposure or experienced maternal tonic-clonic seizures prenatally. According to this study, cognitive outcome was not affected by maternal epilepsy per se. Three studies found no associations between maternal epilepsy type and cognitive (Gaily et al., 2004; Meador et al., 2013) or neurodevelopmental (Bromley et al., 2013) outcomes in the offspring. On the other hand, social and linguistic scores of the offspring did differ depending on maternal epilepsy type in one study (Hirano et al., 2004). When only children born to mothers with idiopathic generalized epilepsy were evaluated (Baker et al., 2015), the children with VPA exposure in this group had significantly lower mean IQ than control children or children with exposure to some other AED.

Blinded randomized controlled trials used to separate the effects of confounding factors from AED treatment in humans are not feasible for ethical reasons, and thus human studies on the subject are observational-register-, hospital-, or population-based studies (McCorry and Bromley 2015). The main prospective AED pregnancy registries are the North American Antiepileptic Drug Pregnancy Registry (NAAPR), the UK Epilepsy and Pregnancy Register, and International Registry of Antiepileptic Drugs and Pregnancy (EURAP). In addition to human studies, experimental animal studies have accumulated valuable information on the effects of prenatal AED exposure, and to some extent on the mechanisms by which these effects are mediated.

2.2.3.1 Animal Studies

A single dose of AED during vulnerable phases of brain development can cause neuronal injury in nearly every forebrain region in rats (Bittigau et al., 2002). One of the most frequently proposed mechanisms of adverse effects at the cellular level is drug-induced apoptotic neurodegeneration (Bittigau et al.,

2002; Bittigau et al., 2003; Ikonomidou, 2010; Inoyama and Meador, 2015), resulting in both structural changes, such as malformations, as well as functional changes, like neurocognitive or behavioral problems. In animal studies, these changes have been associated with prenatal phenobarbital, phenytoin, valproic acid, and carbamazepine exposures (Ikonomidou, 2010; Inoyama and Meador, 2015; McCorry and Bromley, 2015), whereas levetiracetam, even in high doses, did not produce cell death (Kim et al., 2007). Structural changes in animal brains have been demonstrated e.g. in mice treated with phenytoin at the equivalent age of human third trimester: the cerebellum of these mice weighed significantly less than the cerebellum of untreated mice, and the treated mice had impaired spatial learning (Ogura et al., 2002). Mice exposed to carbamazepine *in utero* had fewer neurons in the hippocampus and in the cortex (Aberg et al., 2013).

In addition to structural changes, a recent study (Forcelli et al., 2012) has demonstrated that AEDs may delay or prevent the development of both excitatory and inhibitory synapse function. This functional toxicity presented as synaptic deficits and abnormal synaptic function in rats after a single dose of phenytoin, phenobarbital, and lamotrigine, but not of levetiracetam, on postnatal day 7. With lamotrigine, this delay in synaptic maturation was seen with a lower dose than required for the induction of neuronal apoptotic cell death and it improved over time (Forcelli et al., 2012). These functional alterations play a key role in organization of neuronal networks (Ikonomidou, 2010; Verrotti et al., 2015). *In utero* VPA exposure in animals has been shown to influence the electric brain activity of the offspring as VPA decreased midrange frequencies in all vigilance states (Cusmano and Mong, 2014). Furthermore, several animal studies have implied that prenatal VPA exposure increases autism-like behaviors (Roullet et al., 2013; Sabers et al., 2014).

2.2.3.2 Human studies

Malformations. Major congenital malformations (MCM) are defined as "structural abnormalities of surgical, medical, functional, or cosmetic importance which occur during organogenesis in the first trimester" (Tomson and Battino, 2012).

In general, it has been shown that the risk for major MCM is two to three-fold in children with fetal AED exposure (Tomson et al., 2015c; Verrotti et al., 2015). MCM rate has been reported as 6.1% in AED-exposed children, in contrast with 2.8% in the unexposed children with maternal epilepsy, and 2.2% in children without maternal epilepsy or AED exposure (Tomson and Battino, 2009). The risks of specific AEDs regarding structural teratogenesis depends not only on quality of medication, but also on dosages, exposure on either mono- or polytherapy, timing of the exposure, and possible MCM in

previous pregnancies (Vajda et al., 2013; Gerard and Meador, 2016). It is possible that newer antiepileptic drugs bear a lower risk of MCM (Verrotti et al., 2015).

The most typical MCM encountered with prenatal AED exposure are cardiac malformations associated with carbamazepine, lamotrigine, barbiturate, and phenytoin exposure, neural tube defects associated with carbamazepine and valproate exposure, hypospadias associated with valproate exposure, and oral clefts associated with lamotrigine and topiramate exposure (Tomson et al., 2015c; Verrotti et al., 2015).

Special attention should be paid to valproate, as it has been associated with the highest prevalence of MCMs ranging mainly from 4.7% to 10.0% (Tomson et al., 2015b). At the same time, it is commonly used as an effective regimen for generalized epilepsies like juvenile myoclonic epilepsy. Prenatal valproate exposure carries a 5- to 11-fold risk for major malformations (Tomson et al., 2015c; Gerard and Meador, 2016). In case-control studies based on EUROCAT data, evaluating the risk of prenatal valproate exposure on the incidence of MCMs, showed the odds ratio for spina bifida to be 12.7, for atrial septal defect 2.5, for cleft palate 5.2, for hypospadia 4.8, for polydactyly 2.2, and for craniosynostosis 6.8 (Tomson et al., 2015c). The risk for MCMs with VPA as well as for LTG and CBZ seem to be dose dependent (Hernandez-Diaz et al., 2012; Vajda et al., 2013; Campbell et al., 2014). Higher risk for MCM up to 24.2% has been associated with valproate doses higher than 1500 mg/day (Tomson et al., 2015c).

Tomson et al (Tomson et al., 2015c) conclude that according to register studies, MCM rates of carbamazepine, lamotrigine, and phenobarbital are lower than those of valproate, and phenobarbital is higher than that of lamotrigine or carbamazepine. Levetiracetam is suggested to have similar rates as lamotrigine and carbamazepine but the number of exposures is still somewhat limited. For other AEDs, the number of reported exposures is even more limited and the conclusions of the risk for malformations cannot be made, though it seems that topiramate may have a higher rate of MCMs than LTG or CBZ (Patel and Pennell, 2016). Polytherapy is considered to have a higher risk for MCM though it seems that the main factor to increase the risk is whether the combination includes VPA (Tomson et al., 2015a).

Neurocognition. In addition to structural malformations, AEDs are known to bear functional teratogenicity as well. As with MCMs, the severity and quality of the consequences depend on several variables, including drug-, individual-, and environment-related factors. In addition, the variety of neuropsychological tests used, varying ages of the offspring at testing, demographic differences, lack of control of confounding factors such as maternal IQ and education, or etiology of maternal epilepsy make the

interpretation and comparisons of different studies difficult (Inoyama and Meador, 2015).

In the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, a prospective observational multicenter study of cognitive development, 224 children with prenatal exposure to VPA, LTG, CBZ, or PHT monotherapy were followed up to 6 years-of-age (Meador et al., 2013). After controlling multiple potentially confounding variables, it was found that, irrespective of the dosage, the mean IQ score of the VPA-exposed children was lower (mean IQ score = 97) than the IQ of the children exposed to the other AEDs (mean IQ scores ranging from 105 to 108). When the dosage of VPA was higher than 1000 mg/ day, the negative impact was seen not just on verbal ability, but also on nonverbal ability, executive function and memory (Meador et al., 2013). These results were in line with the cognitive evaluations conducted with these children at 3 and 4.5 years-of-age (Meador et al., 2009; Meador et al., 2012). Similarly, earlier studies with a different demographic background have demonstrated a lower verbal IQ in VPA-exposed children compared to children with CBZ exposure (Gaily et al., 2004; Inoyama and Meador, 2015).

Similar conclusions were drawn from another register study (Baker et al., 2015) when interpreting the results of initially 243 AED-exposed and 287 unexposed children. IQ scores of these children were evaluated at 6 years-of-age and VPA, CBZ, LTG, and control groups were compared taking into account maternal epilepsy type, socioeconomic status, maternal IQ, maternal age, gestational age of child at birth, sex, and exposure to seizures, tobacco, or alcohol. Children with prenatal exposure to high-dose VPA (800 mg per day or more) had lower overall IQ than other children, poorer nonverbal and spatial abilities than CBZ- and LTG-exposed children, and poorer verbal abilities than LTG-exposed children. However, children exposed to less than 800 mg per day of VPA were associated with poorer nonverbal abilities compared to CBZ-exposed children, but were equal to other treatment groups in all other categories of neurocognition. In the polytherapy group, children with VPA had 6.4 points reduction in IQ compared to control children, but if there was no VPA included in the maternal medication, there was no difference. It is noteworthy that mothers and drug-exposed children IQ correlations presented in all other treatment subgroups, except in the VPA group. Maternal IQ, gestational age, and socioeconomic status were noted to influence IQ scores in the offspring.

In the the same study (Baker et al., 2015), children exposed prenatally to CBZ had lower verbal abilities than control children but otherwise the exposure did not seem to affect the neurocognition of these children and no dose dependence was observed in the CBZ group.

However, no correlation between prenatal AED dosage and child's cognitive outcome has been described in some studies (Inoyama and Meador, 2015). For example no dose dependence was observed for carbamazepine (Gaily et al., 2004; Meador et al., 2013), lamotrigine (Meador et al., 2013), levetiracetam (Shallcross et al., 2014), or phenytoin (Meador et al., 2013). Furthermore, mothers with more severe epilepsy and heavier seizure burden are more likely to require higher dosages of AEDs making it even harder to distinguish the effect of medication and the effect of underlying epilepsy.

The practices of AED medications have changed during the last decades while the knowledge on long-term effects of *in utero* exposure to newer drugs lags behind, at least until the exposed children reach an appropriate age for neurocognitive evaluation. Levetiracetam is nowadays used in approximately 13% of pregnancies (Vajda et al., 2010) but few studies report on the effects on offspring cognition. So far it seems that LEV has no major disadvantages compared to LTG or CBZ, and LEV appears to be safer than valproate (Shallcross et al., 2011; Shallcross et al., 2014; McCorry and Bromley, 2015). Preliminary findings indicate that fetal topiramate exposure could have adverse effects on neurocognition (Rihtman et al., 2012). The number of *in utero*-exposed children has been too small to make any conclusions for other newer AEDs.

It has been noticed that children of mothers with periconceptional folic acid supplement had a higher mean IQ (108) at 6 years-of-age compared with the children of mothers without folic acid supplement (IQ 101) (Meador et al., 2013). In contrast, Baker et al. (Baker et al., 2015) found no difference in mean IQ between the two population types. Folic acid supplement is recommended with a daily dose of minimum 0.4 mg prior to conception and during pregnancy, as it may decrease the risk of MCMs in the offspring of women with epilepsy (Harden et al., 2009).

Behavioral consequences. VPA has been associated with a higher risk for neurodevelopmental disorders like autism spectrum disorders (ASD) compared to unexposed children or children exposed to other AEDs (Rasalam et al., 2005; Bromley et al., 2013; Christensen et al., 2013; Wood et al., 2015). Diagnostic criteria for ASD were met in up to 12 % of the offspring with *in utero* VPA monotherapy exposure while in the unexposed children the rate was 1.8% (Bromley et al., 2013). Deshmukh et al. (Deshmukh et al., 2016) have shown a relationship between maternal VPA dose and behavioral outcome. In the same study, children with prenatal VPA exposure had higher risk for adaptive behavioral problems in the areas of socialization, communication, and motor skills.

As the most prominent negative effects are seen with *in utero* valproate exposure, i.e. an increased risk for malformations, developmental and

behavioral problems, specific actions have already taken place. In 2014, the Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) of the European Medicines Agency (EMA) published a warning on the use of valproate in women and girls highlighting the risk of malformations and developmental problems in infants exposed to valproate. Soon after this, the joint Task Force of the Commission of European Affairs of the International League Against Epilepsy (CEA-ILAE) and the European Academy of Neurology (EAN) formed a document titled “Valproate in the treatment of epilepsy in girls and women of childbearing potential”.

2.3 SEROTONIN REUPTAKE INHIBITORS

2.3.1 SEROTONIN

Serotonin, 5-hydroxytryptamine 5-HT, is a widely distributed neurotransmitter in the central nervous system. Serotonin signaling pathways are involved in various regulatory brain functions including cognitive, mood and affective functions. Serotonin has a modulatory role in autonomic, motor, sexual, appetite, aggression, and sleep functions, and it modulates several immunological events like chemotaxis, leukocyte activation, proliferation, cytokine secretion, immune responsiveness, and apoptosis (Millan et al., 2008; Lesch and Waider, 2012; Arreola et al., 2015; Olivier et al., 2015). The dysfunction of serotonin transmission is associated with the pathogenesis of e.g. depression, anxiety, schizophrenia, and chronic pain, and many of the medications developed for treatment of these diseases employ the serotonin system (Anderson, 2004; Olivier et al., 2015). Depression is associated with reduced levels of serotonin, dopamine, and norepinephrine, and increased levels of cortisol (Diego et al., 2004; Moret and Briley, 2011).

Serotonergic neurons act via releasing serotonin into the synaptic cleft where serotonin is bound to pre- or postsynaptic serotonin receptors. The serotonin system constitutes of at least 14 different 5-HT receptor classes (Millan et al., 2008). Serotonin receptors are present e.g. in frontal cortex, hippocampus, amygdala, striatum, hypothalamus, and dorsal horn of the spinal cord, and can be expressed in both excitatory and inhibitory neurons (Olivier et al., 2015). To terminate the action of serotonin in the synaptic cleft, serotonin is reuptaken by the serotonin transporter (SERT) molecule or by surrounding glial cells (Youdim et al., 2006; Olivier et al., 2015). The inhibition of the reuptake by binding to serotonin transporter molecule leads to antidepressant activity of the serotonin reuptake inhibitors (SRIs) though it seems not to be the only antidepressive mechanism of these drugs (Anderson,

2004; Olivier et al., 2015). The chemical structures, pharmacokinetics, metabolism, and interactions of SRIs vary (Preskorn, 2004; Harrington et al., 2013).

The early developmental changes in the expression of SERT gene are known to differ between frontal and deeper brain regions (Homberg et al., 2010; Kiryanova et al., 2013). These SERT expressions are genetically determined, although they can also be affected by various hormonal factors and factors exerting epigenetic effects, such as maternal psychiatric status or fetal drug exposure (Oberlander et al., 2009; Homberg et al., 2010; Kiryanova et al., 2013). In addition, SERT gene polymorphisms, contributed by two length alleles, influence the biological activity of the SERT (Murphy and Lesch, 2008). The low-functioning variant has shown to be particularly vulnerable to stressful life events, in other words the influence of genetic factors on behaviour seems to be dependent on the environmental context (Nordquist and Oreland, 2010).

2.3.2 DEPRESSION AND PREGNANCY

Major depression disorder (MDD) is a major health problem affecting over 350 million people all over the world (Perez-Caballero et al., 2014). Depression and anxiety are common among pregnant women as well: Prevalence of depression during pregnancy is estimated to be 7-18 % (Bennett et al., 2004) and anxiety disorders approximately 8 % (Ross and McLean, 2006).

Human studies have implied that untreated maternal depressive, anxiety, and stress symptoms during pregnancy may have adverse short- and long-term effects on both the fetus and the mother (Graignic-Philippe et al., 2014; Gentile, 2015c). Depression is associated to hyperactivity of the fetus and irregular fetal heart rate, and newborns can have increased cortisol and norepinephrine levels, decreased dopamine levels, reduced vagal tone, altered EEG patterns, and stress- or depressive-like behaviors (Gentile, 2015c). These symptoms have been related to obstetrical problems like a higher risk of preterm delivery, low birth weight, offspring with hypothalamic-pituitary-adrenal (HPA) axis abnormalities, and neonatal and later behavioral problems (Field, 2011; Bourke et al., 2014; Hanley et al., 2015; Jarde et al., 2016). The serotonergic system closely interconnects with HPA-axis functions, and maternal depression is associated with increased levels of cortisol at birth (Diego et al., 2004; Field et al., 2010; Field, 2011; Hermansen and Melinder, 2015). The HPA axis is an important part of the stress response system and high cortisol levels in infancy have been associated with lower scores in neurocognitive examinations, attentional problems, and reduced executive function at school age (Hermansen and Melinder, 2015). Furthermore, children born from pregnancies of depressive, untreated, mothers are

considered to have more internalizing behavior and psychiatric disorders such as depression, anxiety, irritability, and withdrawal (Misri et al., 2006; Tronick and Reck, 2009; Bourke et al., 2014; Gentile, 2015b; Malm et al., 2016).

2.3.3 SEROTONIN REUPTAKE INHIBITORS AND PREGNANCY

The first SRIs were used clinically in the 1980s (Perez-Caballero et al., 2014). Since then, the use of serotonin reuptake inhibitors has increased rapidly in various fields of psychiatry, but particularly in the treatment of depression. Nowadays, SRIs are the most commonly used antidepressants, both among people in general and among pregnant women (Perez-Caballero et al., 2014; Olivier et al., 2015). In the United States, SRI use has increased among pregnant women from 1.5% in 1996 to more than 5% since 2005 (Dawson et al., 2012; Perez-Caballero et al., 2014; Charlton et al., 2015).

Currently, pharmacological treatment of severe maternal depressive and anxiety symptoms is recommended in order to reduce their impact on the mother and offspring (Ray and Stowe, 2014; Gentile, 2015a). In addition, though SRIs can be detected in breastmilk (Weissman et al., 2004; Bourke et al., 2014), their serum concentrations, e.g. fluoxetine, citalopram, and venlafaxine, are usually less than 10% of the concentrations observed in the serum of the mother (Weissman et al., 2004).

2.3.4 SEROTONIN REUPTAKE INHIBITORS AND DEVELOPING BRAIN

2.3.4.1 Animal studies

Numerous animal studies have shown serotonin to have a major role in plastic development of the fetal brain (Borue et al., 2007). Serotonin modulates a wide range of developmental processes, both in the structural formation and the functional activity during brain development.

Changes in fetal serotonin levels have been shown to influence the development of the somatosensory cortex, thalamocortical tracts, visual system, and hippocampus (Nordquist and Oreland, 2010; Bourke et al., 2014; Kepser and Homberg, 2015; Suri et al., 2015; Glover and Clinton, 2016). Furthermore, serotonin has been demonstrated to modulate neural cell proliferation, migration, and proliferation, axonal guidance, synaptogenesis, and efficiency of transsynaptic signaling (Borue et al., 2007; Homberg et al., 2010; Lesch and Waider, 2012; Kiryanova et al., 2013).

Environmental factors can alter serotonergic modulation during development (Erzurumlu and Gaspar, 2012; Lesch and Waider, 2012). One of these environmental factors is SRI medication, as SRIs cross the placenta and are able to alter the reuptake of fetal serotonin (Hendrick et al., 2003; Anderson, 2004; Rampono et al., 2009). SRIs disrupt apoptosis and formation of the cortical subplates in the developing brain (Persico et al., 2001; Persico et al., 2003; Xu et al., 2004; Liao and Lee, 2011; Simpson et al., 2011; Suri et al., 2015). These alterations are similar to those seen in human neuropsychiatric disorders (Nordquist and Oreland, 2010). By disrupting cortical histology, SRIs reduce functional network connectivity of the developing brain and they play an important role in network formation (Simpson et al., 2011; Miceli et al., 2013). High levels of serotonin due to prenatal SRI exposure during the sensitive perinatal period may cause permanent anatomical and functional changes (Bourke et al., 2013; Bourke et al., 2014; Suri et al., 2015). These changes can lead to emotion-related and behavioral consequences in adult animals including increased aggressive behavior, autistic and anxiety-like behavior, aggression, and impairments in social behavior (Borue et al., 2007; Kepser and Homberg, 2015; Glover and Clinton, 2016).

In the review of Harrington et al. (2013) the authors suggest that SRIs could be protective in the regulation of the maternal serotonin system. The protective effects have been hypothesized to be due reversal of the effects of maternal stress (Rayen et al., 2011) or due to increased maternal peripheral serotonin levels induced by SRIs (Harrington et al., 2013). SRIs may also affect plasticity directly through alterations of SERT function (Hermansen and Melinder, 2015).

2.3.4.2 Human studies

Serotonin is already detectable in the brain of a human embryo at the age of 5 weeks (Anderson, 2004). Functional magnetic resonance imaging studies have shown that the brain regions involved in emotion processing and behavior in humans are functionally and anatomically affected by a genetic variation of serotonin transporter genes, and the development of these neural circuits appears to be influenced by fetal serotonin levels (Nordquist and Oreland, 2010). Both maternal serotonin levels and the genotype of the child's serotonin transporter protein influence serotonin signaling during fetal development, implying that the development of two children with similar exposure to SRIs may differ substantially (Oberlander, 2012; Hermansen and Melinder, 2015). Furthermore, the s-allele is suggested to be associated with increased social, emotional, and behavioral reactivity, and increased

sensitivity to social support (Lesch, 2007; Sonuga-Barke et al., 2009; Zimmermann et al., 2009; Mueller et al., 2010; Pluess et al., 2011). This complex network of environmental influences, possibly altered neurotransmission, and underlying genetics makes the assessment of causal connections extremely challenging (Hermansen and Melinder, 2015).

Malformations. The association between prenatal SRI exposure and congenital malformations is not quite clear. Mainly the SRI exposure has been associated with only a slightly increased risk for malformations or no increased risk at all (Malm et al., 2011; Bourke et al., 2014; Reefhuis et al., 2015; Wemakor et al., 2015). However, if the medication is very commonly used, even a slightly increased risk substantially raises the number of children with malformations. The strongest association has been observed between prenatal paroxetine and congenital malformations. In this case, the risk for congenital heart defect is approximately 1.5-fold compared to the offspring of women receiving no SRI medication (Hanley and Oberlander, 2014; Reefhuis et al., 2015). Maternal paroxetine use has also been associated with anencephaly, gastroschisis, and omphalocele (Reefhuis et al., 2015).

Obstetric risks and perinatal outcome. Since the 1980s, prenatal SRI exposure had been associated with adverse neonatal symptoms called postnatal adaptation syndrome. The syndrome includes symptoms of respiratory distress, feeding difficulties, jitteriness, temperature instability, sleep problems, tremors, restlessness, and even convulsions, rigidity, and hypoglycaemia (Bourke et al., 2014; Hanley and Oberlander, 2014). The higher risk for these symptoms remains even after controlling maternal mood (Rampono et al., 2009). In a retropective cohort study from Sweden (Forsberg et al., 2014), 22% of the neonates with prenatal SRI exposure during the third trimester were observed to have mild symptoms, and 3% had severe symptoms. In a review from Hanley and Oberlander (2014), the authors note that the risk of an adaptation sydrome can be influenced by genetic variability of the serotonin transporter molecule. In addition, newborns exposed to SRIs are likely to have lower birth weight and pulmonary hypertension (Kepser and Homberg, 2015). It has been suggested that the postnatal adaptation syndrome is not limited to the first days of life but continues through the first postnatal month (Salisbury et al., 2016).

One important variable when assessing the influence of the SRIs is the timing of the exposure. The risk of admission to the neonatal intensive unit, and the risk of lower Apgar scores are higher for the newborns with a third trimester exposure compared to the newborns with exposure during the first trimester (Malm et al., 2005; Smith et al., 2013). Furthermore, Malm et al. (2015) compared the offspring of mothers prescribed SSRI medication during pregnancy to the offspring of those mothers exposed to no medications but with psychiatric disorders. In this register study, the risk for late preterm or

very preterm birth and cesarean section was lower in the offspring of the SSRI treated mothers. On the other hand, the risk for neonatal complications like low Apgar score and need for monitoring in a neonatal care unit was higher (OR 1.68 and 1.24, respectively) in the exposed newborns. When the study group compared the offspring of both treated and untreated mothers with psychiatric problems, to offspring without prenatal exposure to SSRI and no maternal psychiatric disorders, the risk for both adverse pregnancy outcome and need for neonatal-care-unit monitoring were elevated. The authors suggested that SSRI use during pregnancy could have a protective role for perinatal outcome of the newborns of depressive mothers.

Long-term developmental consequences. Few studies assess long-term developmental consequences of the prenatal SRI exposure, but the effects of the exposure may outlast the neonatal period (Bourke et al., 2014; Kepser and Homberg, 2015). The results are somewhat controversial, but already as toddlers, exposed children seem to have slightly delayed psychomotor development compared to unexposed children despite taking maternal mood into account (Casper et al., 2003; Casper et al., 2011). Furthermore, other studies on later development have indicated cognitive difficulties and behavioral problems (Hermansen and Melinder, 2015).

Autism spectrum disorders are associated with changes in the serotonergic system (Croen et al., 2011; Kepser and Homberg, 2015). Humans have a period of high capacity for serotonin synthesis in the brain during childhood, but this process is disrupted in autistic children (Chugani et al., 1999). Children with prenatal SRI exposure differ from unexposed children at 11 to 40 months-of-age with respect to social and adaptive behavior, even when pre- and postnatal maternal depressive mood is controlled (Casper et al., 2011; Hanley et al., 2013). Furthermore, there was no significant difference in social and adaptive behavior between the children exposed and unexposed to pre- or postnatal maternal depression (Hanley et al., 2013). In a Danish register study, autism spectrum disorders were detected in 1.5% of the children exposed to maternal SSRI during pregnancy compared to 0.7% in the control group (Gidaya et al., 2014). The effect was higher in the group with longer exposure. Likewise Croen et al. (2011) found that SSRI exposure was associated with a 2-fold risk of autism spectrum disorders, whereas there was no increase in risk for the offspring of the mothers with a history of mental health treatment other than SSRIs. Man et al. (2015) have conducted a systemic review and meta-analysis of observational studies concerning prenatal SSRI exposure and risk of autism spectrum disorders. The authors concluded that the risk is increased, but the causality remains unconfirmed. There are also controversial studies such as one by Grzeskowiak et al., 2015, and others mentioned in the review of Hermansen and Melinder (Hermansen and Melinder, 2015).

Overall, prenatal SRI exposure may have consequences in the neonatal period as well as long-term consequences like adverse effects on offspring (Hanley et al., 2013, 2015; Ray and Stowe, 2014). On the other hand, the findings are still controversial (Hermansen and Melinder, 2015) and the effects are altered by various pre- and postnatal factors, including psychological, pharmacological, genetic, and social circumstances. In addition, though prenatal SRI exposure poses risks for offspring, maternal depression during pregnancy imposes potential risks as well. It is especially difficult to know what severity level of maternal symptoms justifies treatment, as the potential risks of untreated maternal depression on the offspring and the mother, and protective role of SRIs during pregnancy, are still poorly understood (Hanley and Oberlander, 2014; Malm et al., 2015). SRIs during pregnancy should thus be used based on a risk-benefit decision on a case-by-case basis (Bourke et al., 2014).

2.4 ELECTRICAL ACTIVITY OF NEWBORN BRAIN

2.4.1 GENERAL ASPECTS OF EEG

Information within the brain and between the brain and other parts of the body is transmitted via electrical signals. Cortical electrical activity can be measured by applying electrodes to the scalp surface to detect electrical voltage potentials of the underlying cortex. This non-invasive EEG method measures the potential difference between two electrodes placed at distinct points as a function of time. Since the introduction of EEG in 1924, it has gained multiple clinical and research applications both in adults and in children, in human and in animal studies.

EEG evaluation has relied largely on visual, i.e. qualitative, assessment. The standardization of visual assessment is nearly impossible, and it relies on individual capacities of the evaluators. Visual interpretation of EEG is always subjective and time-consuming. Fortunately, advances in both quantifiable computational methods, as well as in recording techniques, have emerged during recent years with novel prospects for assessing functional cortical activity (Vanhatalo et al., 2005b; Tokariev et al., 2012; Räsänen et al., 2013; Tokariev et al., 2016;). Due to recent progress, cellular level mechanisms of the EEG phenomena are now better understood (Engel et al., 2013; Hyafil et al., 2015; Sotero et al., 2015).

2.4.2 NEONATAL EEG

EEG has been widely used in clinical settings in neonatal wards focused on evaluating neonatal seizures and predicting the outcome (Cherian et al., 2009). The features of neonatal EEG, with the distinctive temporal and spatial organization, reactivity and maturational changes, differ profoundly from the ones of adult EEG. The interpretation of the neonatal EEG requires special expertise (Andre et al., 2010). The major changes in neonatal EEG with maturation are seen in background activity and organization of the behavioral states (Cherian et al., 2009; Andre et al., 2010).

Background activity. Early cortical brain activity is characterized by two activity modes: relative quiescence that is interrupted by spontaneous activity transients (SAT), also known as bursts (Vanhatalo and Kaila, 2006; Andre et al., 2010). Bursts are short and have an amplitude typically more than 100 uV (Hayakawa et al., 2001). Relatively quiet periods between bursts are called interburst intervals (IBI) and the length and inactivity of these intervals is related to the neurological maturation (Hellstrom-Westas and Rosen, 2005). Along with maturation, the level of discontinuity decreases and the quality of typical background oscillations changes (Andre et al., 2010).

Vigilance states. Another alteration seen with maturation is the development of vigilance states. The length and content of the vigilance states change with maturation (Andre et al., 2010). The sleep-wake alteration in EEG activity is well established from the gestational age of 29 to 30 weeks onwards, however alternation in activity level is seen many weeks earlier (Palmu et al., 2013). At first, the sleep pattern is highly discontinuous (*Tracé discontinu*) which is modified into "*Tracé alternant*" with low voltage activity during the IBIs, and finally, into a continuous sleep pattern, with quiet and active sleep states, typically at around term age (Andre et al., 2010; Palmu et al., 2013). Sleep-wake cycling and behavioral states are some of the basic features evaluated for normality of the neonatal EEG. This demands polysomnographic recording techniques (Andre et al., 2010; Palmu et al., 2013). Computer analyses of sleep states can be used as physiologic biomarkers of developmental neural plasticity (Scher et al., 2009).

Connectivity. The development of higher neurocognitive functions is dependent on interaction between different parts of the CNS. Two major phenomena of the interaction are symmetry and synchronization. Both of these features show maturational changes with time. Interhemispheric synchrony represents temporal co-occurrence of burst activity in the right and left hemispheres. Synchrony develops along with the increase of cortical-cortical connections. Recent studies with automated evaluation of interhemispheric synchrony, namely Activation Synchrony Index (ASI), have shown that interhemispheric synchrony correlates to normal clinical features

and visual EEG assessment of term newborns (Koolen et al., 2015; Koolen et al., 2014). On the other hand, interhemispheric symmetry indicates that the amplitude and frequency content are comparable between the hemispheres.

Recent experimental studies have implied that even more detailed features, like interaction between cortical layers and underlying subplate, could be studied by computational analyses of neonatal EEG (Minlebaev et al., 2007; Colonnese and Khazipov, 2010;). These advanced analyses require multichannel EEG recordings with high potential spatial resolution (Vanhatalo et al., 2005b; Koolen et al., 2014; Koolen et al., 2015).

Modulating factors. Psychoactive drugs are known to modulate neurotransmission during prenatal stages of brain development (Thompson et al., 2009). Many of the studies regard these effects on EEG recordings later in life, only a minority of the studies have examined the effects on neonatal EEG. Neonatal EEG phenomena are affected by postnatal medications (Nguyen The Tich et al., 2003; Young and da Silva, 2000; Malk et al., 2014) and postnatal aminophylline medication is known to accelerate sleep-wake cycle maturation in aEEG in premature neonates (Lee, 2009). Neonates with neonatal abstinence syndrome have more EEG aberrancies during the neonatal period compared to neonates without abstinence symptoms (van Baar et al., 1989).

EEG patterns appear to reflect individual differences in emotion regulation (Goldstein and Klein, 2014). One of the vulnerability markers seems to be frontal asymmetry in EEG, which appears to be associated with stressful events in children's lives, such as pre- and postpartum maternal depressive symptoms, and it may even predict development of depression later in life (Hahn and Tharp, 1990; Goldstein and Klein, 2014; Lusby et al., 2014; Nunes et al., 2014; Peltola et al., 2014). In addition, respiratory distress and circulatory compromise may manifest themselves in a term newborn as long lasting effects in EEG maturation (Hahn and Tharp, 1990; Nunes et al., 2014).

2.4.3 PREDICTIVE VALUE OF NEONATAL EEG

Neonatal EEG reflects both prenatal and postnatal experiences. One of the most widely-used clinical EEG applications in neonatal wards is amplitude-integrated EEG, which is known to have good predictive value, especially on the outcome of hypoxic–ischemic encephalopathy (Merchant and Azzopardi, 2015). However, higher spatial resolution of the conventional EEG recording offers a more detailed insight into the interareal interactions and differences when compared to aEEG monitoring. Automated neurophysiologic methodologies can help to evaluate organization and maturation of the

newborn brain, and act as potential biomarkers for activity-dependent development of the fetal and neonatal brain (Scher et al., 2005; Vanhatalo et al., 2005b). Some of the previous findings enlightening the predictive value of neonatal EEG are listed below.

Background activity. Studies on the predictive value of neonatal EEG are commonly based on evaluating the background activity. Background abnormalities in preterm infants correlate with psychomotor outcome as late as 5 to 6 years-of-age (Okumura et al., 2002; Le Bihannic et al., 2012). One of the most stated predictive markers is the increased discontinuity of the EEG beyond the normal maturation timetable (Menache et al., 2002). Discontinuity correlates with cortical folding (Biagioni et al., 2007b). Prolonged discontinuity and amplitude depression have been associated with an increased risk for later brain dysfunction (Hellstrom-Westas and Rosen, 2005; Le Bihannic et al., 2012). In addition, cortical burst dynamics of pre-term neonates has correlated with later neurocognitive development when evaluated with Bayley scales of infant development II (Iyer et al., 2015). EEG findings may have higher sensitivity than cranial ultrasound, and abnormal EEG findings may precede abnormal findings on ultrasound (Kubota et al., 2002; Okumura et al., 2003; Bowen et al., 2010;). Atypical patterns of EEG activity in response to face stimuli have been seen in children with autism spectrum diseases (Dawson et al., 2012).

As the different aspects of the neonatal EEG are evaluated, particular waveforms or patterns of abnormality have been associated with certain outcomes or certain etiologies (Kubota et al. 2002, Okumura et al. 2003). For instance, positive rolandic sharp waves or sharp waves followed by prolonged low voltage EEG waves in preterm neonates have been associated with intrapartum fetal distress, and postpartum brain damage (Anderson and Thomason, 2013; Kubota et al., 2002; Okumura et al., 2003). In addition, though MRI and ultrasound are considered to be the most significant predictive markers for adverse outcome in e.g. intraventricular hemorrhage or periventricular leukomalacia, EEG is seen to provide independent prognostic value as well after controlling MRI (Tich et al., 2007; Hayashi-Kurahashi et al., 2012).

Connectivity. The importance of early connectivity has been pointed out earlier. To emphasize the importance of the different kinds of connectivity phenomena, certain aspects of the predictive value of connectivity should be highlighted. First, asymmetry between the hemispheres is known to relate to adverse outcome (Selton et al., 2000; Cherian et al., 2009) like the severity of ischemic damage (van Putten and Tavy, 2004; van Putten, 2007). Furthermore, poor synchronization has been associated with poor outcome (Anderson et al., 1985; Lombroso and Matsumiya, 1985). When cognitive capacity is evaluated in detail, ventro-temporal-occipital cortex connectivity

proves the most extensive network that predicts numerical abilities (Evans et al., 2015).

Overall, computational EEG analyses may be employed to assess infant neural plasticity, in both the clinical and in research setting, to predict the neurocognitive or behavioral consequences as well as to monitor or diagnose medical conditions.

2.5 NEUROLOGICAL AND COGNITIVE EVALUATIONS IN INFANCY

The tremendous development during fetal life culminates in, if "everything" goes well, the birth of a highly competent neonate. Sometimes "everything" does not go well. Common perinatal problems include asphyxia, prematurity, and cerebral hemorrhage, all of which pose an increased risk for future development (Mercuri, Cowan 1999). The rapid phase in development and plasticity continues postnatally and new abilities in the fields of motor, early verbal, and social development are obvious to us all. In contrary to parents and other caregivers, health care professionals and researchers need accurate methods to assess the neurological well-being and development of an infant. These methods aim to find functional correlates of the underlying neurobiological changes.

Traditional neurological examination of a child is divided into five subdivisions interpreting different functions of various levels of the nervous system. These subdivisions are: 1) The mental status assessment evaluating the higher brain (cortical) functions; 2) the cranial nerve examination assessing brainstem and cranial nerve function; 3) motor; and 4) sensory examinations assessing functions of the cortex, spinal cord, nerves and muscles; and 5) evaluation of coordination and gait and thus assessing the possible problems in the basal ganglia and cerebellum (Wusthoff 2013).

As the neurological status changes rapidly from prematurity to infancy and further to later childhood, the test protocols must be adjusted to the age group. The requirements of the assessments depend on the circumstances they are used in, the goal of the assessments and the age of the patient (Heineman, Hadders-Algra 2008). In clinical work, the primary goal is quite often to identify infants at risk for developmental problems or in need of interventions. In research work, the requirements can be even more precise and the researcher should be well acquainted with the instrument: what it measures, what are the normal findings, and especially what are the limitations of the

instrument. The instrument should have a high inter- and intra-observer agreement and the best possible positive and negative predictive values.

2.5.1 NEONATAL NEUROLOGICAL ASSESSMENT: CLINICAL INSTRUMENTS

Despite vast improvements to neonatal neuroimaging and electrophysiological techniques and their availability during the last decades, clinical assessment instruments still have a profound impact on neonatal evaluation in the clinic and in informing the need for further investigations (Wusthoff, 2013). The advantages of clinical examination include non-invasiveness, inexpensiveness, and repeatability (Wusthoff, 2013).

The same principals of neurological examination apply in neonates as in older children but some adjustments are required. According to Wusthoff et al. (2013), the most important aspect in neonates is usually behavioral observation. This includes evaluation of the alertness, responses to environment, and orientation to external stimuli. Posture, tone, deep tendon reflexes and strength should be tested to evaluate the motor system. Cranial nerve testing is performed very much like it is done in older children but the evaluation of the sensory responses of a neonate may be difficult. Observations of generalized movements and primitive reflexes are an important part of the assessment, as gait, coordination, or purposeful movements cannot be evaluated.

In contrast with older children and adults, the abnormalities observed in neonatal neurological examinations are usually non-specific and global, not focal (Wusthoff, 2013). For example, increased extensor tone in extremities or trunk muscles has been associated with diffuse lesions with cortical, white matter, and basal ganglia involvement, suggesting adverse motor and cognitive outcome (Mercuri et al., 1999). Another aspect to be remembered is the evolution of the clinical presentation of neonatal brain injury resulting in a changing external status of the neonate that may include an initial period of deterioration followed by a period of pseudo normalization and only later a more permanent motor or cognitive dysfunction decline (Wusthoff, 2013). Alterations in the clinical status emphasize the importance of repeatable instruments in neonatal assessment (Mercuri, Cowan 1999).

A variety of instruments may assess neonatal neurology. These instruments are highly utilized in neonatal intensive care units, including a high proportion of premature neonates. In a recent review (Noble and Boyd, 2012), the authors found eight instruments suitable for use in preterm infants up to 4 months of corrected age. Of these eight, they considered the Prechtl's Assessment of

General Movements (GMs) (Einspieler and Prechtl, 2005), the Test of Infant Motor Performance (TIMP) (Campbell, 2005), and the Neurobehavioral Assessment of the Preterm Infant (NAPI) (Korner and Constantinou, 2001) to have both the strongest psychometric properties and a good clinical utility when assessing preterm neonates. GMs are spontaneous movements involving the whole body and are endogenously generated (Snider et al., 2008). Noble et al. (2012) suggested that GM testing has the best predictive value, with the advantage of not handling a fragile preterm, but it requires serial video monitoring of the quality of specific movement patterns (Cioni et al., 1997). Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) (Lester and Tronick, 2004; Lester et al., 2004) seem to have good validity and strong psychometric qualities, but due to its more laborous assessment (up to one hour) it was considered to have more utility in research work. Interrater reliability has been considered good (>0.74) in Hammersmith Neonatal Neurological Examination (HNNE) and in NNNS in assessing preterms (Eeles et al., 2016), and even higher (0.96) in HNNE when assessing term neonates (Dubowitz et al., 1999; Lester et al., 2004). Furthermore, NNNS requires extensive organized training and an accreditation.

Hammersmith Neonatal Neurological Examination (HNNE) is a widely-used standardized instrument to evaluate and follow neurological status, in both clinical and in research work. HNNE was first introduced in 1981 and revised in 1999 (Dubowitz et al., 1999). The revised version consists of 34 items organised into six categories: tone, tone patterns, reflexes, movements, abnormal signs, and behaviors, and thus comprises various aspects of neonatal neurological function (Dubowitz et al., 1999). HNNE is easy to perform, does not need a formal certification, and takes only 10 to 15 minutes (Dubowitz et al., 1999; Dubowitz et al., 2005). It was first validated in term neonates, including 224 clinically healthy neonates at the postnatal age of 6 to 48 hours and later in preterms as well (Dubowitz et al., 1998; Ricci et al., 2008). The predictive value of HNNE is considered to be good (Dubowitz et al., 1998; Woodward et al., 2004; Ricci et al., 2008; Wusthoff, 2013). For example, a higher number of abnormal findings in HNNE has correlated with more severe outcome at 2-year follow-up when 380 low-risk preterms (born under 35 weeks gestation) and 85 preterm infants with major ultrasound abnormality were evaluated (Ricci et al., 2008). Optimality scores at 9-14 months-of-age have been associated with motor outcome at 2 and 4 years-of-age (Haataja et al., 2001). Woodward et al. (2004) examined 66 preterm neonates (mean gestational age 28 weeks) by using HNNE and MRI at term age. Sensitivity of HNNE for identifying abnormalities in MRI was 88% and specificity 46%. The negative predictive value of HNNE was calculated to be 92%, but the positive predictive value to be only 34%. Furthermore, in a prospective study (Setänen et al., 2014), HNNE at term age predicted the neurological outcome at 2 years-of-age. The predictive value of MRI and cranial ultrasound were improved

when combined with HNNE compared to either of these imaging procedures alone.

It seems that HNNE identifies neonates needing further investigations well but it cannot be used as a sole method to diagnose neurological challenges (Woodward et al., 2004). Isolated deviant items seem to have little diagnostic value (Dubowitz et al., 2005; Setänen et al., 2014). Furthermore, it has to be remembered that HNNE reflects only the current status of the neonate and non-neurological factors, like ongoing systemic disease or medication, may contribute to the examination without necessarily affecting outcome (Dubowitz et al., 2005). This disadvantage can be minimized by repeating the measurement and thus confirming the persistence of the symptoms, as in full-term neonate a normal HNNE examination at the postnatal age of two weeks is considered to be a reliable predictor of neurological outcome (Mercuri and Cowan, 1999).

2.5.2 NEUROLOGICAL EVALUATION IN INFANCY: CLINICAL INSTRUMENTS

Neurological evaluation during the neonatal period represents a holistic view of neurological well-being, but after that time, more detailed neurological assessment will be possible. Neurological status and developmental aspects are then mainly assessed with separate tools though occasionally these aspects overlap as illustrated in a systematic review from Heineman and Hadders-Algra (2008). The authors reviewed currently-available methods of the evaluation of neuromotor function in infancy. They included fifteen instruments and classified them into four groups: 1) Comprehensive neurological examinations; 2) Procedures with standardised scoring; 3) Observation of milestones; and 4) Assessment of quality of motor behavior or motor patterns.

Comprehensive neurological examinations like Hammersmith infant neurological examination (HINE) (Dubowitz and Dubowitz, 1981; Haataja et al., 1999; Haataja et al., 2003;), Touwen infant neurological examination (de Groot et al., 1992), and Aiel-Tison neurological examination (Aiel-Tison and Grenier, 1980) were considered to have good construct validity (the degree to which a test measures what it claims to be measuring). They also offer good predictive validity for development of major motor disorders like cerebral palsy. Data to evaluate their predictive validity for minor developmental problems were available only for Touwen infant neurological examination. In addition to predictive value, the tools differed at the level of intra- and inter-

observer agreement, in construct validity, and concurrent validity (measure of how well a particular test correlates with a previously validated measure).

Hammersmith Infant Neurological Examination (HINE) is a simple, scorable method designed for neurological evaluation of 2 to 24 month-old infants (Haataja et al., 1999; Haataja et al., 2003;). HINE is easily applicable, requiring no formal training, and takes only 5 to 10 minutes to complete. Different aspects of infant neurology are assessed with 37 items. These items are divided into three sections: 1) Neurological items (cranial nerves, posture, movements, tone and reflexes); 2) Motor development; and 3) Behavioral state. In addition to original aspect of a clinical tool, optimality scores have been developed for research purposes (Haataja et al., 2003; Haataja et al., 1999). For optimality scores, each item is scored from 0 to 3. Optimality for each age group is defined so that it includes at least 90% of low-risk, normally-developed infants (Haataja et al., 1999; Haataja et al., 2003). In a recent meta-analysis on the predictive value of HINE (Romeo et al., 2016), HINE was shown to have good sensitivity. In very low birth weight infants, HINE performed at the corrected 6-15 months-of-age had predictive value for motor function (walking) at 2 years-of-age, with a sensitivity of 98% and specificity of 85% (Frisone et al., 2002). The predictive value persisted even if HINE was performed as early as 3 months post-term (Romeo et al., 2016). HINE may provide a tool to follow high-risk infants during the first year of (corrected) age identifying the early signs of even the mildest form of cerebral palsy (Haataja, 2016; Romeo et al., 2016).

Griffiths Mental Developmental Scale (Griffiths and Huntley, 1996) and *Bayley Scales of Infant Development* (BSID) (Bayley, 1993, 2006) are two widely-acknowledged developmental tests for infants. When examining children under 2 years-of-age, Griffiths Developmental Mental Scale constitutes five different areas of abilities: Locomotor (scale A); Personal–social (scale B); Hearing and speech (scale C); Eye–hand coordination (scale D); and Performance (scale E). From these subscales, a total Developmental Quotient can be calculated. BSID-III is designed to evaluate the cognition of infants and toddlers of 1 to 42 months-of-age and includes three subtests: 1) Cognitive scale; 2) Language scale; and 3) Motor scale. Original raw scores are first converted to scale scores and then further to composite scores.

The scores of the developmental quotient of Griffiths-II and Bayley-II (Bayley, 1993; Griffiths and Huntley, 1996) have been suggested to be interchangeable, meaning that the results for a given child should be the same regardless of the instruments (Cirelli et al., 2015). Both of these instruments should have calibrated norms for the cultural context in which they are used, or the cohort of controls should be large enough to make conclusions. For the current version of BSID (III), normative data for Finnish infants is available

(Salo et al., 2009). The predictive validity of Mental Developmental Index of BSID-II for cognitive function at school age has been considered the be poor (Hack et al., 2005). On the other hand, Griffiths scales in children with neonatal encephalopathy at 1 or 2 years-of-age are considered to be a good predictor of impairment at school age (Barnett et al., 2004). However, a normal score in the early years cannot preclude later neurological, perceptual-motor, or cognitive abnormalities (Barnett et al., 2004).

Overall, prediction of developmental outcome at an early age is difficult and the best achieved through combining multiple, complementary instruments (Heineman and Hadders-Algra, 2008). The most important consideration in choosing the instrument is the ultimate goal that the instrument needs to serve.

2.5.3 NEUROLOGICAL EVALUATION IN INFANCY: EYE-TRACKING BASED METHODS

The clinical instruments evaluating infantile development are, though standardized, vulnerable to bias related to human-to-human interaction and interrater disagreement. Automated testing procedures of specific cognitive processes, in particular involving visual functions, have been developed (Gredeback et al., 2010; Oakes, 2012; Ahtola et al., 2014; Jones et al., 2014; Kulke et al., 2015; Leppänen et al., 2015). These methods allow the evaluation of infants' sensory and cognitive processes with completely automated technology.

Already as a newborn, a child has the ability of visual fixation. The subcortical brain systems involved in the maturation of facial recognition and infants' attentional abilities are functional already at birth (Johnson, 2005). Infants' visual attentional system undergoes rapid development during the first few months of life (Hunnius, 2007; Leppänen and Nelson, 2009; Johnson et al., 2015) and even before spoken language, infants acquire information by interpreting facial expressions (Leppänen and Nelson, 2009). This makes the maturation cascade vulnerable to prenatal adverse events.

Instrumental measures to study infants' eye movements were first introduced in the 1970s, but only during the last decade has the development in corneal reflection methodology allowed wider usage of eye-tracking-based tests in evaluating infant cognition, measuring infants' visual acuity, visuospatial orienting, and attention to social stimuli (Gredeback et al., 2010; Braddick and Atkinson, 2011; Oakes, 2012; Wass et al., 2014; Ahtola et al., 2014; Jones et al., 2014; Brooks and Meltzoff, 2015; Kulke et al., 2015; Leppänen et al., 2015). These processes serve as early "building blocks" for the development of later advanced cognitive, academic, and social skills (Rose et

al., 2003; Leppänen and Nelson, 2009; Johansson et al., 2015; Stjerna et al., 2015). For example, speed of visuospatial orienting in infancy is suggested to predict cognitive and academic performance at 4 and 11 years-of-age (Dougherty and Haith, 1997; Rose et al., 2003) and similarly, attentional bias for faces in infancy are considered to predict socioemotional development at 14 months-of-age (Peltola et al., 2015). In addition, eye-tracker procedures have been tested to measure visual acuity in preverbal children from 2 to 12 months-of-age (Jones et al., 2014) and to detect visual fields defects (Murray et al., 2009).

In both the research and clinical settings, eye-tracker measurements are being increasingly implemented. These measurements are non-invasive, easy to carry out, and fairly inexpensive, providing a potential indicator for early detection of autism spectrum disorders, for example (Senju and Johnson, 2009; Chawarska et al., 2010; Bedford et al., 2014; Bolte et al., 2016; Chita-Tegmark, 2016; Klin et al., 2015; Pierce et al., 2016). Abnormal visual disengagement seems to be an early marker of autism spectrum disorders (Sacrey et al., 2014). In addition, eye movement testing has been used to evaluate the effects of prenatal alcohol (Green et al., 2009; Paolozza et al., 2013), and opioid agonist exposure (Konijnenberg and Melinder, 2015). SSRI administration has been observed to affect the perceptual processing of face stimuli in adults (Jonassen et al., 2015), and administration of oxytocin has shown to have an immediate effect both on eye contact (Auyeung et al., 2015), and on emotion recognition (Lischke et al., 2012; Kanat et al., 2015) even with adult individuals with autism spectrum disorder (Domes et al., 2013).

In conclusion, compared to traditional testing methods, eye-tracking-based testing allows complete automatization of the test procedure and accurate, transparent physiological metrics of the sensory and cognitive processes in infants (Leppänen et al., 2015).

3 AIMS OF THE STUDY

Previous studies have highlighted the potential risks of AEDs and SRIs on the developing brain. The mechanisms of these adverse consequences remain unclear. While the molecular and histological effects of the prenatal drug exposures are not attainable in live human newborns, brain function can be studied in human neonates. Relatively subtle, yet significant problems in neurocognition and behavioral problems can only be detected later in life, usually at 5 to 6 years-of-age when many confounders have been at play. Non-invasive methods and objective quantitive measurements are needed to detect indicators for later developmental problems already in infancy. Thus, these considerations are addressed in this thesis by investigating the following specific aims:

1) To investigate whether prenatal AED or SRI exposure changes newborn brain activity (I, III)

2) To evaluate whether the prenatal AED exposure affects visual attention and/or emotion-related attention in 7-month-old infants by using eye-tracker methodology (II)

3) To characterize functional connectivity in healthy term newborns (IV)

4 METHODS

4.1 RECRUITMENT

All studies included were conducted in the Helsinki University Hospital (HUH) and the ethics committee of the HUH has approved the study. The recruitment for Studies I, II, and IV took place between October 2009 and December 2013, and for Study III between January 2012 and June 2014. A written informed consent was obtained from all study and control mothers. The pregnant women with desired prenatal medication (AED or SRI) were recruited two different ways depending on the medication:

Studies I and II (AED): For Studies I and II, the pregnant women with epilepsy (PWE) were recruited during their first visit in the HUH adult epilepsy clinic during the ongoing pregnancy. The HUH epilepsy clinic is responsible for epilepsy follow-up of all PWE in the Helsinki area. During the recruitment period, 118 PWE visited the clinic. There were 12 miscarriages and 43 PWE were excluded from the study due to miscarriages, refusing to participate, insufficient language skills, unavailability to follow-up, non-epileptic seizures, alcohol or drug abuse, or unstable use of AEDs. Thus 63 pregnancies were included. Seven newborns were excluded during the neonatal period due to malformations, adrenal medullary neuroblastoma, prematurity, or parents' withdrawal. Altogether 56 AED-exposed newborns were included to Studies I and II.

Study III (SRI): For Study III, 22 pregnant women with SRI medication were recruited either during routine prenatal follow-up visits in the Health Care Centers in Espoo, Finland, or via advertising in newspapers and public places.

Control group. A shared cohort of 67 pregnant women for Studies I, II, and III were recruited either by a nurse during regular pregnancy monitoring in an outpatient clinic or by a newspaper announcement.

Study IV: The study subjects of Study IV comprised 38 newborns of the control group who had underwent two EEG recordings instead of one.

4.2 DATA COLLECTION

4.2.1 BACKGROUND INFORMATION

Studies I and II: Background information including prospective, detailed information of exposure (including drug serum levels), socio-demographic characteristics, smoking, and alcohol use during pregnancy was obtained during outpatient visits in every trimester. Data on pregnancy outcome was obtained retrospectively through medical records including obstetric information.

Study III: Background information including above-mentioned data of the SRI medication group was obtained by self-questionnaires from both parents during the last week of pregnancy. The medication data was also assessed in an interview by a psychiatrist at the same time point. Pregnancy outcome was obtained retrospectively through medical records as in Studies I and II.

Study IV and control group: The above-mentioned items of background information were obtained from the medication and control groups (including Study IV subjects) prospectively with interviews by a research nurse during each trimester and/or by completing the questionnaires during pregnancy as described above. Pregnancy outcome was obtained retrospectively through medical records.

4.2.2 CLINICAL EXAMINATIONS OF THE CHILDREN

Studies I and III: The author examined newborns during the first two postnatal weeks by using Hammersmith Neonatal Neurological Examination, HNNE (Dubowitz et al., 1999). To assess possible withdrawal symptoms, the Modified Finnegan Neonatal Abstinence Scoring System (Finnegan and Kaltenbach, 1992) was used in Study II, because of the increased risk for the postnatal adaptation syndrome in the newborns with *in utero* SRI exposure (Rampono et al., 2009; Bourke et al., 2014; Forsberg et al., 2014; Hanley and Oberlander, 2014).

Study II: Infants were examined at the 7 months-of-age with Hammersmith Infant Neurological Examination, HINE (Haataja et al., 1999; Haataja et al., 2003) to assess the clinical neurological status, and with Griffiths Mental Development Scale (Brandt and Sticker, 2001) to evaluate cognitive development.

4.2.3 EEG

The newborn brain activity EEG was evaluated in Studies I, III, and IV. The EEG recording procedures and initial visual EEG reviews were performed with identical methodology. The only exception was that in Study I there was only one EEG recording (within three weeks after birth) but in Study III and IV there were two recordings: The first within a week after birth (Rec 1), and the second about two to three weeks postnatally (Rec 2). This was done in order to distinguish acute withdrawal reactions from longer-lasting EEG effects (Study III) or to assess the individual maturation (Study IV).

The EEG signal was collected by using NicOne EEG amplifier (Cardinal Healthcare/Natus, USA) and EEG caps with 20-32 electrodes (sintered Ag/AgCl electrodes; Waveguard, ANT-Neuro, Germany). Electrodes were positioned according to the International 10-20 standard. Sampling frequency Fs was 250 or 500 Hz. The polygraphic channels were used for sleep state assessment according to standard criteria (Andre et al., 2010) and included chin electromyogram, electrocardiogram, eye movements, and respiratory sensors. Hardware filters were not applied.

4.2.4 EYE TRACKER

The eye-tracking test was designed to assess infants' visuospatial orienting and attentional bias for faces. The overall mean duration of the fixations (infant's ability to disengage his or her gaze from the stimulus at fixations to a new stimulus in the visual periphery) corresponds the general efficiency of infants' visuospatial orienting. Longer duration is linked to atypical development (Elison et al., 2013; Papageorgiou et al., 2014). On the other hand, the relative lengthening of the fixation in the context of faces, i.e. infant's ability to inhibit the gaze disengagement when the infant is fixating to a neutral, happy, or fearful expression, and thus to make a difference between non-face patterns and faces, reflects infants' attention bias for faces (Leppänen, in press).

During the 15-minute long eye-tracker test, infants were sitting in their parent's lap and watched a screen with changing objects. A sequence of visual stimuli was presented on a 17-inch TFT monitor. The monitor was integrated in a Tobii T120 eye-tracker device (Tobii Technology AB, Stockholm, Sweden). First, a calibration procedure was performed (Ahtola et al., 2014). Our eye-tracking study protocol constituted of 32 trials. Each 4000 ms trial had two phases. The first 1000 ms phase constituted attracting the infant's attention to the center of the screen using simple audiovisual animations, which was then replaced by an image of a non-face pattern ('sham') or a face displaying neutral, happy, or fearful expression. After this central image, a peripheral

stimulus was added to the edge of the screen corresponding the second 3000 ms phase of the trial.

4.2.5 ASSESSMENT OF MOTHERS

Studies I and II: Cognitive abilities of 48 AED-exposed and 20 control mothers were evaluated (Stroop, 1935; Rey, 1941; Wechsler, 1997) within 12 months postpartum. In addition, the same neuropsychologist had evaluated two of the exposed mothers in the previous seven years.

Study III: During the last week of pregnancy, a psychiatrist interviewed all mothers with SRI medication and 37 mothers of the control group. The Research Version of The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)–interview was completed and medication was ascertained. In addition, well-validated symptom scores were used to assess the severity of current symptoms of depression (Beck Depression Inventory, BDI (Beck et al., 1961), anxiety (Beck Anxiety Inventory, BAI) (Beck et al., 1988), and harmful alcohol use (Alcohol Use Disorders Identification Test, AUDIT; Babor et al., 2001).

4.3 DATA ANALYSES

4.3.1 DEVELOPMENT AND CLINICAL NEUROLOGY

Studies I and III: From the raw scores of the 34 HNNE items six categories (Tone, Tone patterns, Reflexes, Movements, Abnormal signs and Orientation and behaviour) and Total Score were calculated according to Dubowitz (Dubowitz et al., 1999). Categories represent different aspects of neurological wellbeing of a newborn. As the conceptional ages during the neurological examination differed significantly ($p=0.01$, Mann-Whitney test) between the AED-exposed (mean 42.2 weeks (range 30.4 - 44.4 weeks, SD 0.87) and control groups (mean 41.6, range 39.1 - 43.6, SD 1.07), Compound and Total Optimality Scores were employed, taking into account the conceptional age (Dubowitz et al., 1999) in Study I.

Study II: Raw scores from Griffiths Mental Development Scale were converted to five Subscales (Locomotor, Personal-Social, Hearing and Language, Eye and Hand Co-ordination and Performance) and to total Developmental Quotient according to Brandt and Sticker (2001).

4.3.2 EEG

The author performed the initial visual EEG review by NicoletOne Reader software and selected artefact-free EEG epochs of active (AS) and quiet (QS) sleep for further analyses. The epochs were converted to European Data Format (EDF) and were further quantitatively analyzed by using custom scripts in Matlab (Version R2012b, MathWorks, Natick, MA, USA).

The quantitative EEG analyses aimed to evaluate both the local and global cortical function and computational analyses included the following features: oscillations, phase-amplitude interactions, interburst intervals, interhemispheric synchrony and frequency spectra (Studies I and III), and different aspects of functional connectivity (Study IV).

4.3.2.1 Oscillations

Frontal alpha and temporal theta frequency oscillations are normal phenomena seen in a neonatal EEG. Bipolar derivations Fp1-F3 and Fp2-F4 (alpha), and T3-T5 and T4-T6 (temporal theta) from active sleep (both active sleep preceding quiet sleep (AS1) and active sleep following quiet sleep (AS2)) were used to assess these oscillatory bouts quantitatively. First, the signals were band pass filtered at 10-13 Hz for frontal alpha and at 4-6 Hz for temporal theta. Second, the amplitude envelopes were extracted by applying Hilbert transform (Omidvarnia et al., 2014a; Tokariev et al., 2012). Third, Savitzky–Golay method (Savitzky and Golay, 1964) was used to smooth amplitude envelopes, and an amplitude threshold was set to be three times the median over the whole EEG epoch. Finally, the epochs with signal exceeding the threshold were taken as the FA or TT bouts. FA bouts with duration less than 0.2s, and TT bouts with duration less than 0.4 s were rejected as these extremely short bouts were reasoned not to be physiological. Then the following metrics were computed for each baby: average bout duration, cumulative proportion of bouts out of the whole recording epoch, and bout frequency (#/min).

4.3.2.2 Phase-amplitude correlation

The local integration between oscillatory frequencies was assessed by measuring phase-amplitude coupling with nestedness coefficients (NC). NC is a measure characterizing cross-frequency interaction during spontaneous activity transients in the neonatal EEG (Vanhatalo et al., 2005a; Tokariev et al., 2012). It depicts coordination of spatially-overlapping but functionally-distinct neuronal networks (Engel et al., 2013; Hyafil et al., 2015; Man et al.,

2015; Sotero et al., 2015). NC was calculated from all 19 electrodes as phase locking value (PLV) (Jervis et al., 1983; Lachaux et al., 1999) between lower frequency ('nesting') and higher frequency ('nested') oscillations in the same EEG signal, within the given epoch (length, 4min). The EEG was first filtered with 0.2-0.6 Hz. Then amplitude envelopes were extracted for nested components. Envelopes were filtered, and Hilbert transformation and phase functions were applied. The NC estimates were compared between exposure groups at the electrode level, but also by computing global average to represent global nestedness.

4.3.2.3 Interburst Interval

Interburst interval (IBI) is one of the signs of newborn EEG representing maturity (Biagioni et al., 2007a). For calculating IBIs bipolar derivations F3-P3, F4-P4, C3-O1 and C4-O2 from quiet sleep epochs were used. The signals were first filtered within frequency range 3-15 Hz. Then a nonlinear energy operator (NLEO) (Mukhopadhyay and Ray, 1998) was applied and the output was smoothed using Savitzky-Golay approach (Savitzky and Golay, 1964). Finally, an amplitude threshold was set for each EEG channel as three times the median value. The episodes below this threshold were taken as IBI. IBIs between 2 and 10s were considered as physiologically relevant for term age infants (Andre et al., 2010) and were included in the analyses. The results from F3-P3 and F4-P4 were pooled into F/P group and C3-O1 and C4-O2 into C/O group. The median IBI durations were computed for F/P and C/O for each infant.

4.3.2.4 Interhemipheric synchrony

Interhemispheric synchrony in the neonatal EEG represents a temporal relationship between pairs of EEG signals taken from two hemispheres. We used a previously-described measure, the Activation Synchrony Index (ASI) (Räsänen et al., 2013). ASI provides a statistical measure for the temporal coincidence of two quantized EEG amplitudes, increasing as the temporal dependence of the signal pair approaches zero timelag. In this study, 2.5-minute-long EEG epochs of quiet sleep were used (Koolen et al., 2014). ASI was computed for bipolar derivations (F3-P3, F4-P4, C3-O1 and C4-O2) for each subject, and then a single average, global ASI value was assigned for each newborn.

4.3.2.5 Spectral analysis

The frequency spectra calculations were designed to cover the whole physiologically-relevant range of frequencies in term babies (Vanhatalo et al., 2005b). For studies I and III, 4 min EEG epochs of both active and quiet sleep from all available electrodes were used for frequency spectra analyses. Frequency spectra were computed from bipolar derivations via amplitudes. The mean of amplitude envelopes in each frequency band was calculated yielding the frequency-amplitude spectra. Amplitude differences, both at the electrode level, as well as the global average, were compared between groups. In Study I, analyses were performed using 13 different frequency bands (from 0.5 to 10 Hz with 0.5 Hz frequency binning). In Study III, EEG signals were filtered into four physiologically-reasoned frequency bands: 0.2-3, 3-8, 8-15, and 15-30 Hz as for hemispheric amplitude asymmetry analyses it was sought to cover the previously studied alpha range (8-15 Hz) (Thibodeau et al., 2006; Field and Diego, 2008; Diego et al., 2010; Goldstein and Klein, 2014; Lusby et al., 2014). For the hemispheric amplitude asymmetry analyses, amplitude difference between symmetrical electrodes was computed as the amplitude difference in each electrode pair for each infant (for example, frontal asymmetry: Fp2 – Fp1; temporal asymmetry: T4 – T3).

4.3.2.6 Connectivity analysis

In Study IV, three different functional connectivity values were calculated to reveal the degree of connectedness between different brain areas: Phase-phase correlations (PPC), amplitude-amplitude correlations (AAC), and phase-amplitude correlations (PAC). Functional connectivity was assessed between all pairs of EEG electrodes for all frequency bands in each baby. We formed spatial groups to compare connectivity estimates within and between hemispheres, as well as the ratio of intrahemispheric to interhemispheric synchrony at the single subject level.

The EEG epochs were first re-referenced into current source density (CSD) montage with 19 derivations (Tenke and Kayser, 2012). Then the EEG signals were filtered into 13 frequency bands with central frequencies of 0.5, 0.7, 1, 1.4, 2, 2.8, 4, 5.7, 8, 11.3, 16, 22.6, and 32 Hz. Hilbert transformation was applied to obtain the complex representation of signals and the amplitude and phase time series were used in connectivity analyses.

PPC (Phase-phase correlation) was evaluated between the phase time series by using the above-mentioned phase locking value (PLV, see section 4.3.2.2). *AAC (Amplitude-amplitude correlation)* was estimated with the Pearson correlation coefficient (CC) of the amplitude time series. PLV and CC

were used to test whether EEG networks change their spatial extent and strength between vigilance states and with the maturation. *Phase-amplitude correlations (PAC)* were estimated by using nestedness coefficient (NC, see section 4.3.2.2). We computed connectivity density (Estimate K) for both PLV and CC at each frequency band to quantify the spatial extent. (K+) indicated increase and (K–) decrease of the fractions of statistically-significant observations in the group comparisons. The network strength assessment was completed using absolute values. In addition, a grand mean amplitude value was computed over 19 channels for each subject at every frequency band and for both vigilance states. This allowed the comparison of amplitudes between sleep states, as well as their correlation with age for each condition separately.

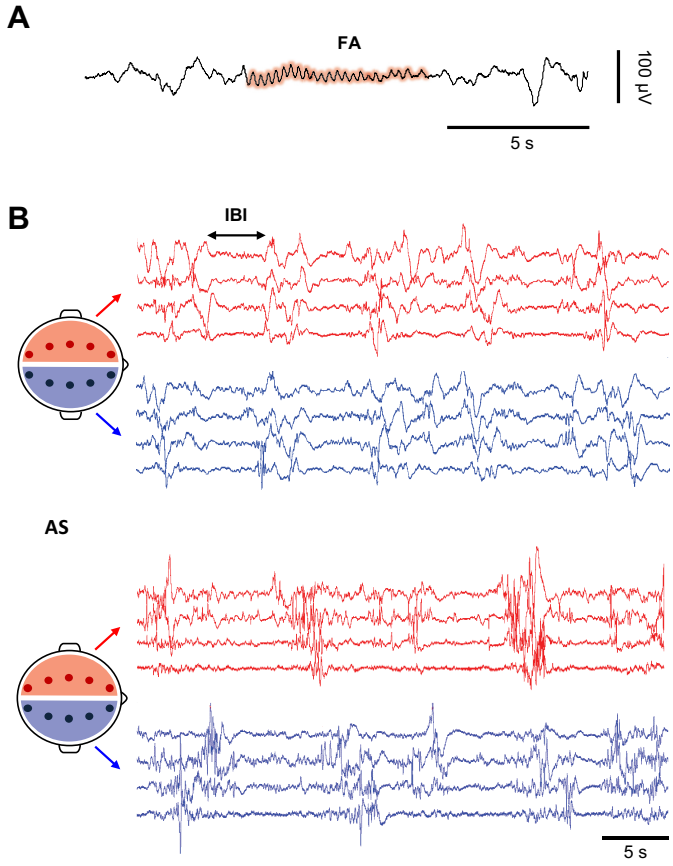

Figure 1 Schematic illustrations of the EEG measures. A) Frontal alpha bout (FA, marked with a red background) is a common neonatal EEG feature, recognized as a visually prominent epoch of alpha frequency activity in the frontal EEG signals. B) Activation Synchrony Index (ASI) measures interhemispheric synchrony (co-occurrence of bursts in both hemispheres). The example above shows high interhemispheric synchrony (high ASI), typical of normally developing term infant. The example below shows low interhemispheric synchrony (low ASI), typical of abnormal EEG function in at term age. IBI = Interburst interval. As a courtesy from Anton Tokariev (modified from Study III).

4.3.3 EYE TRACKER

Eye-tracker data processing was completed automatically by using gazeAnalysisLib, a library of MATLAB (Mathworks, Natick, MA) routines for offline analysis of raw gaze data. A 15-sample median filter was applied for removing technical artefacts in the gaze data. Data segments with a maximum of 200 ms of missing eye position data were filled by continuing the last recorded x- and y-coordinates until the tracking came back online. Then invalid trials were removed from the analyses.

Of the accepted trials, the duration of gaze fixation at the first stimulus after the peripheral stimulus onset was calculated for each stimulus condition. This duration (index) is the proportion of gaze fixation on the first stimulus. The overall mean duration of the fixations corresponds to the general efficiency of infants' visuospatial orienting.

4.3.4 STATISTICAL ANALYSES

First, all examiners were blinded to the exposure status of the infants in all assessments and analyses.

Studies I and II: The AED-exposed and unexposed neonates were compared with each other with regard to neurological, EEG, and eye-tracker findings. Additional subgroup analyses were conducted between the neonates exposed to AED polytherapy, or AED monotherapy (as a group and each medication separately) and unexposed neonates.

Study III: The neurological and EEG values of SRI-exposed neonates were compared to those of the unexposed neonates. In the additional analyses, to evaluate the significance of maternal mood and anxiety on the results, the findings of exposed and unexposed neonates were pooled and the relationship of mood and anxiety evaluated with parameters.

Study IV: To evaluate the changes in the EEG networks between vigilance states and with maturation, we compared the degree of connectedness between different brain areas (both within and between hemispheres) at the two time points (Rec 1 and Rec 2) and between the sleep states (active and quiet sleep) similarly at both time points.

As some of the data was not normally distributed, and group sizes were relatively small and unbalanced, the primary comparisons were executed

using non-parametric statistics: Fisher's Exact test, Pearson Chi-Square test, Wilcoxon signed rank test (within individual), Wilcoxon rank sum test (between individuals), Kruskal-Wallis test (between individuals), or Spearman correlation coefficient. In Study II, additional statistics (one-way between-groups analysis of covariance and two-way between-groups analysis of covariance) were used when evaluating the impact of age of the infant, maternal education and maternal intelligence. The level of significance was set at $p<0.05$. In cases with multiple comparisons, Bonferroni correction was applied, or when a much higher number of statistical comparisons were performed (Study I, III, and IV) correction for multiple comparisons was done by removing five percent from the total number of tests (i.e., the expected fraction of false positives from the all statistically significant observations so that the least significant observations were removed).

5 RESULTS

5.1 STUDY I

The AED group included 40 infants exposed prenatally to monotherapy and 16 to polytherapy. The number of newborns exposed to different drugs were OXC 10 (18%) or CBZ 9 (16%), VPA 5 (9%), LTG 8 (14%), LEV 7 (12%), and TPM 1 (2 %). There were no significant differences between the AED-exposed and unexposed neonates in the history of maternal cigarette smoking, alcohol consumption, folic acid supplementation, age, or parity. The duration of pregnancy (gestational age, GA), hemoglobin level of the newborn, or the conceptional age (CA) at the time of performing EEG examinations did not differ significantly either. However, there was a modest difference between the groups in the mean CA during the neurological examination as the mean CA of the AED-exposed newborns was 0.6 week higher than mean CA of the controls. Furthermore, birth weight, one-minute Apgar scores and educational level of the mother differed significantly between the groups. In our post hoc inspection, the difference in one minute Apgar was found to be due to one outlier (Apgar =2) in the control group. Recruitment was earlier in cases with AED exposure compared to control cases due to study design. When newborns of different etiologies of epilepsy, or with a different number of seizures during the pregnancy were compared, no differences in neurological or brain activity measurements were observed. Numbers of exposed and unexposed newborns are shown in Table 1.

5.1.1 CLINICAL NEUROLOGY

The most important findings in the neurological assessment (HNNE) were the significantly higher scores of AED-exposed neonates in the Compound Optimality Scores (COS) for categories of Tone and Deviant Signs, and in the Total Optimality Score (TOS) (Table 2).

In the subgroup analyses, no differences in the neurological assessment were found between newborns exposed to AED polytherapy and monotherapy. A significant difference was seen between polytherapy and control groups in the COS for Tone (mean 5.14, SD ±2.25 vs. 7.33, SD ±1.47, $p<0.001$) and the Total Optimality Score (22.7, SD ±2.94 vs. 25.75, SD ±0.35, $p=0.011$).

The findings imply that newborns with *in utero* AED exposure may have slightly lower limb and axial tone.

Table 1. Background information

	AED (n=56)	Controls (n=67)	p
GA* (weeks)	40.1 (37.4-42.3, 1.24)	40.4 (38.4-42.1, 1.05)	0.21
CA during EEG** (weeks)	42.2 (40.3-44.4, 0.91)	42.3 (40.0-43.7, 0.75)	0.72
CA during neurological examination** (weeks)	42.2 (40.4-44.4, 0.87)	41.6 (39.1-43.6, 1.07)	0.01
Enrollment (GA* weeks)	7.20 (3-24, 3.20)	15.20 (5-22, 7.19)	0.02
Educational level of the mother*** (median)	2 (1-3, 0.59)	1 (1-2, 0.43)	<0.001
Age of the mother (yrs)	32.0 (24.0-41.0, 4.34)	32.52 (21.0-41.0, 4.15)	0.39
Smoking during the third trimester (%)	4%	0%	0.13
Neuropsychology of the mothers			
VIQ[#]	111 (69-137, 13)	114 (97-134, 10)	0.53
PIQ [##]	117 (62-138, 12)	122 (100-138, 11)	0.07
Executive problems (no/slight)	76%/24%	90%/10%	0.32
Gender (Male %)	59%	65%	0.53
Apgar at 1 min (median)	9 (7-10, 0.52)	9 (2-10, 1.57)	0.04
Folic acid amount during the 1st trimester (mg)	3.1 (0.6-4.0, 1.71)	3.0 (0-8.0, 2.30)	0.25
Birth Weight (grams)	3456 (2370-4590, 525)	3705 (2808-4800, 450)	0.02

Table 1. *Background information (Studies I and II). AED-exposed are compared to control group. Values, if not otherwise stated, are expressed as mean (range, SD). *GA = Gestational Age, **CA =Conceptional Age, ***Educational level: (1) = tertiary, (2) = secondary, (3) = primary, (4) = illiterate, #=Verbal Intelligence Quotient, ## =Performance Intelligence Quotient. AED group include 40 infants exposed prenatally to monotherapy and 16 infants exposed to polytherapy.*

Table 2. Effects of Prenatal Antiepileptic Drug Exposure on Newborn Neurology

	AED** (n=56)	**Controls** (n=67)	**Sig.**
Tone COS*, mean (SD)	6.03 (1.83)	7.33 (1.47)	**<0.001**
Tone patterns COS*	3.50 (0.86)	3.59 (0.68)	0.822
Reflexes COS*	3.93 (0.93)	3.78 (0.79)	0.214
Movements COS*	2.69 (0.45)	2.59 (0.50)	0.260
Deviant signs COS*	2.56 (0.61)	2.84 (0.67)	**0.007**
Orientation and Behaviour COS*	5.54 (1.05)	5.85 (1.02)	0.155
Total Optimality Score	24.06 (2.64)	25.75 (0.35)	**0.007**

Table 2. *Neurological outcome of the AED-exposed and control neonates. Values are expressed as mean, range, and SD. Neonates with and without exposure are compared with each other. *COS = Compound Optimality Score and Total Optimality Score of Hammersmith Neonatal Neurological Examination according to Dubowitz 1999. **Newborns exposed to AED. Significant differences after Bonferroni correction are marked in bold.*

5.1.2 BRAIN ACTIVITY

Automated analysis revealed several significant differences in the neonatal EEG between the AED-exposed and control newborns.

Oscillatory events. The average duration of FA bouts ($p=0.004$) and the percentage (the cumulative duration of FA to the epoch length) ($p<0.001$) differed significantly between AS1 and AS2 in the control group whereas they did not differ significantly in the AED group. In addition, newborns exposed to AED had fewer bouts with the typical medium duration than what was seen in the control group ($p=0.03$).

Interburst intervals. There were no differences in IBI lengths between AED and control groups. However, IBIs were significantly longer in the posterior electrodes compared to frontal electrodes in the unexposed newborns, but this

uneven spatial distribution of IBIs was not found in the AED-exposed newborns.

Interhemispheric synchrony. AED-exposed newborns showed a significantly higher (p=0.002) ASI in their frontal (6.81±1.48) compared to posterior (5.49±1.41) brain areas but no significant spatial difference was found in the control group (frontal 6.57±1.83, posterior 5.81±1.73, p=0.18). There were no significant differences in the ASI values between AED and control groups in the frontal, posterior brain areas, or their average.

Spectral analysis. AED-exposed newborns had significantly lower amplitudes at multiple derivations and frequencies during both active and quiet sleep than unexposed newborns. The most prominent differences were at lower frequencies during active sleep and in the frontoparietal derivation. In addition, newborns exposed to monotherapy showed generally higher amplitudes, including multiple significant differences, throughout the frequency range.

5.2 STUDY II

The background, obstetric outcome and exposure status are already described in section 5.1. Neuropsychological evaluation (Stroop 1935, Rey 1941, Wechsler 1997) was performed for 48 mothers of the medication group and 20 mothers of the control group. Maternal verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), or clinically-measurable relevant executive-functioning skills did not differ significantly between the AED and control groups: mean VIQ 111 (range 69-137, SD +/-13, AED group) vs. 114 (range 97-134, SD +/-10, controls), p=0.54; mean PIQ 117 (range 62-138, SD +/-12, AED) vs. 122 (range 100-138, SD +/-11, controls), p=0.07; executive problems (no problems/slight problems) 76%/24% (AED) vs. 90%/10% (controls), p=0.32. The educational level of mothers of the AED group was significantly lower than of the control group mothers.

Infants in the AED group were significantly younger than control infants at the time of both the eye tracker (7.31 mo. vs. 7.47 mo., p=0.009) and the clinical examination (7.25 mo vs. 7.46 mo, p=0.001).

5.2.1 CLINICAL NEUROLOGY

The mean score for General Quotient and three out of five mean Sub-Quotients (“Locomotor”, “Personal-Social”, and “Hearing and Speech”) of the Griffith Mental Developmental Scale were significantly lower in the AED-exposed

infants compared to the scores of the unexposed infants. Additional analyses were also conducted using two-way between-groups analysis of variance and one-way between-groups analysis of covariance to measure the impact of maternal educational level and infant's age on the mean developmental quotients. There was still a statistically significant main effect for AED exposure in "Personal/Social" ($p<0.001$), "Hearing and Speech" ($p=0.01$), "Eye and Hand" ($p<0.001$) and "General Quotient" ($p<0.001$) categories after adjusting for the mother's educational level. After further adjusting for infant age, the significant difference between AED and control groups in "Locomotor" ($p=0.001$), in "Personal-Social" ($p<0.001$), in "Hearing and Speech" ($p<0.001$), and in General Quotient ($p<0.001$) persisted (the independent variable was the exposure status of the infant, the dependent variables were the mean scores of the Griffiths scale, and the age of the infant was used as the covariate).

In subgroup analyses, infants with CBZ, OXC, and VPA monotherapy exposure had significantly lower mean developmental Sub-Quotients in the category of hearing and speech than control infants. In addition, CBZ-exposed infants had significantly lower mean personal-social Sub-Quotient, and VPA-exposed infants had significantly lower mean General Quotient, compared to control infants. In the monotherapy group, results were consistent with the results of all AED groups, but no significant differences were observed when comparing the polytherapy group to controls.

The AED group also demonstrated an overall lower mean score of HINE when compared to the control group (mean score 50, range 46-52, SD +/- 2 vs. 51, 48-52, +/- 1.0, $p<0.001$). In the individual HINE scores, only one statistically significant difference was evident between the exposed and unexposed infants: Fewer of the AED-exposed infants showed a prompt reaction to "Lateral tilting" in section "Reflexes and reactions" than control infants (45 % vs. 55%, $p=0.004$). In HINE analyses, the age of the infant has a major role and therefore we excluded those infants of the control group that were older than 7.7 months at the time of the clinical examination from the analysis. After the exclusion, the mean age at the clinical examination did not differ significantly between the groups (controls: n=47, mean age 7.34 mo, range 6.83-7.69, SD +/- 0.24, and AED: n=55, mean 7.25 mo, range 6.50-8.27, SD +/- 0.37, $p=0.09$).

Table 3. Developmental quotients at 7 months-of-age, infants exposed to antiepileptic drugs vs. unexposed infants

Developmental quotients	**AED** (n=56) mean (range, SD)	**Controls** (n=59) mean (range, SD)	**p**
Locomotor	101 (73-141, 14)	114 (81-166, 22)	**0.002**
Personal/ Social	96 (66-127, 13)	105 (84-123, 9)	**<0.001**
Hearing and Speech	87 (65-119, 11)	94 (80-110, 7)	**<0.001**
Eye and Hand	94 (73-120, 11)	95 (79-117, 9)	0.49
Performance	95 (79-117, 9)	93 (79-117, 6)	0.18
General Quotient	95 (77-117, 8)	100 (85-113, 6)	**<0.001**

Table 3. *Sub-Quotients and General Quotients of Griffiths Mental Developmental Scale with prenatal antiepileptic drug exposure (AED) and control infants at 7 months-of-age. Values are expressed as mean, range, and SD AED group is compared to control group (Mann-Whitney test). Significant differences after Bonferroni correction are marked in bold. AED group include 40 infants exposed prenatally to monotherapy and 16 infants exposed to polytherapy.*

5.2.2 VISUAL ATTENTION

The number of valid trials in the AED and control groups were comparable as the percentage of infants having the maximum (eight) trials were (AED vs. controls): Sham 69% vs. 71 % (p=0.13), Neutral 69% vs. 71% (p=0.85), Happy 73% vs. 68% (p=0.17), and Fear 73% vs. 66% (p=0.54). One infant from AED group was excluded from the analyses due to insufficient number of accepted eye-tracker trials (< 3 per stimulus).

The eye-tracker indexes between AED-exposed and control infants did not differ significantly. Neutral, Happy, Fear, and Sham indexes were calculated separately. As an additional post-hoc analysis, one-way between-group analysis of covariance was conducted to measure the impact of age on the parameters of eye-tracker examination. After adjusting for age, there was no significant difference between AED and control groups: Index of Sham (p=0.21), Index of Neutral (p=0.42), Index of Happy (p=0.46), and Index of

Fear (p=0.07) (the independent variable was the exposure status of the infant, the dependent variable was the index of the eye-tracker examination, and the ages of the infants were used as the covariate). There was no statistically significant association between the age of the infant and the eye-tracker indexes, as indicated by a partial eta-squared value of 0.01 for index of Sham, of 0.01 for index of Neutral, of 0.01 for index of Happy, and of 0.03 for index of Fear.

In subgroup analyses, eye-tracker indexes did not differ between infants with monotherapy exposure and controls, polytherapy exposure and controls, or between monotherapy and polytherapy exposure. The comparisons of each AED monotherapy group against controls showed no significant differences between the groups, but eye-tracker indexes were overall higher in infants exposed to levetiracetam, implying that visual-orienting responses were slower in the levetiracetam group, but the result was non-significant when taking into account Bonferroni corrections. The mean ages of the infants in levetiracetam and control groups were comparable at the time of eye-tracker examination.

5.3 STUDY III

The psychiatric evaluations, background information on smoking, alcohol consumption and educational level of the parents are summarized in Table 4. Mothers using SRI more often held a lifetime diagnosis of MDD or anxiety disorder, or a diagnosis of current anxiety disorder (but not current MDD), and these differences were also reflected in the symptom scores at the time of delivery (BDI and BAI). Breastfeeding was equally common in both groups (80%) at the time of the EEG recordings and clinical examinations. Information about breastfeeding was not reliably available from about one sixth of the mothers (five out of SRI mothers; nine out of control mothers).

The prevalences of SRI medications and average daily dosages used were sertraline 6 (47.5 mg), escitalopram 6 (8 mg), citalopram 6 (17.5 mg), paroxetine 2 (30 mg), venlafaxine 2 (75 mg), duloxetine 1 (60 mg), and mirtazapine 1 (15 mg). Four mothers had SRI polytherapy. Most of the mothers reported having SRI medication throughout pregnancy (16 out of 22), 21 mothers had the medication in the first and second trimester, one finished and one started SRI at the end of the second trimester and four finished SRI during the last two to four weeks before delivery.

Table 4. Characteristics of the mothers with and without Serotonin Reuptake Inhibitor use in pregnancy

	SRI (n=22)	Controls (n=62)	p
Age of the mother (yrs)	32.9 (28.0-38.0, +/-3.25)	32.2 (21.0-41.0, +/-4.05)	0.54
Educational level of the mother (tertiary/secondary/primary)	13%/67%/20%	53%/40%/7%	**0.004**
Smoking during the third trimester	27%	0%	**0.001**
Alcohol consumption more than 1 portion/ wk during pregnancy	7%	6%	0.88
BDI*, 3rd trimester	8.5 (2-18, +/-5.65)	5.00 (0-19, +/-4.31)	**0.06**
BAI, 3rd trimester**	9.9 (0-54, +/-14.66)	3.13 (0-12 +/- 3.59)	**0.02**
Major depressive disorder, lifetime	76%	39%	**0.02**
Any anxiety disorder, lifetime	88%	19%	**<0.001**

Table 4. *Characteristics of the mothers with and without Serotonin Reuptake Inhibitor (SRI) use during pregnancy. Values are expressed as mean, range, and SD or alternatively as percentages. Mothers with and without exposure are compared with each other. *BDI = Beck Depression Inventory, **BAI = Beck Anxiety Inventory. Significant differences after Bonferroni correction are marked in bold.*

5.3.1 DEVELOPMENT AND CLINICAL NEUROLOGY

Newborns with *in utero* SRI exposure showed no major significant differences in the neurological examination (HNNE) at the mean postnatal age of ten days, except in the HNNE category of "Abnormal signs or patterns" (p=0.02), which includes aspects of tremor, hand and toe posture, and startle reaction. The subscore analysis showed that the newborns exposed to SRI had more tremors during wakefulness (p=0.05). At the same postnatal age, no signs of abstinence syndrome could be detected using the Finnegan score (SRI group 1.7 (0-10, +/-2.55, Controls 1.8 (0-7, +/-1.74, p=0.24), suggesting that the acute SRI-withdrawal effects had tapered by that time.

The perinatal clinical information did not differ between the exposed and control groups. Only a marginal, clinically unremarkable difference was seen in the cord pH. In the SRI group, mean cord pH was 7.25 (range 7.12-7.38, SD 0.08) and in the control group mean 7.29 (range 7.08-7.43 SD 0.08), p=0.06. There was one outlier in one minute Apgar (Apgar=2) in the control group, but though this outlier was excluded, the mean score for Apgar did not differ significantly between the groups (SRI group: mean 8.7, range 6-10, SD 0.81, Controls: 8.6, 5-10, SD 1.07, p=0.64). The gender, weight, and mode of labour did not differ between the exposed and unexposed newborns, nor did the gestational ages, or the postnatal and conceptional ages at the time of the neurological or at the time of the two EEG recordings.

5.3.2 BRAIN ACTIVITY

There were significant differences both in the local and global brain activity measured by EEG between the newborns with or without *in utero* SRI exposure.

Local brain function. The local ability to sustain periodic oscillatory bouts was significantly different between the SRI and control groups in the first EEG recordings. The mean length of frontal alpha bouts was shorter in SRI than in control groups (0.34 sec, SD 0.06 vs. 0.44 sec, SD 0.10, p=0.005). This group difference disappeared by the second EEG recording. On the other hand, the measure of local cross-frequency integration (NC) was different between groups at the second EEG recording time. The newborns exposed to SRI showed lower mean levels of NC over the whole range of frequencies as compared to the control newborns, but the group difference in frequency-specific analyses reached statistical significance only at 5.7 Hz (SRI group: mean 0.17, SD 0.06 vs. controls mean 0.19, SD 0.06, p=0.03). This 5.7 Hz

frequency is within the dominant frequency band of bursting network activity in the term neonatal EEG (Tokariev et al., 2012).

Global brain function. ASI (measure of interhemispheric connectivity) showed lower levels of global integration in the newborns exposed to SRI compared to controls during both the first (4.26, SD 2.27 vs. 6.42, SD 1.80, $p=0.006$) and the second recording (3.91, SD 1.71 vs. 6.01, SD 1.24, $p<0.001$). The ASI levels remained relatively constant within the groups from the first to the second EEG recording, suggesting a developmental persistence of interhemispheric synchrony. The global average of spectral amplitudes showed significant differences between the control and SRI groups at all lower frequencies (Figure 2). A further spatial analysis with electrode-level group comparisons showed that the significant difference is concentrated to frontal brain regions. In addition, median occipital interburst interval (IBI), measuring the global intermittency of activity, was shorter in the SRI group during the second recording (4.71, sec SD 0.61 vs. 5.07 sec, SD 0.57, $p=0.037$).

No global-level group differences were observed between SRI and control newborns when comparing hemispheric asymmetries at any frequency. However, an electrode-level comparison disclosed a group difference between SRI and control newborns at the alpha and beta frequencies of both frontal and temporal brain regions.

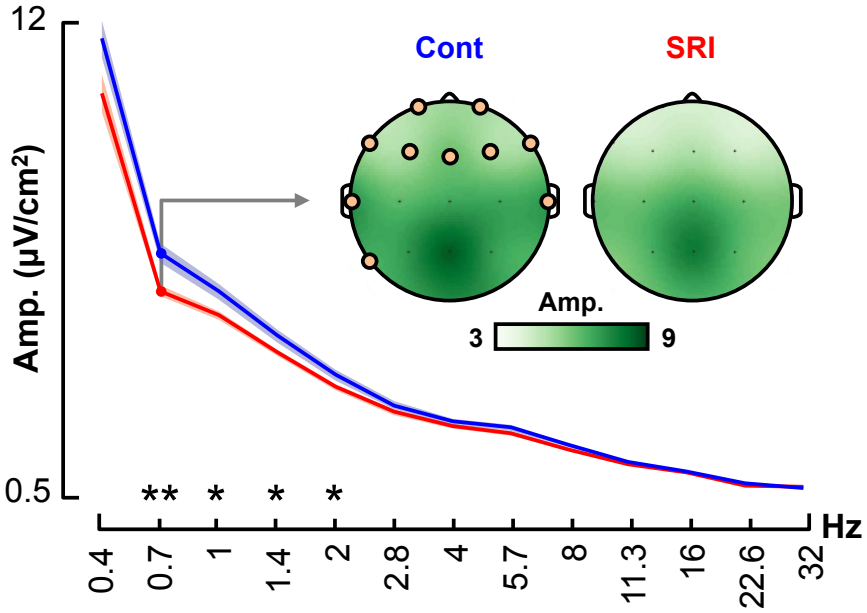

Figure 2 Frequency spectra. Amplitude spectra comparison between SRI (red) and control (blue) groups shows that lower frequencies are significantly higher in the control infants (results shown from quiet sleep Rec 1; mean ± SEM, ** p<0.01, * p<0.05; Wilcoxon rank sum test). The amplitude distribution over the scalp is shown on topoplots for one of the significantly differing frequencies (0.7 Hz), and the orange circles in the topoplot depict individual electrodes with significant group differences (p<0.05) suggesting that the group difference is frontally dominant. As a courtesy from Anton Tokariev (modified from Study III).

Newborn brain function and maternal psychiatric assessments. Assessment of whether the newborn EEG findings could be explained by an unknown inherited 'endophenotype' like mothers' lifetime history of depression or anxiety (Goldstein and Klein, 2014) or if the newborn EEG findings were related to mood or anxiety related factors was sought with post hoc analyses. In these analyses with cases and controls pooled together, the EEG parameters suggested very few relations to maternal mood or anxiety. The main findings were more likely explained by medication exposure or an interaction with medication and mood/anxiety rather than by lifetime or current depression or anxiety. Furthermore, neither the EEG parameters nor the clinical findings differed significantly in respect of maternal educational level.

5.4 STUDY IV

5.4.1 BRAIN ACTIVITY

All functional connectivity parameters changed significantly between vigilance states and matured rapidly after normal birth. Vigilance state effects were evaluated by comparing active sleep (AS) and quiet sleep (QS) periods, while the maturational changes were assessed by estimating the correlation between functional connectivity and the conceptional age (CA) at the time of EEG recording.

Functional connectivity between brain areas was quantified with three different metrics: phase-phase correlations (PPC), amplitude-amplitude correlations (AAC), and phase-amplitude correlations (PAC). Both PPC and AAC analyses were done at the level of EEG electrode pairs, and the findings were expressed as the fraction of statistically significant connections mirroring the spatial extent of the network change. In addition, hemispheric metrics were computed by grouping sets of signals together to examine changes that may occur at a spatially larger level, e.g. inter- or intrahemispheric level. On the other hand, the analysis of PAC was computed for each EEG signal separately as a measure of a cross-frequency interaction between local slow (nesting) and faster (nested) oscillations.

5.4.1.1 Phase-phase correlations, PPC

Functional connectivity via PPC was changed at a wide range of frequencies when the infant shifted from a vigilance state to another. Neonatal brain had more significantly stronger connections in QS at the lower (< 1 Hz) and higher (~ 4-22.6 Hz) frequencies, whereas the stronger connections in AS was seen more significantly in the middle range (~ 1-4 Hz). Corresponding frequency ranges showed significant differences in both intra- and interhemispheric PPC confirming the global difference.

When PPC was correlated to infant age, significant developmental changes were seen within the first few postnatal weeks. This maturation was differently expressed between the vigilance states as well as among the oscillatory frequencies, and it was generally smaller in magnitude compared to differences between vigilance states. The early postnatal maturation seems to affect PPC only at lower frequencies suggested by hemispheric metrics that showed a significant maturational increase in interhemispheric PPC at 1–2 Hz, as well as a decrease in the ratio of intra-/interhemispheric PPC at the same frequencies. No apparent topological patterns were observed.

5.4.1.2 Amplitude-amplitude correlations, AAC

AAC showed wide, frequency-dependent shifts between vigilance states. Both AS and QS were associated with wide, significant, and frequency-dependent differences in AAC. At frequencies ≤ 2 Hz, most of the connections had significantly higher AAC in AS than in QS. On the other hand, in QS a significantly increased AAC in most signal pairs was observed at higher frequencies. Hemispheric metrics suggested these effects to be global, as the significant differences in both intra- and interhemispheric connections were seen at the same frequency bands.

Correlations between AAC and conceptional age at the time of EEG recording showed that postnatal maturation was associated with significant decreases in AAC for large number of connections throughout the frequency range. The most notable changes were seen at the low (0.7-1 Hz) and high (8-22 Hz) frequencies. Significant decreases in AAC coupling were found in both intra- and interhemispheric connections at a wide range of higher frequencies (> 2 Hz). Intrahemispheric AAC coupling was also reduced with maturation at low frequency (0.7-1 Hz), and though the maturational decrease of higher frequency AAC coupling was global, there was a stronger relative decrease in the intrahemispheric AAC coupling at all lower frequencies (< 2Hz).

5.4.1.3 Phase-amplitude correlations, PAC

Nestedness of higher frequencies was examined with respect to two lower frequencies, 0.7 Hz and 2 Hz. The 0.7 Hz frequency range is known to nest higher activities in the neonatal EEG (Vanhatalo et al. 2005). This study sought to distinguish between these SAT-related vs. SAT-unrelated nestedness. Nestedness for 0.7 Hz was higher than nestedness for 2 Hz throughout the whole range of higher frequencies, and the finding was similar in both vigilance states. Comparison of individual EEG signals showed that the vigilance state effect in 0.7 Hz was significant in 53-84% of electrodes, but in 2 Hz the change between AS and QS was seen only between a limited frequency range (5.7-16 Hz) and in a small proportion (5-37%) of EEG signals.

These findings suggested that nestedness was stronger within lowest frequencies and it was strongly and globally modulated by the vigilance state.

5.4.1.4 Developmental changes in oscillation amplitudes

It has been suggested that oscillation amplitude changes in adults could be a significant source of error in PPC studies (Palva et al. 2005; Palva and Palva 2012). It may also be a significant source of error in newborns and might change spectral properties of neonatal EEG rapidly. To evaluate this, the amplitudes in QS and in AS were examined: amplitudes in QS were higher up to 11.3 Hz, whereas the amplitudes at frequencies above this up to 32 Hz were higher in AS. With respect to maturational changes in AS, only one frequency (11.3 Hz) showed a significant relationship. However, amplitudes in QS were significantly increased with age at the midrange and decreased at the higher frequency. These frequency profiles were not directly comparable to our PPC and ACC findings thus suggesting that the connectivity findings were not explained by changes in amplitudes.

6 DISCUSSION

This thesis has demonstrated the potential of neonatal EEG in assessing functional connectivity and in explaining the mechanisms of the adverse effects of *in utero* AED and SRI exposures. Studies I and III appear to be the first investigations demonstrating that *in utero* AED and SRI exposure are associated with several changes in the cortical activity of the neonatal brain. In addition, data from Study II supports the observations of earlier studies suggesting that prenatal AED exposure is associated with later developmental problems (Christensen et al., 2013; Meador et al., 2013; Baker et al., 2015) although not in the visual domain. However, the neurocognitive effects of prenatal AED exposure have not previously been evaluated as early as 7 months-of-age or by using eye-tracker based measurements as described in Study II. In Study IV, EEG of a human newborn was demonstrated to provide key measures of functional connectivity. Furthermore, the functional connectivity of the neonatal brain changes between vigilance states and matures rapidly over the couple of weeks after term birth.

6.1 NEONATAL BRAIN ACTIVITY

Recent research has been largely focused on clinical and basic sciences for biochemical, molecular, anatomical, or physiological indicators, so-called 'biomarkers' that could predict, measure, or indicate the presence or progress of disease or the effects of treatment (Bale, 2015). Computational EEG analysis could be one prospect for such a biomarker. Early brain activity, measured here by EEG, is known to be crucial for early brain wiring (Anderson and Thomason, 2013), the foundation of all later neurocognitive functions. Furthermore, recent advances in signal analyses (Vanhatalo et al., 2005b; Tokariev et al., 2012; Räsänen et al., 2013; Koolen et al., 2014) have opened a potential translational bridge between experimental animal work and human EEG recordings at the level of neuronal network mechanisms.

6.1.1 NEONATAL EEG AND NEURONAL COUPLING

Study IV provides the first systematic insight to the electric brain networks during the first few weeks of postnatal life in a human neonate. Our findings suggest significant maturational and vigilance state-related changes in neuronal coupling. The observed changes were frequency-specific, most salient in amplitude-amplitude correlation coupling, and their development

was compatible with the known development of structural cortico-cortical connectivity. On the other hand, these results found no specific patterns in the spatial network topologies that are often reported in earlier fMRI studies (Fransson et al., 2011; Smyser et al., 2011; Ball et al., 2014; Collin et al., 2014).

Study IV supports the idea that different connectivity measures reflect different modes of early cortical operation. Recent studies combining knowledge from animal and human EEG recordings (Vanhatalo and Kaila, 2006; An et al., 2014) suggest that early EEG development involves two cortical mechanisms: First, the spontaneous activity predominant in AS; and Second, an immature type of brain network activity characterized by intermittent occurrence of complex multi-frequency events predominant in QS (Vanhatalo et al., 2005b; Seelke and Blumberg, 2010; Myers et al., 2012). Measuring of phase-phase connectivity reflects mainly the first mechanism and amplitude-amplitude connectivity the second.

Phase-phase correlation (PPC) coupling. This investigation has shown that PPC coupling seems to be related both to anatomical maturation and to reorganization of functional connectivity between vigilance states. These findings are compatible with the known early histological development of cortical networks. Histological studies of fetal human brain have demonstrated that intrahemispheric cortico-cortical connections precede the growth of interhemispheric connections. Precise networks required for higher frequency PPC grow over long periods after establishing the overall wiring (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2010). The Study IV results are compatible with this as PPC was relatively stronger at lower frequencies and in interhemispheric connections during AS, while during QS it became relatively stronger at higher frequencies and in intrahemispheric connections. Furthermore, PPC was first established at lower frequencies and shorter distances that may operate with less anatomical precision, suggesting that the intrahemispheric connections mature first. In addition, in both PPC and in PAC coupling, the difference between vigilance states is compatible with the idea that the brain is occupied by training the precise intrahemispheric connectivity during QS (Minlebaev et al., 2007; Brockmann et al., 2011; Kirkby et al., 2013; An et al., 2014), while connectivity is related to synchronizing between hemispheres during AS.

Amplitude-amplitude correlation (AAC) coupling. This work demonstrates that early postnatal maturation of AAC is wide scale and state specific. A rapid decline in AAC with maturation was measured, in line with earlier studies showing that the incidence of the main cortical mechanism underlying AAC coupling (Spontaneous activity transients, SAT) decreases from prematurity towards term age (Vanhatalo et al., 2005b; Myers et al., 2012). In the visual EEG review used in clinical settings, the closest correlate for AAC is interhemispheric synchrony (Lombroso, 1979; Räsänen et al., 2013;

Koolen et al., 2014), describing the apparent co-occurrence of burst events in two hemispheres during QS. This synchrony is known to increase during the last trimester (Lombroso, 1979). The results elaborate this information on synchrony as they show that AAC coupling develops differentially between and within hemispheres and this yet unexplored intrahemispheric coupling is relatively stronger than the maturation between hemispheres.

6.1.2 NEONATAL BRAIN ACTIVITY AND *IN UTERO* EXPOSURE OF AED AND SRI MEDICATION

Few studies have been published on the effects of prenatal drug exposure on neonatal EEG (Young and da Silva, 2000; Nguyen The Tich et al., 2003). These detailed quantitative computational EEG analyses showed an association between *in utero* AED, or SRI, medication exposure, and changes in both focal and global newborn brain activity. Thus, these studies indirectly suggest that altered electrical activity of the neonatal brain may constitute one of the mechanisms by which AED or SRI medications may affect development of the child.

Study I shows that individual oscillatory bouts, wider band spectra, and functional brain networking may be altered by *in utero* AED exposure. In addition, temporal organization and spatial coordination of the functional networking differed between the AED-exposed and unexposed newborns: Interhemispheric synchronization was higher frontally than posteriorly in AED-exposed newborns, while control babies had longer IBI posteriorly than frontally. These two measures interpret two different aspects of how early network events are generated and coordinated (Omidvarnia et al., 2014b) and are fundamentally important for early brain development (Vanhatalo and Kaila, 2006).

Because prenatal SRI medication has been associated with postnatal adaptation syndrome (Oberlander et al., 2009; Forsberg et al., 2014; Ray and Stowe, 2014), the EEG of the SRI-exposed newborns was recorded twice to exclude the possible reflections of the withdrawal symptoms. The peak incidence of the abstinence symptoms has been found to occur 2 to 90 hours postnatally (Ter Horst et al., 2008; Warburton et al., 2010; Salisbury et al., 2011; Forsberg et al., 2014; Ray and Stowe, 2014). Indeed, some of the changes in the EEG were only observed during the first postnatal week. However, several changes were still seen during the second recording at the mean postnatal age of over two weeks suggesting that the SRI effects on EEG would more likely reflect effects on brain development rather than direct drug effects on brain activity. These results are in line with the recent study from Salisbury (Salisbury et al., 2016) suggesting that neurological effects of SRI exposure can outlast the time period of the immediate withdrawal syndrome.

Prenatal SRI exposure in this study triggered lower interhemispheric connectivity (ASI), lower local cross-frequency integration (NC), and changes in quiet sleep (IBI). These findings were interpreted to be more long-lasting developmental effects of prenatal SRI exposure and are fully compatible with recent experimental work in rodent models. These models have suggested a range of neurodevelopmental effects, histological, and electrophysiological changes in the brain due to early SRI exposure (Xu et al., 2004; Homberg et al., 2010; Liao and Lee, 2011; Simpson et al., 2011). Indeed, *in utero* SRI exposure may result in significant reduction in the callosal nerve fibres, as well as a reduction in cortico-cortical synchronization of neuronal activity (Simpson et al., 2011). The reduced interhemispheric synchrony reported here in human infants after *in utero* SRI exposure may be interpreted to reflect similar mechanisms in humans as has been reported previously in experimental studies (Simpson et al., 2011).

Clinical studies have suggested that maternal depression and/or anxiety may have an association with the newborn EEG activity (Field and Diego, 2008; Lusby et al., 2014; Thibodeau et al., 2006). Thus in Study III, the relationships and frequencies between newborn EEG and maternal psychiatric symptoms were examined. However, the results were inconsistent with the presence of a neonatal EEG 'endophenotype' of maternal depression (Goldstein and Klein, 2014). The findings suggested that the observed electrophysiological changes were likely due to medication or an interaction with medication and mood/anxiety rather than maternal depression or anxiety per se. One explanation for this discrepancy could be an analytical confounder, as the prior studies have not distinguished between vigilance states (Field and Diego, 2008; Diego et al., 2010; Lusby et al., 2014). Pooling EEG epochs from different sleep states may cause the EEG measures to reflect infant's sleep stage rather than a genuine brain phenotype. In addition, previous studies have generally used less EEG data, and more variable amounts of EEG recordings were included into the analyses. In partial accordance with the earlier studies, the data reported here suggested EEG asymmetry with greater left side amplitudes. This asymmetry was related to prenatal SRI treatment, however, rather than maternal psychiatric status. The EEG effect of asymmetry was also reported at a wider frequency range, as well as in wider brain areas, than previous studies.

6.2 CLINICAL ABERRATIONS

6.2.1 NEWBORN

In utero exposure to phenobarbital, phenytoin, valproic acid, and benzodiazepines has been associated previously with increased apathy and hyperexcitability (Koch et al., 1996). In line with these findings, the work presented in this thesis showed lower axial and limb tone in newborns with prenatal AED exposure, with currently used AEDs. Similar to earlier studies (Viinikainen et al., 2006; Artama et al., 2013), birth weight was lower in the AED-exposed newborns.

No major differences were observed in clinical neurology between the SRI-exposed and control newborns, though the SRI-exposed newborns seemed to have more tremors, which could be a sign of increased irritability. The acute perinatal abstinence syndrome of fetal SRI exposure is known to include neurological symptoms such as jitteriness, irritability, and lower habituation (Oberlander et al., 2009; Forsberg et al., 2014; Ray and Stowe, 2014).

6.2.2 INFANT

Supporting the findings of earlier studies on older children (Gaily et al., 2004; Meador et al., 2013; Baker et al., 2015), Study II reported prenatal AED exposure to compromise the development of early language and social skills, as well as overall neurodevelopment at 7 months-of-age. This is the first known study to assess the neurocognitive effects of prenatal AED exposure as early as 7 months-of age. These results suggest that the precursors of verbal impairments observed at 4.5 to 6 years-of-age (Meador et al., 2013; Baker et al., 2015;) may already be detected in infancy. The subgroup comparisons imply that prenatal exposure to VPA, CBZ, or OXC monotherapy may have effects on the development of the exposed children, and they can already be observed at 7 months-of-age. Deviations in early development have been discovered before in children at 8 months-of-age with *in utero* phenobarbital or phenytoin medication, but no studies have been conducted with currently used AEDs at this early age. In line with a recent study from Baker et al. with the 6-year-old children (Meador et al., 2013; Baker et al., 2015) the results of this thesis study implied that LTG and LEV might differ from CBZ, OXC, and VPA also in regard to early language abilities.

One of the Study II aims was to assess the effects of AEDs on infant's visual orienting and attention. The eye-tracker-based evaluation of visual function in 7-month-old infants suggested that prenatal AED exposure has no affect on the general speed of visuospatial orienting or attentional bias for faces.

6.3 STRENGTHS AND LIMITATIONS

The main strengths of this study were:

1) The newborns were evaluated during the first postnatal weeks thus minimizing the impact of the environmental confounders, including mother-child interactions (Studies I, III, and IV),

2) Stringent recording and signal analysis were used in all our studies,

3) Clinical outcome variables were measured using structured or quantitative methods (Studies I, II, and III),

4) All AED exposure data were gathered prospectively (Studies I and II) in contrast to many previous studies using retrospective or register-based data collection, and

5) The neuropsychological (Studies I and II) and psychiatric evaluation of the mothers including current and lifetime mood and anxiety (Study III) using well-established methods (Stroop, 1935; Beck et al., 1961; Beck et al., 1988; Wechsler, 1997).

Furthermore, Studies I and II used a tertiary center cohort with exposure information on all excluded pregnancies, allowing a better estimation of the recruitment bias than that achieved in register studies. In addition, the range of medications in Study I and II (CBZ, OXC, LEV, LTG, VPA) corresponds to current medication trends (Vajda et al., 2010) .

When comparing Study III with previous literature there is one more methodological detail that should be considered. Patients were recruited based on SRI use instead of based on the need for psychiatric intervention for MDD, thus the sample included individuals with no or mild symptoms of depression. The study population with mixed SRI indications and a more variable psychiatric status is unlike the population in most previous studies, permitting the effects of maternal drug treatment and psychiatric symptoms to be distinguished analytically.

The strength of Study II was the use of quantitative eye-tracker testing, which has been described and tested in previous studies (Ackers et al., 2009;

Ahtola et al., 2014). Compared to traditional testing methods, eye-tracking-based testing allows complete automatization of the test procedure and accurate, transparent physiological metrics of the sensory and cognitive processes in infants (Leppänen et al., 2015).

The main limitations of this study were:

1) While the overall effects of AED and SRI medications on newborn brain activity were clear, subgroup comparisons between specific drugs were limited due to the number of newborns available in each group (Studies I, II, and III),

2) With this study, or with any studies on human subjects, questions related to causal relations are difficult or impossible to answer,

3) In Study II, the mean infant age during the examination, and the educational level of the mothers, were higher in the control group though the results remained similar even if these confounding factors were taken into account,

4) Whether maternal epilepsy could have some unidentified, direct effects on fetal development as opposed to the medicine used for treating the epilepsy could not be determined (Studies I and II), and

5) Treatment-resistant epilepsy was likely to be overrepresented in the pregnant women with epilepsy recruited for Studies I and II, since polytherapy was received twice as often as reported for all Finnish PWE during the study period (Artama et al., 2013).

Furthermore, valproic acid exposure was relatively uncommon in both recruited and not recruited groups (Studies I and II). This is likely to be due to both avoidance of valproic acid based on the increasing information on teratogenic risks and overrepresentation of treatment-resistant focal epilepsy.

The possibility that some AED or SRI was still present in the infants during EEG recordings cannot be excluded, as most of the newborns in the Studies I, II, and III were breastfed, which might partially account for the reported EEG effects. Considering the elimination halftimes of the AED and SRIs (Gentile, 2005; Ter Horst et al., 2008; Italiano and Perucca, 2013) and the ages of the newborns (16 days in the AED and 17 days in the SRI group), the drug levels in the newborn serums through transplacental transmission were considered to be extremely low at the time of EEG recordings. Unfortunately, as the plasma levels of SRIs or AEDs in newborns at the time of EEG recordings were not available, the possibility of newborns receiving medications via breast-

feeding could not be excluded. Similarly, the number of non-breastfed newborns exposed to SRIs or AEDs was too small to allow statistical comparisons.

6.4 CLINICAL CONSIDERATIONS

The results of this thesis suggest that both AED and SRI exposure may interfere with neonatal brain activity, but given statistical correlations and group differences, these studies do not provide direct evidence for a causal reasoning. In addition to studies on causality, further studies are needed to reveal the developmental significance of individual observed EEG changes. Due to the lack of knowledge on the causality and developmental significance, these findings should not affect the current guidelines of AED or SRI treatments during pregnancy. Nor should these findings raise additional concern among pregnant women with either SRI or AED medication. At present, no conclusion can be drawn as to whether these findings have any long-term effects, adverse or protective, on the well-being of the offspring.

Treatment with AEDs through pregnancy is recommended for women with epilepsy and the vast majority of pregnancies of women with epilepsy result in healthy offspring. Findings on the potential adverse effects of AEDs in earlier studies have already prompted current guidelines that women with epilepsy should be treated with an appropriate AED during pregnancy with the lowest effective dose (Tomson et al., 2015d). In line with Baker et al. (Baker et al., 2015), the clinical evaluation at 7 months-of-age (Study II) suggested that infants prenatally-exposed to LTG or LEV may have better early language abilities than infants exposed to CBZ, OXC, or VPA. This finding is in line with the current guidelines that special attention should be applied with the use of valproic acid.

The complex effects of maternal mood, anxiety, hereditary factors, as well prenatal SRI medication, on the offspring remain unclear; it has been difficult to create precise guidelines on whether, when, and which SRIs should be used during pregnancy. SRI medication is currently advised to be used during pregnancy based on a risk-benefit decision on a case-by-case basis (Bourke et al., 2014). In case of psychotic or severe depression, antidepressive medication is suggested through pregnancy. With less severe mood disorders the results of this thesis study favor the importance of finding non-medical treatments for depressive and anxiety symptoms during pregnancy.

Guidelines should be applied already when planning pregnancy or, preferably, for all women of childbearing age. All decisions on medication should be made by consensus between the patient and the clinician with up to

date knowledge on the possible adverse effects of the medications and the underlying medical condition. Stringent follow-up of both the mother during the pregnancy and post-partum time and the offspring is needed. With AED medication, therapeutic drug monitoring during pregnancy and folic acid supplementation are recommended (Patel and Pennell, 2016).

6.5 FUTURE CONSIDERATIONS

Though the developmental significance of the specific EEG changes remain unknown, the identification of these early EEG metrics does hold promise for developing functional biomarkers for future studies on the developmental effects of drugs, neurological adversities or their treatments. To search for the developmental significance of the observed EEG changes a follow-up study will be pursued at 2- and 6 years-of-age. Studies with larger cohorts and with quantitative EEG metrics will be essential to better understand the effects of timing and interaction with other clinical events. Any characterized neonatal EEG biomarkers could also possibly be used in a much wider context, as they could disclose long-term effects of both pre- and postnatal adversities, thus facilitate early diagnoses and therapeutic interventions.

An important future direction of research would be combining electrophysiological and neuroimaging. The functional and developmental correlates of network states in the newborn opens possibilities to further understand functions of newborn neurocognition and to examine the pathological network mechanisms underlying neurological adversities common in this age group (Bonifacio et al., 2011).

The cellular-level mechanisms of computational EEG features are already understood (Engel et al., 2013; Hyafil et al., 2015; Sotero et al., 2015). According to the recent basic science data, interplay between cortical layers and the developmentally transient subplate circuitry can be studied by measuring specific cross-frequency interactions in the neonatal EEG (Minlebaev et al., 2007; Colonnese and Khazipov, 2010). The observed EEG changes could be used in future preclinical studies with animal models to test the already promising intervention strategies like neuroplasticity-based therapeutics in autistic patients (Zhou et al., 2015). In addition, more clinical studies are needed to evaluate if other adverse clinical circumstances would display similar changes in brain activity, like exposure to other medications, maternal smoking, perinatal ischemia, or prematurity.

Larger studies with prospective study design and up-to-date AED medication are needed to evaluate the impact of individual drugs on the cognitive and behavioural development of the offspring and to differentiate, at least to some extent, the effect of etiology of epilepsy from the effect of the medications. Likewise, larger prospective studies to differentiate the effect of maternal depression and the individual SRI medication should be carried out.

Automated non-invasive methods to assess infant cognition and visual fields are sparse. Eye-tracking-based cognitive testing in infancy could benetfit from the evaluation of the impact or severity of adversities in visuospatial orienting and/or face perception, such as vascular or postoperative lesions, certain epilepsies, or autism. Some of these studies have already been reported (Senju and Johnson, 2009; Pratesi et al., 2015;). Studies with these patient groups might facilitate the use of eye-tracking methodology in clinical settings as an easy-to-administer method to evaluate the need for additional support or to direct clinical examinations.

7 SUMMARY AND CONCLUSIONS

The main outcome of this thesis was to demonstrate that *in utero* AED and SRI medications may interfere with neonatal brain activity, and to identify correlates of AED and SRI exposure in human EEG.

Studies I-III. In utero AED and SRI exposure was shown to be associated with changes in individual oscillatory bout and wider band spectra activity, as well as in functional brain networking. Some of the changes were slightly more prominent in the SRI-exposed than in AED-exposed newborns: Interhemispheric and local connectivity (ASI, NC) were lower and interburst intervals (IBI) were shorter in SRI-exposed than in the control newborns, whereas in AED-exposed children, changes in these domains were seen only as temporal or spatial changes.

Findings in Study II showed that *in utero* AED exposure is associated with lower scores in overall neurodevelopmental, early language, and social skills in the clinical assessment at 7 months-of-age. However, visuospatial orienting or attentional bias for faces measured by eye-tracking methodology were unaltered.

Study IV. Study IV showed significant maturational and vigilance state-related changes in neuronal coupling during the first few weeks of postnatal life. The main findings in Study IV were: 1) During active sleep, phase-phase correlation (PPC) is relatively stronger at lower frequencies and in interhemispheric connections, while during quiet sleep PPC was stronger at higher frequencies and in intrahemispheric connections; 2) PPC is first established at lower frequencies and shorter distances; 3) Amplitude-amplitude correlation (ACC) declines rapidly with maturation; and 4) Phase-amplitude correlation is frequency-dependent and strongly related to vigilance state.

Treatment with AEDs through pregnancy is recommended for women with epilepsy. These women should be treated with the appropriate AED at the lowest effective dose. Current guidelines recommend that special attention should be paid to the use of valproic acid.

SRI medication should be used during pregnancy based on a risk-benefit decision on a case-by-case basis (Bourke et al., 2014). Both non-medical and medical treatments should be considered. Guidelines on AED and SRI medications should be applied already when planning pregnancy.

This thesis also provides further understanding of how the electric brain networks develop during the first few weeks of postnatal life in a human neonate showing significant maturational and vigilance state-related changes in neuronal coupling.

In summary, computational EEG analysis could be used in the near future as a biomarker in infants to assess neural plasticity, both in clinical and in research settings, to predict the neurocognitive or behavioral consequences in addition to monitoring or diagnosing medical conditions.

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