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Specific Targeted Research Project

SIXTH FRAMEWORK PROGRAMME
LifeSciHealth Priority-5
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Publishable final activity report

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Project coordinator name: Prof. Dr. Gerd Schulte-Körne
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Publishable final activity report

1. Project execution

Introduction

NeuroDys was established in June 2006 and commenced in June 2009. With the funding of the European Union the main aims of NeuroDys were to 1) identify dyslexia genes; 2) test for the presence of gene-gene and gene-phenotype relationships; 3) investigate neurobiological correlates of dyslexia; and 4) ensure that knowledge and skills derived from NeuroDys reach and inform the research community, affected individuals, healthcare services and providers, policy makers and wider society. In order to reach these goals multiple collaborations within Europe were formed. Altogether, the expertise of scientists from Austria, England, Finland, France, Germany, Holland, Hungary, Sweden and Switzerland came together to form the NeuroDys consortium. This collaboration brought together knowledge from a very broad scientific community. The research strengths of NeuorDys were based on the common and proved expertise amongst members in dyslexia research. This expertise ranged from backgrounds in dyslexia relating to genetics, behavioural, neurofunctional, neurophysiological, developmental and clinical.

An important success of NeuroDys to date is the establishment of the world's largest database consisting of phenotypic and genotypic data on children with dyslexia. A total of 1644 children with dyslexia and 1281 healthy matched controls were recruited from across Europe. The database consists of the results from a comprehensive task battery of cognitive measures assessing nonword decoding, spelling, phonological awareness, phonological short-term memory, rapid automatized naming and the DNA samples of all participants. This large collection of data enables the NeuroDys consortium to investigate a number of important questions regarding the causal nature of dyslexia. Once the genetic analyses are complete, the research will focus on the elucidation of dyslexia endophenotypes. Highlighting the promising nature and immense research impact this dataset has, NeuroDys members have already successfully published papers. Furthermore, publications in top journals regarding the neural and phenotypic data have emerged, or are being prepared. Numerous future publications are planned. The database will also be used to answer future questions regarding the genetic nature of dyslexia, and will also be exploited to explore gene-behaviour relationships. Finally, the data can be used to understand how genetic codes might contribute to deviant neurofunctional, neuroanatomical and neurophysioliogical findings.

The following sections describe the successes, progress and future directions of the seven workpackages (WP) in NeuroDys.

WP 1: Linkage disequilibrium mapping

WP Leaders: Markus Nöthen, Anthony Monaco

1. Project execution

The principal objective of WP 1 is to assess the presence of susceptibility genes for dyslexia at five chromosomal loci previously genetically linked to dyslexia (2p11-p13, 2p15-p16, 6q21, 15q15-q21, and 18p11-q12). Due to advances in technology WP1 altered the original objectives. The strategy changed from fine mapping of known dyslexia loci to a genome-wide association approach. A total of 600 cases and 2400 population based controls were quality checked and then genotyped using the Illumina Infinium-II technology resulting in at least 300K single-nucleotide polymorphism (SNP) genotypes for each sample. Following quality controls measures, the genotypes were then sent to the statistical work package (WP4). These SNPs were then analyzed for association to dyslexia. The most highly ranked SNPs were then selected for further genotyping in all replication samples available to the Consortium. These included 1409 cases and 1959 controls collected from Austria, Finland, France, Germany, Hungary, Netherlands, Switzerland and the UK. Genotyping was performed using Sequenom's iPLEX technology. An assay of 36 highly ranked SNPs was created for genotyping in the replication samples. After quality control measures the genotypes for 34 successfully genotyped SNPs were then sent WP4 for statistical analysis, but there were no results consistent with the original genome-wide screen. Therefore, a new and higher density genome-wide screen with 1 million SNPs on new samples was performed. This new screen employed a pooled-samples strategy rather than genotyping individual samples. Three geographically separate pairs of pools were created, consisting of 532 cases and 912 controls from central Europe, 286 cases and 321 controls from Finland and 426 cases and 219 controls from the UK and analyzed. Based largely on the most highly ranked SNPs, 40 SNPs were selected for further genotyping in all samples available to the Consortium. These samples included 1526 cases and 2261 controls from Austria, Cardiff, France, Hungary, Germany, Netherlands, Oxford and Switzerland. Genotyping was performed using Sequenom's iPLEX technology. Following quality control measures, 33 SNPs were then analysed in all samples (WP4). Despite no SNP showing consistent results across all samples, which is not unexpected given their heterogeneous ancestries, there were consistencies for some SNPs with several samples.

WP2: Ascertainment and phenotypic assessment of cases and controls

WP Leaders: ***Karin Landerl, Franck Ramus***

1. Project execution

The main objective of this activity area is to increase understanding of the genetic and behavioural correlates of reading and spelling in dyslexic children, in order to increase our knowledge of the underlying mechanisms and to facilitate the deconstruction of the genetic components of dyslexia. This workpackage is particularly innovative as it will look at dyslexia-related endophenotypes. It has considerable power as the analysis are underpinned by a European-wide collection and the (to date) largest sample available.

Table1 lists all partners involved and the numbers of cases and controls that were ascertained by each partner

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Collection center	**Sample size (cases and controls)**	**Molecular genetic reference center**
Cardiff	278 cases / 152 controls	Cardiff
Munich	207 cases / 216 controls	Bonn
Salzburg	186 cases / 209 controls	Bonn
Zürich	30 cases / 45 controls	Bonn
Maastricht	153 cases / 174 controls	Bonn
Jyväskylä	233 cases / 214 controls	Stockholm
Budapest	119 cases / 197 controls	Bonn
Oxford	272 cases / 0 controls	Oxford
French national sample (incl. Toulouse)	166 cases / 74 controls	Paris
Total	**1644 cases / 1281**	

All participants were in the age range 8 to 12 years (2^{nd} to 6^{th} grade). They were selected based on nationally widely used word reading tests (dyslexics: < -1.25 SDs below age or grade level; controls within age or grade level: > .85 SDs). Children with general learning deficits (low IQ) and children with ADHD were excluded. children had the test language as their first language. These exceptionally stringent selection procedure required immense investments from partners in order to screen large numbers of potential participants and exclude all those who did not fulfil all criteria.

For analysis of endophenotypes, each partner devised a task battery of cognitive measures assessing nonword decoding, spelling, phonological awareness, phonological short-term memory, rapid automatized naming. Parents were asked to fill in a questionnaire collecting information on familial transmission and early neurological or environmental risk factors. DNA from each participant was collected (blood or saliva samples).

This comprehensive data set allows to test for specific genetic links for each of these endophenotypes. A further interesting research question is whether the associative patterns of phonological awareness, phonological short-term memory and rapid automatized naming with reading and spelling measures differ between languages/orthographies. Until recently, research has largely focussed on English, a rather untypical alphabetic orthography characterised by low consistency of grapheme-phoneme correspondences. The languages involved in Neurodys cover a wide range of alphabetic orthographies with different levels of consistency ranging from English to the most transparent alphabetic orthography of Finnish

(1:1 mapping between sounds and letters, simple linguistic structure) with French, Dutch, German, and Hungarian representing different intermediate levels of consistency allowing the investigation of the impact of orthographic/linguistic differences on the manifestations of dyslexia. These analyses are currently under way.

WP3: Dyslexia susceptibility genes

WP Leaders: ***Julie Williams, Juha Kere***

1. Project execution

WP3 brings together the findings of WP1, WP5, WP6, and WP7 and the resources of WP2 and WP4. There are four overall objectives to refine the replicated SNP associations observed in WP1, through intensive genetic analysis; to test for genotype/phenotype interactions with gene loci; to test for gene-gene interactions and co-actions; to provide associated genotypes/haplotypes to test for gene-environmental relationships as described in WP5.

Due to falling genotyping costs, it became feasible to perform a genome-wide association (GWAS) study as opposed to the originally planned five chromosomal dyslexia susceptibility locations. As a result, the strategy of WP3 was altered accordingly. Thirty-four SNPs showing most significance in the WP1 GWAS were genotyped in a replication case/control sample collected as part of WP2. This consisted of a total of 1258 cases and 1974 controls ascertained from the UK (537 cases; 556 controls), Germany (308 cases; 879 controls), Netherlands (115 cases; 106 controls), Austria (116 cases; 201 controls), Finland (156 cases; 189 controls) and Switzerland (26 cases; 43 controls). Although there were no results consistent with the original WP1 GWAS, 1 SNP did show increased significance when both datasets were combined in a meta-analysis. This SNP lies within a gene desert on chromosome 5.

In an effort to identify additional SNPs, the replication sample was pooled, and a higher-density GWAS was performed on the pools using the Illumina Human1M-Duo chip. As such, almost 1,000,000 SNPs were genotyped in the pooled replication sample. In total, 1333 cases and 1452 controls were divided into three geographically separate pairs of pools representing the UK (426 cases; 219 controls), Central Europe (532 cases; 912 controls) and Finland (286 cases; 321 controls). Thirty-seven of the most significant SNPs were individually genotyped in the replication sample, but none achieved genome-wide significance, which is not unexpected given heterogenous ancestry. We are imputing unobserved SNPs in the WP1 GWAS in order to compare with the genome-wide results of the pooling study. We will seek further funding to follow up on SNPs showing evidence of association with dyslexia in both datasets. It is anticipated that we will publish the GWAS data.

Given that genome-wide data was produced, testing for genotype interactions was not feasible. However, quantitative analyses on reading-related traits such as reading fluency and accuracy, spelling, phonological decoding and awareness and orthographic processing are currently being performed on all the cases that have been genotyped.

Finally, newly developed highly efficient algorithms and increased computing power, along with newly released data from the International HapMap project are allowing us to impute unobserved SNPs in the WP1 GWAS in order to compare with the genome-wide results of the pooling study.

WP4: Genetic and behavioural statistics

WP Leaders: Peter Holmans, Andrew Morris

1. Project execution

Investigators at the Wellcome Trust Centre for Human Genetics have developed an "Integrated Genotyping System (IGS) for cleaning, parsing and disseminating complex phenotype and genotype data. The database infrastructure provides a common forum for co-ordination, integration and standardization of the phenotype information collected from multiple sites as part of WP2. The database can also parse genotype call directly from a variety of platforms, including the Illumina 317K and 550K products. The database has a strong security basis to maintain confidentiality and offers a secure link for remote access by members of WP2. The database has been used to manage phenotypic and related environmental data for samples collected as part of WP2, and to link it to available genotype data from WP1. The infrastructure has allowed investigators to have secure access to the joint phenotype-genotype data for a variety of statistical analyses.

The Consortium changed the objective of fine-mapping of known dyslexia loci in 800 trios to a whole genome association study of 600 dyslexia cases (200 each from Bonn, Cardiff and Oxford) and 2400 population-based controls (900 from Germany and 1500 from the 1958 British birth cohort). The majority of case-control samples were genotyped on the Illumina 317K array, with the remainder genotyped on the Illumina 550K array (contractors 10a, 11 and 14 for WP1). The overlap between these products provided more than 300,000 SNPs typed on all 3000 individuals. With this approach, the Consortium was not limited to fine-mapping in established dyslexia loci, but would have sufficient power to detect novel common causative variants of modest effect across the whole genome. Such an approach has proved successful in identifying novel loci for type 2 diabetes, coronary artery disease, obesity and Crohn's disease for example. Population-based controls (900 from Germany and 1500 from the 1958 British birth cohort) were obtained by contractors 10a and 11 through external resources, at no additional cost to NEURODYS. The change to the study design has also lead to major alterations in the downstream analysis protocol.

Our primary analysis focussed on association between dyslexia (as a binary case-control phenotype) and each of the 300,000 SNPs typed on all 3,000 individuals. Genotype data from WP1 were transferred to databases in the UK and Germany, together with quality assessment scores for each called genotype. The quality of genotype data from the two Illumina products was assessed for each cohort separately. The quality of genotype data for the UK samples was marginally inferior to that of the German samples. As a result, the genotypes of the UK samples were re-assigned using a novel genotype calling algorithm (ILLUMINUS) at the Wellcome Trust Sanger Institute. Sample quality control filters were applied based on call rate, heterozygosity, duplication and possible relatedness, and non-North-Western European ancestry. Subsequently, single-locus analyses, using an allelic trend test and genotypic test, were performed for each SNP passing quality control filters based on call rate, deviation from Hardy-Weinberg equilibrium and minor allele frequency.

To increase power, we performed a combined analysis of genotype data from the samples from both Germany and the UK. To allow for population differences, principal components analysis based on a measure of relatedness between individuals was undertaken to identify axes of genetic variation across Europe. Single locus analyses were then performed in a logistic regression framework on the combined samples, adjusting for significant axes of variation and a fixed-effect for the possible non-genetic differences between the two populations. Multi-locus analyses were undertaken by imputation of SNPs not typed as part of the genome-wide association study, but present on a reference panel of CEPH haplotypes from the international HapMap project. The results of these primary analyses failed to

identify any SNPs associated with dyslexia at a genome-wide level of significance (p<5.7x10-7).
To add support to the results of the primary GWA study, we undertook a pooling experiment on 1M SNPs. Pooling was conducted in three case-control pools with several replicates: 532 cases and 912 controls from Central Europe (Austria, Germany, Netherlands and Switzerland) were analysed in four replicates, 286 cases and 321 controls from Finland in six replicates and 426 cases and 219 controls from the UK in six replicates. The 40 top SNPs were taken forward into individual genotyping. However, no genome-wide significant results could be obtained.
We have also undertaken analysis of genome-wide association data generated in WP1 using quantitative phenotypes used to define dyslexia in the 600 cases from the UK. This analysis will detect associations of SNPs with specific intermediate phenotypes (such as spelling and reading ability) which contribute to dyslexia. We followed the same quality control protocols as described for the primary analysis. Raw phenotypes were transformed to an approximate normal distribution to allow the application of standard statistical analysis techniques. Within each case cohort, we undertook single-locus analyses of the directly genotyped SNPs from WP1, as well as multi-locus analysis using imputed SNPs derived as part of the primary analysis.
The intermediate phenotypes used to define dyslexia differed between samples from the three different cohorts (Cardiff, Oxford and Bonn), primarily due to language differences between the UK and Germany. Contractor 1 provided details of the most comparable phenotypes between the cohorts. In order to maximise power, we then combined the association result, where possible, for comparable phenotypes using fixed-effects meta-analysis across cohorts.
Across case cohorts, we combined the following comparable phenotypes: reading, spelling, phonological decoding, phoneme awareness and orthographic processing. In performing our quantitative trait association analyses, we observed potential discrepancies between cohorts in the distribution of phenotypes we believed to be comparable. We are currently investigating the source of this heterogeneity before performing our final analysis of the data. The final results of this analysis, together with SNPs identified from the initial genome-wide association study and pooling experiment, will inform the selection of SNPs for follow-up in replication samples collected as part of WP2.

WP5: Environmental Factors, early predictors and gene-environment interplay

WP Leaders: Heikki Lyytinen, Robert Plomin

1. Project execution

The aims of WP5 were to investigate genotype-environment (GE) interaction and correlation for reading in a large study, to investigate GE interaction and correlation in the same sample using specific genes identified in WP3 as well as in other research and to identify early environmental, neuropsychological and neurophysiologic predictors for dyslexia
In the Jyväskylä Longitudinal Study of Dyslexia (JLD) we have currently 106 children at risk of dyslexia and their families and 93 matched controls and their families from four birth cohorts who have been followed intensively from birth to puberty. Associated with the Neurodys workpackage 5 (the work of one month funded specifically from it) our aim has been to elaborate (for the purposes of illustrating results related to the theme of the package) JLD-findings associated with early predictors of dyslexia including neurophysiological (ERPs recorded in the context of speech perception designs at month 6), neuropsychological, psychological (motor, language, memory skills) and home environmental factors (maternal education, parents reading problems, parent-child shared reading, child's access to reading materials, and child's reading interest) in order to delineate the contributions of gene-

environment interplay in dyslexia. We also took blood samples from these children and their parents for genotyping (see WP 3) but associated analyses have not yet been made.
We have so far conducted several analyses on prediction of reading including both child skill measures and measures of the environment they live in. These analyses have shown that as a group, the at-risk children performed more poorly than the control children on most of the language and literacy skills assessed, starting with very early vocabulary development. Also, the amount of support in the family environment was similar in the at-risk and control groups. Children's interest in reading prior to school age was also found to be similar in the at-risk and control families. The at-risk group is, however, heterogeneous in both skill development and the amount of environmental support. Environmental factors were related with skill development in the following way: Prior to school age shared parent-child book reading was found to be associated with vocabulary development and vocabulary mediated its effect on phonological awareness. Letter name learning, on the other hand, was associated with letter name teaching at home. At school the effect of being a member of a specific classroom on children's reading skills was small but significant, varying between 4 and 10 %, depending on reading skill and time of assessment. Poor readers at school age had had less shared reading experiences with parents at a very early age than good readers and good readers also engaged in more solitary reading than poor readers, already before school entry. The accumulation of multi-domain risk factors (familial risk for dyslexia, parental risks such as parental depression or stress, and neurocognitive risks such as poor performance in memory, language or motor tasks) assessed 1-6 years of age were found to predict cognitive (IQ), academic (reading fluency), and social adaptive behaviour at 8 – 9 years. The parental risk factors predicted particularly social adaptive behaviour whereas the neurocognitive risks factors predicted especially cognitive and academic task performance. Finally, dyslexia risk factor acted as a moderator in most analyses in that the associations were stronger among at-risk group than in the control group.

WP6: Structural and functional brain studies

WP Leaders: Leo Blomert, Heinz Wimmer

1. Project execution

The project set out to identify possible brain dysfunctions related to reading acquisition anomalies characteristic of developmental dyslexia. We decided to focus on two main skills that children must acquire to read fluently. First; fluent reading is fast and effortless in normal readers and laborious and slow in dyslexic readers. Brain research has informed us that there is an area in the left posterior part of our brain that seems to have specialized for the recognition of visual words. We therefore wanted to know if dyslexic readers would show deviant processing of letters and words in this area. We further wanted to know if the children in different orthographies would use the same brain areas for recognizing words. To study these processes we used fMRI, functional neuroimaging of brain activations during the performance of cognitive tasks like reading.
Our results show that first, the brain areas involved in processing written words were very similar in all three countries. We therefore pooled all data and found that dyslexic children showed less activation in the specific Visual Word Form Area (VWFA). Even more interesting it was shown that the compensatory activity in dyslexia in frontal brain regions was much more pronounced than these underactivations in the posterior word recognition regions (Maurer et al, *in prep*.). The lexical decision study with short and long words and pseudowords confirmed the results from the pooled analysis and revealed robust underactivation of the VWFA and overactivations of frontal brain areas. Furthermore, we found that dyslexic children, like older dyslexic readers, lacked key neural signatures of skilled visual word processing. These observations suggest that the brains of dyslexic children

do not just show global over- and underactivations during reading but react in a fundamentally different way during reading (Sturm et al., *in prep*.; Kronbichler et al., *in prep*.). We further showed that dyslexic children lack multiple specialization for print extending beyond the VWFA into the entire Visual Word Form System: A posterior-to-anterior gradient of print specificity and a constant sensitivity to orthographic familiarity was present in typical readers, but lacking in children with dyslexia. This double deficit also indicates that children with dyslexia show impaired specialization for both print and orthography (Van der Mark et al., 2009).

The second objective was to investigate the very first knowledge children have to acquire to make learning to read possible; i.e., the association of letters to speech sounds. Recent brain research has shown us that although all children seem to know these relations within a year, it takes years to automate these associations. The results of the present study revealed that dyslexic children did not automate these basic associations between letters and speech sounds even after years of reading instruction. Worse dyslexic brains did not make a difference between letter-speech sound pairs that existed in the language and pairs that did not exist (Blau et al, *in revision*).

Because we found clear functional abnormalities in dyslexia we also investigated the possibility of structural brain anomalies. Although recent brain research points to the thickness of the cortex of the brain as possibly relevant for cognitive functioning, we did not find any differences in cortical thickness between normal and dyslexic brains although we used several different existing methods and even controlled all measurements manually (Reithler et al, *in prep*). Since we did not find any cortical thickness differences we hypothesized that the structural brain differences might reside in the connectivity between brain areas. We therefore used a method, DTI Diffusion Tensor Imaging, to investigate the patterns of connectivity in dyslexic and normal brain areas. We expect to finish this last part of the project soon.

The convergence of our structural and functional findings in three different countries provides new exiting insights in the possible causes and consequences of reading failure in dyslexia and provide key insights for a theory of reading development and reading failure.

WP7: Cross-linguistic ERP study on speech perception in dyslexic children

WP Leaders: Paavo Leppänen, Valeria Csépe

1. Project execution

The main objective of the *Cross-linguistic ERP study on speech perception in dyslexic children* workpackage (WP7) was to identify genetically driven basic dysfunctions in speech sound processing in dyslexic children compared to those with good reading skills. Specifically, the aim was to investigate neural substrates of pre-attentive, automatized speech perception in a cross linguistic study design by means of brain event-related potentials (ERPs), and to investigate the relationship of brain measures to susceptibility genes for dyslexia.

The main prerequisite necessary for starting reading acquisition is efficient speech perception and formation of phoneme representations. Neural substrates of pre-attentive, automatised speech perception have been investigated in a cross-linguistic study design using brain event-related potentials (ERPs). The cross-linguistic nature of this approach has allowed us to see whether possible speech perception deficits are related only to a dyslexic reader's own language or whether dyslexics have a more common or general speech deficit. Another important objective is to investigate the genetic background of speech perception in dyslexic individuals linking neural substrate profiles for genotyping data. This will be done when the genetic data becomes available.

We have applied a classical ERP-experimental design (an oddball paradigm) in order to investigate the mismatch negativity elicited by synthesized speech stimuli in four language groups (Finnish, French, Hungarian, German). Mismatch negativity component of the ERP is thought to reflect the brain's capability to store very short term auditory information and passively detect deviations from this information. Based on our previous findings (Schulte-Körne et al. 1998, 2001, Leppänen et al. 1999, 2002, Csépe et al. 2004) and findings from cross-linguistic ERP studies (Näätänen et al. 1997, Peltola et al. 2003), we first aimed to investigate brain responses to prototypic vowels from each language in 50 dyslexic and 50 control children in each language. We have also applied comparable non-speech stimuli in order to investigate whether the language influences are specific to speech.

The cross-linguistic research design was developed in a collaboration of all the four WP7 participant research groups, Finland/ Jyväskylä (Jyväskylä from here after), France/ Toulouse, Germany/ Munchen (formerly Marburg), Hungary /Budapest. The stimuli were created in collaboration with Dr. Jyrki Tuomainen (then at University College London, now professor in Åbo Akademi). The vowel stimuli and the MMN paradigm with a standard common euro-i and deviant /y/s representing prototypical /y/-vowels in the languages of the participating countries were tested in all partner countries. This work resulted in July 2007 in the final paradigm with a euro-i and three different /y/s (Finnish-Hungarian, French, and German) as well as corresponding non-speech stimuli. By May 2009, a total of 211 control and 230 dyslexic children (54 controls, 58 dyslexics from Finland, 56/59 from France, 57/63 from Germany, and 44/50 from Hungary, respectively) at the 3-4th grade have participated in ERP and behavioral discrimination studies. This endeavor is unique, to date, in the sense that this is the first time that large groups of children, in particular clinical groups, are measured with the same experimental protocol (including the common stimulus presentation and data analysis procedures) in four different countries. The WP7 collaborative action has involved ca. 2-3 meetings a year to deal with various issues related to the research design, measurement and analysis issues. The partners have also developed large scale web-based data sharing procedures with a common database for the ERP and behavioral data as well as common data processing and analysis procedures.

The preliminary behavioral data analyses were carried out in the spring 2008 and the final analyses involving a manuscript preparation are under way. The basic brain response data analyses were carried out by May 2009, with 2 article manuscripts under preparation involving common data across the 4 partner laboratories and 4 involving the national data sets (see below; for details, see Publishable final activity report, 2. Dissemination and use). To facilitate ERP analyses, an analysis workshop was held in Munich 21-23.4.2008. Because the data were collected in different laboratories with different amplifiers, the systems were calibrated by measuring EEG to calibrator generated fixed pulses created with the same calibrator device circulated among all the partner laboratories. It also became apparent during the analyses that a solution needs to be developed for different EEG-electrode systems (for recording of brain waves) used in the different laboratories (128 sensor net-systems in Jyväskylä and Munich, vs. recording systems following the international 10-10 scheme for a 33 electrode gap in Budapest and 64 and 31 electrode gaps, for adults and children, respectively, in Toulouse). The solution was a mathematical transformation of the EEG data for the virtual standard electrode system with the commonly available electrodes in each lab. Common data analysis procedures have been carried out in all laboratories to get comparable data across language settings.

Currently, several articles to be published are under preparation. The article involving adult participants to test the ERP paradigms will outline the rationale for the paradigm used and describe major issues in combining the data, for the first time in ERP history, from four different laboratories using the same cross-linguistic paradigm in four countries. The first child article will describe the cross-linguistic and long-term native language exposure effects

for the pre-attentive change detection response, MMN, in children with dyslexia using the data from all four countries. Further, national articles with specific topics and different angles, either content wise or from the analysis point of view, were planned to be authored by doctoral student level researchers from different universities; either with an emphasis on the exogenous brain responses (in Jyväskylä), comparing non-linguistic and linguistic MMN responses and attention related P3a responses in Munich, and applying specific analyses approach (running t-tests) and comparison to behavioral data in Toulouse. An article on the stimulus creation and tests with adult participants is also under way. (all articles are aimed to be published in high standing and recognized neuropsychological and cognitive neuroscience journals; for details, see Publishable final activity report, 2. Dissemination and use). Further articles, involving modeling of ERP, behavioral speech discrimination and reading measure data have also been planned to be published as a collaborative work. Plans also involve presenting the WP7 data in several expertise level as well as applied international conferences. The updating of the common database (upheld by Jyväskylä) and continued collaboration in the data analyses have also been agreed upon. Comparisons of brain responses with the genetic data will be started upon the availability of the genetic data. In addition of the 4 partner universities, Oxford, UK will participate in these efforts.

2. Dissemination and use

The following section provides a summary of NeuroDys' publishable Results.
Given the lag between project onset and the production of results in a publishable form, and the subsequent lags to submission and publication, many papers will be published after the end of the project.

Publications acknowledging NeuroDys Support

Blau V, Reithler J, Seitz J, Gerretsen P, Goebel R, Blomert L. (in revision). Deviant processing of letters and speech sounds as proximaate cause of reading failure in a fMRI study of dyslexic children. *Brain*

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Maurer U, Bucher K, Brem S, Benz R, Kranz F, Schulz E, van der Mark S, Steinhausen H-C, Brandeis D. (2009). Neurophysiology in preschool improves behavioral prediction of reading ability throughout primary school. *Biological Psychiatry, 66,* 341-348.

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Willburger E, Landerl K. (submitted). *Anchoring the deficit of the anchor deficit: Attention rather than dyslexia.*