

Altered Low-Gamma Sampling in Auditory Cortex Accounts for the Three Main Facets of Dyslexia

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SUMMARY

It has recently been conjectured that dyslexia arises from abnormal auditory sampling. What sampling rate is altered and how it affects reading remains unclear. We hypothesized that by impairing phonemic parsing abnormal low-gamma sampling could yield phonemic representations of unusual format and disrupt phonological processing and verbal memory. Using magnetoencephalography and behavioral tests, we show in dyslexic subjects a reduced left-hemisphere bias for phonemic processing, reflected in less entrainment to ≈ 30 Hz acoustic modulations in left auditory cortex. This deficit correlates with measures of phonological processing and rapid naming. We further observed enhanced cortical entrainment at rates beyond 40 Hz in dyslexics and show that this particularity is associated with a verbal memory deficit. These data suggest that a single auditory anomaly, i.e., phonemic oversampling in left auditory cortex, accounts for three main facets of the linguistic deficit in dyslexia.

INTRODUCTION

Developmental dyslexia is a specific learning disability of reading and spelling affecting around 5% of schoolchildren, which cannot be attributed to low intellectual ability or inadequate schooling (Lyon et al., 2003; World Health Organization ICD-10, 2008). It is widely agreed that for a majority of dyslexic children, the proximal cause lies in a phonological deficit, i.e., a deficit in representing and/or processing speech sounds (Vellutino et al., 2004). Three main symptoms of the phonological deficit are well established: poor phonological awareness, i.e., the ability to pay attention to and mentally manipulate individual speech sounds; poor verbal short-term memory, i.e., the ability to repeat, for instance, pseudowords or digit series; and slow performance in rapid automatized naming (RAN) tasks, where one must name a series of pictures, colors, or digits as fast as possible (Vellutino et al., 2004; Wagner and Torgesen, 1987).

However, there remain several theoretical perspectives on both the nature and the underlying basis of the phonological

deficit. One issue is whether phonological representations themselves are degraded, or whether the ability to retrieve them from or store them into working and/or long-term memory is limited (Ahissar, 2007; Ramus and Szenkovits, 2008). Another issue is whether the phonological deficit is restricted to speech sounds (Mody et al., 1997; Ramus et al., 2003; Rosen and Mangani, 2001), or whether it follows from a more basic auditory processing deficit (Chandrasekaran et al., 2009; Tallal, 1980; Vandermosten et al., 2010). Theoretical disagreements stem in a large part from diverging interpretations as to which levels of representation and processing are targeted by related cognitive tests (Ramus, 2001). In the present study, we use a neurophysiological paradigm that circumvents these limitations by relying exclusively on bottom-up cortical responses to passively heard auditory stimuli, thus tapping into the first steps of auditory cortical integration without calling upon any explicit task. We thereby specifically explore the novel hypothesis that auditory sampling might be altered in dyslexia (Goswami, 2011). We assume that an alteration of fast auditory sampling, reflected in cortical oscillations, would yield phonemic representations of an unusual temporal format, with specific consequences for phonological processing, phoneme/grapheme associations, and phonological memory.

While cortical oscillations have been implicated in several aspects of human cognition, including sensory feature binding, memory, etc. (Engel et al., 2001), their role in organizing spike timing (Kayser, 2009) could be determinant for sensory sampling (Schroeder et al., 2010; Van Rullen and Thorpe, 2001) and connected speech parsing (Ghitza, 2011). In auditory cortices, the most prevalent oscillations at rest match rhythmic properties of speech. They are present in the delta/theta and low-gamma bands (Giraud et al., 2007; Morillon et al., 2010) and hence overlap with the rates of the strongest modulations in speech envelope, i.e., the syllabic (4 Hz) and phonemic (about 30 Hz) rates, respectively. As theta and low-gamma intrinsic oscillations are amplified by speech, we and others have argued that they could underlie syllabic and phonemic sampling (Abrams et al., 2009; Ghitza and Greenberg, 2009; Giraud et al., 2007; Morillon et al., 2010; Poeppel, 2003; Shamir et al., 2009).

Auditory cortical oscillations at delta/theta and low-gamma rates are not independent. They usually exhibit nesting properties whereby the phase of delta/theta rhythm drives gamma power (Canolty and Knight, 2010; Schroeder and Lakatos, 2009). Oscillation nesting could hence be a means by which

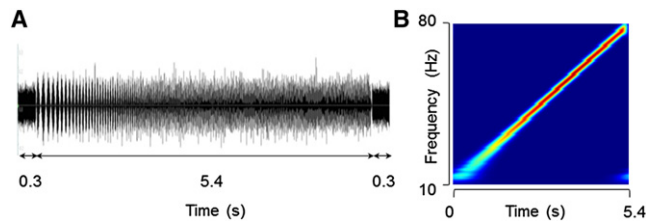


Figure 1. Stimulus' Waveform and Spectrogram

(A) Waveform of the stimulus used to elicit auditory steady-state responses. The stimulus is a 5.4 s amplitude modulated (AM) noise with AM linearly increasing from 10 to 80 Hz.

(B) Spectrogram of the stimulus.

See also Figure S1.

phonemic and syllabic sampling organize hierarchically, such that information discretized at phonemic rate is integrated at syllabic rate. This mechanism is plausible because cortical oscillations modulate neuronal excitability, yielding interleaved phases of high and low spiking probability at gamma rate, and interleaved phases of low and high gamma power at theta rate (Schroeder et al., 2010). Periodic modulation of spiking is equivalent to information discretization, i.e., an engineering principle through which continuous information is processed over optimal temporal chunks (Xuedong et al., 2001) and forwarded to the next processing step (Roland, 2010).

While discretization of neural information likely operates ubiquitously in the brain, it is crucial in speech perception that it occurs at a rate compatible with the encoding of relevant spectrotemporal information, i.e., fine structure and formant transitions (Rosen, 1992). Theoretical work recently demonstrated that the shape of a prototypical 50 ms diphone-like stimulus can be represented by a three-bit code corresponding to three ≈ 40 Hz gamma cycles (Shamir et al., 2009). Such a binary encoding by the low-gamma rhythm represents a critical and necessary downsampling step in the process of transforming acoustic into phonological representation after which many spectrotemporal details of speech are lost.

While others have put forward the hypothesis that syllabic sampling at theta rate might be altered in dyslexia (Abrams et al., 2009; Giraud et al., 2005; Goswami, 2011), we focus here on the complementary idea that an anomaly in phonemic sampling at low-gamma rate could have direct consequences for phonological processing. We hypothesize that the oscillatory behavior in the low-gamma band observed in typical control participants is the optimal phonemic sampling rate, and that too slow or too fast sampling would affect the format of phonemic representations. More specifically, gamma oscillations downshifted relative to controls would result in diminished phonemic discrimination (Tallal et al., 1993), whereas too fast gamma sampling by oscillations shifted upward might flood the auditory system with overdetailed spectrotemporal information and thereby saturate theta-based auditory buffer capacity (Hsieh et al., 2011) and phonological working memory.

To assess these hypotheses, we compared auditory cortex gamma oscillations in 23 dyslexic and 21 control participants. We used a frequency tagging magnetoencephalography (MEG) experiment with source reconstruction, in which auditory steady

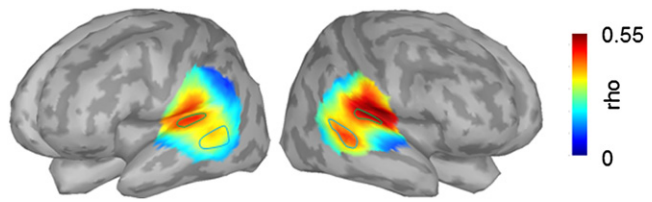


Figure 2. Surface Rendering of the Main Response Sources

Grand average of individual correlation coefficient between the stimulus' spectrogram and the ASSR time-frequency matrix. Colored areas correspond to the two selected auditory regions of 650 vertices in each hemisphere. ASSR maxima are found at two locations, one in the planum temporale (cyan) and one in the STS (green). Subsequent analyses are performed in each of these locations. See also Figure S2.

state cortical responses (ASSR) were evoked by a white noise with a range of amplitude modulations (10–80 Hz; Figure 1) that broadly covered the phonemic sampling domain. We predicted that phonological performance in dyslexics should reflect a deficit in low-gamma oscillations within a 25–35 Hz frequency window centered on the dominant 30 Hz phonemic rate. Consistent with the asymmetric sampling theory (AST) that postulates stronger low-gamma sampling in left than right auditory cortex (Giraud et al., 2007; Morillon et al., 2010; Poeppel, 2003; Telke-meyer et al., 2009), we further assumed that the low-gamma deficit in dyslexics should be more pronounced in the left than in the right hemisphere.

RESULTS

Low-Gamma ASSRs Are Not Left Dominant in Dyslexic Individuals

In both dyslexics and fluent readers, oscillatory responses were observed for acoustic amplitude modulations presented at the same rate (Figure S1 available online, maximal responses on the diagonal). We identified two regions within each hemisphere where entrainment by the modulated sound was maximal. One localized to the planum temporale (PT) immediately behind and overlapping with the posterior part of Heschl's gyrus (Bidel-Cau-let et al., 2007; Brugge et al., 2009; Steinmann and Gutschalk, 2011), and the other to the superior temporal sulcus (STS) (regions delimited by blue and green contours, respectively, Figure 2). Group and hemisphere comparisons were subsequently conducted at these two locations, identical in both groups. Because our hypothesis focuses on a deficit in the auditory association cortex, i.e., PT (as specified by AST, Poeppel, 2003), we report here the results obtained from the PT, while those for the STS are presented as supplemental material (Figures S2 and S4). The mean ASSR spectrum for each group in the PT (Figure S2, upper panels) confirms previous observations that ASSRs peak at 40 Hz and are overall stronger in right than in left auditory cortex (Ross et al., 2000, 2005; Poulsen et al., 2007).

Consistent with our predictions, we observed in controls a left-dominant entrainment to acoustic modulations within a restricted frequency range that covers the hypothesized phonemic sampling rate (Figure 3A; Figure S4A for STS). Left lateralization was significant in the 25–35 Hz (sound, S)/25–35 Hz (response, R) range (cluster significant at $p = 0.04$ in

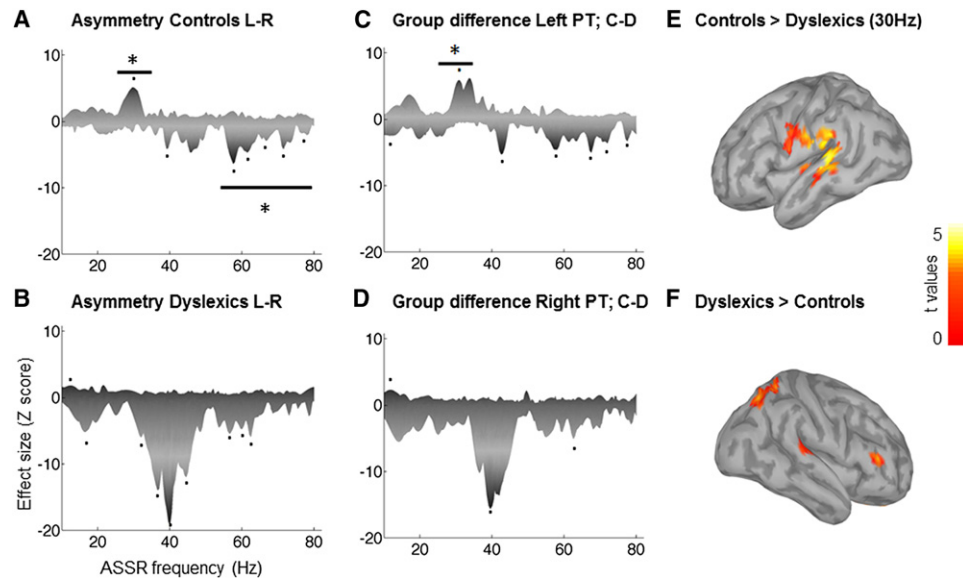


Figure 3. ASSRs Obtained in Response to the 5.4 s Noise Modulated in Amplitude between 10 and 80 Hz in the Planum Temporale

(A) ASSRs (left minus right) in controls show a left dominance in the 25–35 (sound)/25–35 (response) Hz range and a right dominance to AM frequencies above 55 Hz.

(B) Left dominance around 30 Hz is absent in dyslexics.

(C) In the left PT, controls show significantly stronger 30 Hz entrainment than dyslexics, and dyslexics display significantly stronger responses above 40 Hz.

(D) In the right PT, dyslexics display stronger responses at 40 and 60 Hz. Lines delimit significant clusters ($p < 0.05$). Points indicate significant local values (two-tailed t test, $p < 0.05$ uncorrected).

(E and F) Surface projection of the group difference at 30 Hz (representation of t values, one tailed, $p < 0.05$ minimum cluster size = 18).

See also Figure S3.

the PT). Around 40 Hz and in the upper gamma range (55–80 Hz), asymmetry reversed and responses became right dominant (cluster significant at $p = 0.025$, Figure 3A).

Unlike controls, dyslexic participants did not show left-dominant auditory entrainment to phoneme-level modulation frequencies (Figure 3B). A significant group difference in the left PT in the 25–35 Hz (S)/25–35 Hz (R) range (Figure 3C; cluster significant at $p = 0.049$), and a group-by-hemisphere interaction (cluster significant at $p = 0.02$) confirmed reduced left dominance in this critical window. Note that there was also an interaction at 40 Hz, in this case indicating that the right dominance typically observed in controls at precisely 40 Hz (Ross et al., 2005) was even more pronounced in dyslexics. Dyslexic participants additionally showed enhanced responses at frequencies above 50 Hz relative to controls in both auditory cortices (Figures 3C and 3D; Figure S4). Hence these results do not only denote impaired sensitivity of left auditory cortices to 25–35 Hz sound modulations (within the hypothesized 25–35 Hz frequency window) but also increased bilateral sensitivity to faster modulations in dyslexics relative to controls.

Low-Gamma ASSRs Anomalies Extend to Left Prefrontal and Right Temporal Cortices

To explore whether other brain regions show reduced cortical entrainment specifically in the 25–35 Hz range, we performed a whole-brain analysis at the stimulus frequency where the group-by-hemisphere interaction was statistically strongest (at 30 Hz, Figure S3). This analysis showed that the alteration in

dyslexic individuals was not strictly confined to the auditory cortex (Heschl and immediate PT) but extended to left articulatory and somatosensory cortices and supramarginal cortex (Figure 3E), all of which involved in phonological processing (Hickok and Poeppel, 2007; Jacquemot and Scott, 2006). In addition, dyslexics exhibited enhanced response entrainment in the right PT at 30 Hz, contralateral to the left location where there was an entrainment deficit (Figure 3F).

Left-Dominant Low-Gamma Entrainment Correlates with Phonological Processing

Our next aim was to relate the ASSR asymmetry (left minus right) in the PT within the 25–35 Hz window to behavioral measures. We first checked whether reading fluency (as assessed by reading speed) correlated with ASSRs in the low-gamma band. We found a significant correlation in controls on both sides (Figure 4A, black frames) but no correlation in dyslexics on either side. To explore this global effect in greater depth, we conducted correlation analyses with scores from tests of phonological skills that are presumed to underlie the reading deficit (Table 1; Table S1). A principal component analysis performed on behavioral data revealed two well-known factors, one loading on rapid naming tasks, and the other on phonological awareness (nonword repetition, spoonerisms, and digit span). By hypothesis, each task contributing to the PHONO factor relies on early auditory cortical sampling processes but investigating RAN was also of interest to us because it requires coordination of left temporal and prefrontal cortices (Holland et al., 2011).

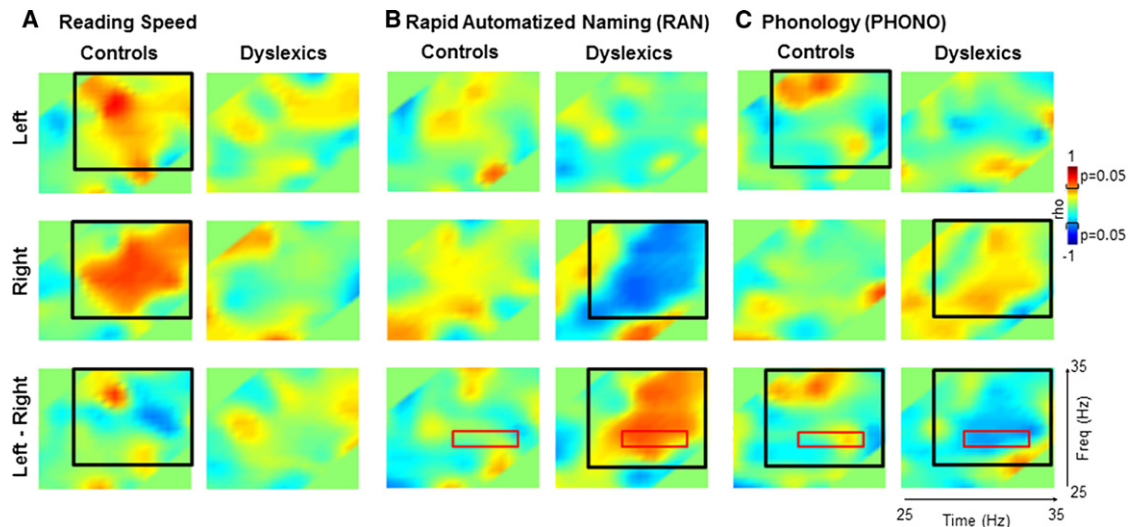


Figure 4. Correlation between Low-Gamma ASSRs and Behavioral Scores

Correlations between behavioral markers of dyslexia (Z-scores) and ASSR magnitude in left (upper panels) and right (middle panels) PT and left-right (asymmetry, lower panels) within the 25–35 Hz range in controls and dyslexics. Black frames indicate ranges with strongest correlations. Red frames indicate range used for correlation in Figure 5.

- (A) Controls show positive correlations between ASSR around 30 Hz and reading speed in PT, bilaterally. No correlation is found in dyslexics.
(B) ASSR asymmetry is positively correlated in dyslexics with scores obtained in the rapid automatized naming task (RAN). A negative correlation is present in the right PT in dyslexics.
(C) ASSR asymmetry is positively correlated in controls and negatively correlated in dyslexics with the phonology composite measure scores (PHONO). Positive correlations are observed in the left PT in controls and in the right PT in dyslexics.

Subsequent analyses were therefore conducted on the average Z-score of rapid naming tasks (RAN, Table 1), and the average Z-score of spoonerisms, nonword repetition and digit span tasks (PHONO, Table 1). We tested for correlations between the ASSR power in the 25–35 Hz window and each of these two composite phonological variables. In controls, we found no significant correlation with RAN on either side (a positive trend in Figure 4B), and a positive correlation with PHONO in the left PT only (Figure 4C). In dyslexics, there was no correlation with RAN and PHONO in the left PT (Figures 4B and 4C, upper panels). Conversely, in the right PT there was a negative correlation with RAN and a positive correlation with PHONO (note that there was also a positive correlation with nonword repetition when

tested on its own). With respect to asymmetry (left-right, Figures 4B and 4C, lower panels), the correlation appeared positive for RAN in dyslexics due to the strong negative correlation in the right PT. The correlation was positive for PHONO in controls and negative in dyslexics.

To understand how individual subjects contributed to these effects, we first plotted the two behavioral variables against one another (Figure 5A). Usually, there is a positive correlation between the phonological scores, i.e., RAN and PHONO (Wolf et al., 2002). Our data overall confirmed this relationship in controls ($C, r = 0.532, p = 0.013$), but not in dyslexics ($r = -0.413, p = 0.070$). Instead, and consistent with Wolf et al. (2002), most dyslexic individuals show both deficits (Figure 5A)

Table 1. Summary of Statistics

Task	Controls Sample Size Z Score	Dyslexics Sample Size Z Score	Difference	Correlation with Asymmetry Controls+ Dyslexics	Correlation with Asymmetry in Controls	Correlation with Asymmetry in Dyslexics	Group x Asymmetry Interaction
Reading fluency	N = 21 0.11 ± 0.21	N = 23 −2.35 ± 0.15	p < 0.001	r = 0.352 p = 0.019	r = 0.010 p = 0.967	r = 0.014 p = 0.951	p = 0.848
PHONO_Z (phonology composite measure)	N = 21 −0.01 ± 0.22	N = 20 −1.19 ± 0.22	p < 0.001	r = 0.034 p = 0.831	r = −0.045 p = 0.847	r = −0.450 p = 0.047	p = 0.306
RAN_Z (Rapid Automatized Naming composite measure)	N = 21 0.06 ± 0.22	N = 23 −1.93 ± 0.40	p < 0.001	r = 0.498 p = 0.001	r = −0.037 p = 0.873	r = 0.552 p = 0.006	p = 0.002

Boldface indicates significant values. See also Table S1.

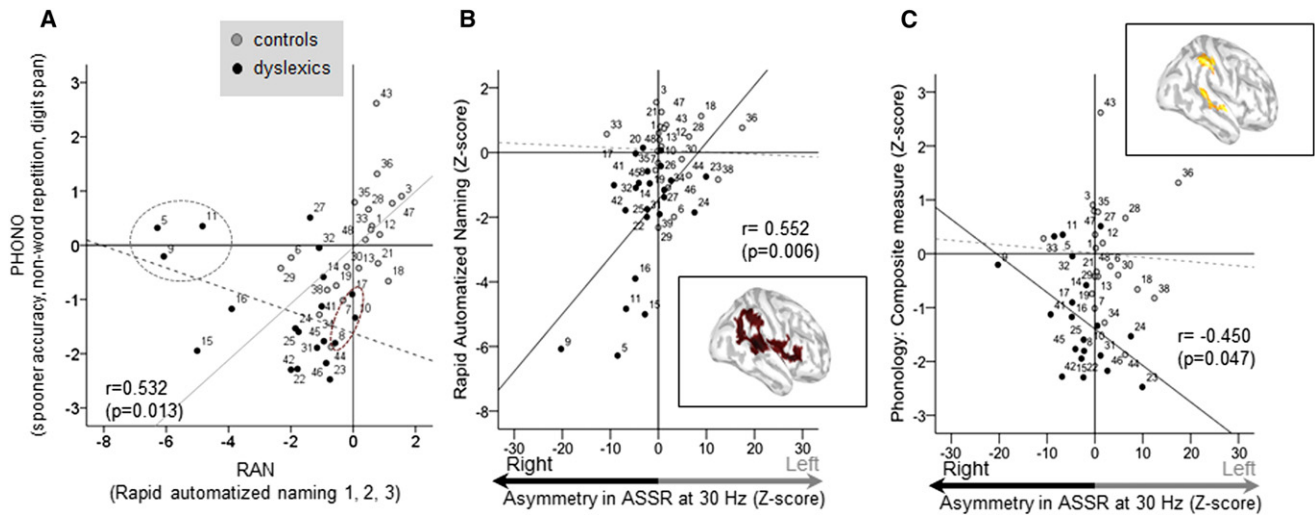


Figure 5. Individual Scores in Phonological Tasks and ASSR Asymmetry at 30 Hz

(A) Subjects distribution in each group along the two behavioral dimensions extracted from the test battery (PHONO and RAN, see Table S1). The gray circle indicates individuals with no phonological deficit but strong RAN impairment. The dark red circle indicates individual with no RAN deficit but strong phonological impairment.

(B and C) Correlations between the asymmetry in cortical entrainment at 30 Hz (positive and negative values indicate left and right dominance, respectively) in the planum temporale and behavioral dyslexia markers (Z-scores) obtained in both population samples. Positive correlation between ASSR asymmetry and RAN in dyslexics (A). This measure admittedly reflects phonological output as the input is nonverbal. There is no correlation in controls. Negative correlation between ASSR asymmetry and the average Z-score of PHONO (spoonerism, nonword repetition and digit span) is significant in dyslexics (B). PHONO spans the phonological input deficit. Surface renderings in (B) and (C) show the correlation between the behavioral measures and ASSR at 30 Hz in the right hemisphere of dyslexics. Colored areas represent p values < 0.05, dark red and yellow for positive and negative correlations, respectively.

See also Figure S4.

but frequently either a PHONO or a RAN deficit subtype (circles). We then computed the correlations between ASSR magnitude asymmetry in the PT at 30 Hz, i.e., where the group effect was statistically strongest, and each phonological variable within and across groups, and the interactions between asymmetry and the group factor on each phonological variable (Table 1). We observed a significant positive correlation between low-gamma asymmetry and the RAN variable (Figure 5B) among dyslexics: the worse scores for rapidly naming visually presented items were observed in those dyslexic participants who had the strongest right-dominant response at 30 Hz. Five dyslexic individuals who had extremely low RAN scores contributed importantly to this effect. Inverted laterality of responses at phonemic rate in dyslexics appeared a strong predictor of a marked naming deficit. Note, however, that there was no correlation in controls (flat slope, no trend) at 30 Hz, reflecting the bilateral trend for a positive correlation seen on Figure 4B.

For the PHONO variable, the correlation was not detected in controls at 30 Hz, but only when taking a larger frequency frame (Figure 4C, upper left panel). This is due to the fact that the strongest group-by-hemisphere interaction was not observed at the exact same frequency where controls showed a positive correlation. In dyslexics, the negative correlation ($r = -0.45$, $p = 0.047$; Figure 5C) confirmed that the best scores were associated with right-dominant responses at 30 Hz. This effect in dyslexics was mostly driven by nonword repetition ($r = 0.44$, $p = 0.04$). To address whether the effect reflected the ability to represent complex new sequences of phonemes or more

broadly phonological working memory, we computed the correlation between ASSR asymmetry at 30 Hz and nonword repetition scores, after partialing out the effect of digit span, i.e., that of our phonological tasks with the strongest working memory component. As the negative correlation was only mildly weakened ($r = -0.41$, $p = 0.07$), we conclude that the deficit at 30 Hz in the left auditory cortex more closely reflects phonological representations than phonological memory.

High-Gamma ASSRs Correlate with Phonological Working Memory

As mentioned earlier, in dyslexics the phonemic sampling rate could be shifted either upward or downward. We speculated that an upward shift could result in phonological/verbal working memory deficits. Our data show that altered asymmetry in the 25–35 Hz window in dyslexics was accompanied by enhanced entrainment of auditory cortices at high frequencies (above 50 Hz), which suggests auditory “oversampling.” We hence tested whether these “abnormal” high-frequency oscillations in dyslexics’ left auditory cortex could account for their poor phonological working memory. We found negative correlations between the ASSR response and the digit span measure in dyslexics across a wide range of frequencies (45–65 Hz) (Figure 6A). We projected onto the whole-brain responses at 58 Hz (the frequency at which the group difference of ASSR response was largest) and found that increased high-frequency responses in dyslexics relative to controls were present not only in the left PT, but also in the left STS and inferior prefrontal cortex

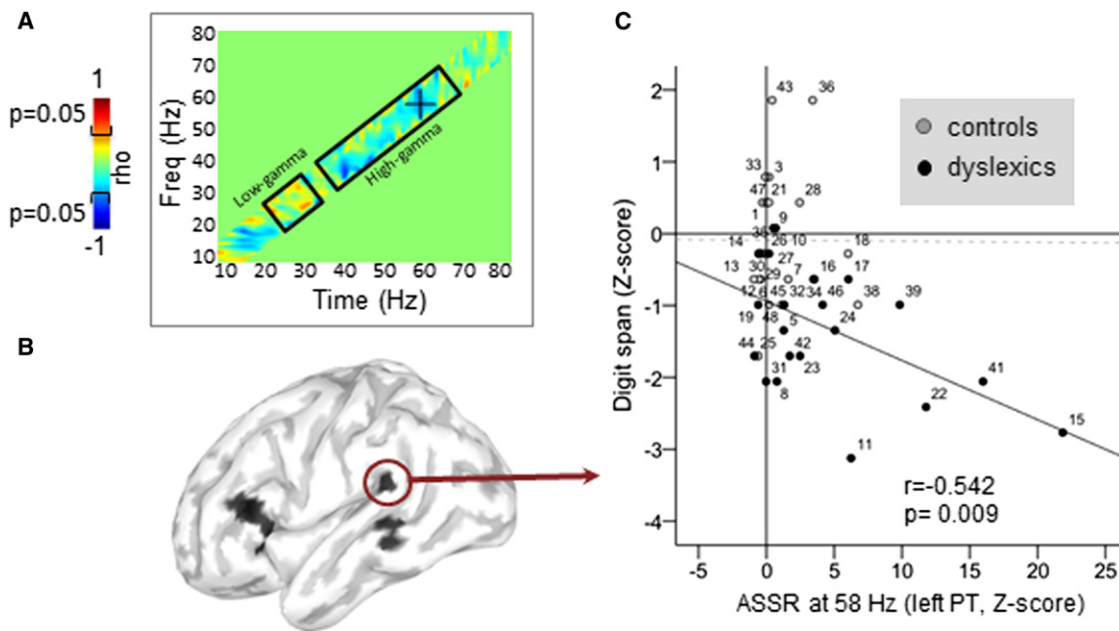


Figure 6. Oversampling and Working Memory Deficit in Dyslexics

(A) Correlation between ASSR magnitude over the whole 10–80 Hz frequency range in dyslexics' left auditory cortices and behavioral scores for the digit span task. The black cross indicates where the difference between groups (ASSR magnitude above 50 Hz) is maximally significant.

(B) Cortical surface rendering of the left ASSR group difference (dyslexics > controls) at 58 Hz (black cross on A). The colored area represents p values <0.025 (one-tailed).

(C) Correlation between ASSR magnitude at 58 Hz in dyslexics' left auditory cortex and the behavioral Z-score for digit span (this measure reflects short-term memory) is significant in dyslexics but not in controls in each of the three colored areas.

(Figure 6B). In the PT, the mean response (spatially averaged) in dyslexics negatively correlated with the verbal working memory measurement (Figure 6C). The absence of correlation in controls reflects very low ASSR values at high frequencies in this group. Finally, high-gamma responses and verbal memory were also negatively correlated in the left prefrontal cortex and the STS ($r = -0.486$, $p = 0.022$ and $r = -0.511$, $p = 0.015$, respectively).

DISCUSSION

We could confirm in controls the predictions of AST; within a restricted 25–35 Hz range of acoustic modulations, auditory cortical entrainment was left dominant, indicating that oscillations in the low-gamma band (Lakatos et al., 2005) are stronger or more selectively amplified in left than in right auditory cortex. In this framework, this denotes a better phonemic sampling ability of the left auditory cortex. Auditory sampling at 30 Hz theoretically yields 33 ms cycles, during which there is a ≈ 16 ms phase of high neuronal excitability and another ≈ 16 ms of low excitability. Such short windows of integration are adequate to capture transient broadband bursts of energy and fast formant transitions that can be as brief as 20 ms (Rosen, 1992). Our findings hence indicate that left auditory cortex acts as a filter that selectively amplifies those acoustic amplitude modulations that carry phonemic information, which we assume enhances phonemic parsing.

We observed maximal ASSR responses both in the PT and the STS, but left dominance in low-gamma responses was less

marked in the STS. This result is consistent with the assumption that phonemic parsing constitutes an early step in speech processing after which neural information is downsampled. The PT and the STS represent two successive steps in speech processing, as the STS receives connections via the PT but not directly from A1 (de la Mothe et al., 2006). In speech processing, the STS combines auditory and visual speech events (Arnal et al., 2009, 2011) within temporal frames of about 200 ms, i.e., in the theta range (Chandrasekaran et al., 2009; van Wassenhove et al., 2008). Because of its higher position in the auditory hierarchy and its long time constants in audiovisual binding, we did not expect the STS to exhibit a strong speech parsing-related left dominance in the low-gamma band.

Unlike controls, dyslexics did not exhibit the hallmarks of lateralized amplification of acoustic modulations in the low-gamma range. Entrainment to 25–35 Hz acoustic modulations was globally reduced in the left auditory cortex, with a maximal deficit at 30 Hz. For phonemic cues, this deficit should translate into an impairment of selective extraction and encoding by the left hemisphere, and thereby be detrimental for the interhemispheric triage of auditory information based on dual-scale temporal integration (Poeppe, 2003). Such a lateralized and focal impairment is not expected to affect global sensitivity to amplitude modulation, as perceptual acoustic processing relies on bilateral auditory cortices. Our findings thus remain compatible with previous studies in dyslexics that showed inconsistent deficits in perceptual amplitude modulation or no effect at all (Lorenzi et al., 2000; Rocheron et al., 2002).

That ASSR properties, which are observed with linguistically meaningless auditory stimuli, are functionally relevant for language processing can already be derived from our observations in controls. Their left dominance of ASSR within the 25–35 Hz window positively correlated with both reading speed and the composite phonological measure (PHONO). This lateralized effect could not be found in dyslexics (Figure 4), supporting our central hypothesis that left dominance in low-gamma oscillatory activity is at the core of phonological abilities, and contributes to reading skills.

Correlations between behavioral measures and left dominance in ASSR at precisely 30 Hz, where the group difference was maximal, revealed opposite effects for the composite phonological measure (PHONO) and the naming measure (RAN) in dyslexics. The correlation was positive for RAN but negative for PHONO. Given that there was no handedness difference between groups, a possible interpretation of this negative correlation is that a subgroup of the dyslexics compensate with the right auditory cortex for deficient phonemic analysis in the left. Indeed, right auditory cortex showed enhanced entrainment to 30 Hz modulations in dyslexics relative to controls and compared with their own left auditory cortex (Figure 3F). The notion that weaker oscillatory entrainment in left PT might be compensated for by greater entrainment in the right is further supported by functional MRI studies in dyslexic subjects that have shown left hypoactivations associated with right contralateral hyper activations (Démonet et al., 2004). That enhanced resonance at 30 Hz in the right PT extended to the right prefrontal cortex is also in line with prior findings showing that activation in the right prefrontal cortex correlates with reading recovery gain (Hoeft et al., 2011).

Compensation by the right hemisphere for a deficit in the left is a common and useful adaptation to a large variety of unilateral language deficits (Kell et al., 2009; Preibisch et al., 2003). However, such an adaptation rarely yields full behavioral compensation (Kell et al., 2009; Preibisch et al., 2003). In the case of dyslexia, it might actually enhance already abnormal lateralization of phonemic parsing and thereby worsen some components of subsequent phonological processing. Accordingly, while enhanced responses in the right auditory cortex seemed to have a positive effect on phonological analysis (positive correlation with PHONO in the right PT, Figure 4C), they did not appear to be beneficial to phonological output processing (negative correlation with RAN, Figure 4B). Note that this negative effect was also significant at 40 Hz in dyslexics; it was the only significant behavioral correlate of the right excess in 40 Hz ASSRs. Our results hence show a double dissociation denoting that defective phonological perception can be compensated for by the right auditory cortex, whereas phonological production (as probed by naming tasks) cannot, presumably because it relies on an extended strongly lateralized network encompassing left-hemispheric inferior prefrontal (BA44/45) and parietal (BA40) cortices (Morillon et al., 2010; Price, 2010). It ensues that those participants who compensate well with the right auditory cortex, e.g., dyslexic subjects 9, 5, 11, appear impaired only on tasks requiring a transfer of phonological material to the left-lateralized speech production system. Conversely, those who are strongly impaired in tasks requiring phonological analysis are not neces-

sarily impaired in phonological output if phonological processing remains globally left-lateralized, e.g., dyslexic subjects 23, 24, 31, 46, etc. As reading relies on phonological input, storage, and output processes, this dissociation could explain why the asymmetry measure does not correlate with reading fluency in the dyslexics group (Figure 4A).

Altogether, our results suggest that a single oscillation entrainment anomaly in the left auditory cortex, the absence of specific resonance in the 25–35 Hz window, may have distinct behavioral effects depending on how it is individually compensated for. These findings are hence consistent with the notion that dyslexics exhibit different profiles of phonological deficit (Wagner and Torgesen, 1987; Wolf et al., 2002). What determines individual trajectories of neural compensation, however, remains unexplained by the current data.

Oscillatory anomalies in dyslexics were observed over a large part of the language network. Such a broad distribution is in line with widespread morphological anomalies as, for instance, ectopias, which have been observed in dyslexia both postmortem and using brain imaging (Démonet et al., 2004; Eckert, 2004; Galaburda et al., 1985). At a mechanistic level, neocortical oscillation anomalies are compatible with the function of the genes that have been incriminated in dyslexia. These genes typically control neuronal migration, axonal guidance, and the spatial organization of cortical layers (Galaburda et al., 1985; Rosen et al., 2007), which may all contribute to the generation of periodic interactions across excitatory and inhibitory cortical neuronal populations (pyramidal cells and interneurons) (Börgers and Kopell, 2005), and across cortical layers (Roopun et al., 2008). Our results also suggest that genetic variants associated with specific oscillatory phenotypes might be good candidates for the susceptibility to dyslexia. While our framework only predicted that early auditory sampling at low-gamma should be altered in dyslexia, we made other observations pointing at anomalies in articulatory motor and somatosensory cortices and indicating that low-gamma oscillatory dysfunction could spread across the speech perception/production loop (Guenther et al., 2006; Ito et al., 2009).

In addition to “deficient” properties compared to controls, dyslexics exhibited a supranormal entrainment of bilateral PT to fast temporal modulations in the 50–70 Hz range, suggesting that their auditory cortices oversample the acoustic flow (Figure 3; Figure S4). We had hypothesized that the abnormal presence of high-frequency auditory oscillations in dyslexics could indirectly affect phonological/verbal memory. While such a deviant physiological property might not interfere with speech perception in the right hemisphere, its presence in the left hemisphere could distort the representation of the speech phonemic structure. This could entail a greater amount of subphonemic perceptual chunks per time unit integrated into theta-based processes that underlie both auditory buffer capacity (Hsieh et al., 2011) and syllabic integration (Ghitza, 2011). Accordingly, left-dominant oversampling in the posterior temporal cortex was associated with poor phonological working memory. Holding auditory information in short-term memory is equivalent to filling a limited capacity buffer with sequential “representations.” One can speculate that the more abstract these representations, the larger the amount of information that can later be retrieved. If the auditory

system oversamples speech, one consequence might be that it propagates excessively detailed spectrotemporal information to more advanced processing stages, at the cost of delayed abstraction; i.e., the time point when the system encodes the stimulus with an atemporal, symbolic type of representation, for instance with sparse or rate codes (Bendor and Wang, 2010; Chang et al., 2010; Panzeri et al., 2010; Roland, 2010).

Finally, high-gamma responses also correlated negatively with verbal memory in the left prefrontal cortex and STS. As during linguistic tasks, both the left inferior prefrontal cortex and the STS do align their oscillatory properties with those of the auditory cortex in the high-gamma band (Arnal et al., 2011; Canolty and Knight, 2010; Morillon et al., 2010), the current observation possibly reflects their cooperation to common functions, such as verbal memory. This specific issue, however, remains to be explored.

Conclusions

Our results indicate a potential neurophysiological mechanism to explain previous MEG and fMRI findings of deviant responses to brief sounds and certain formant transitions in dyslexia (Nagarajan et al., 1999; Temple et al., 2000). They are also broadly consistent with earlier intuitions of disrupted timing of auditory processing in dyslexia, particularly in the range relevant to phonemes (Merzenich et al., 1993; Tallal et al., 1993). Yet, given the contrasting effects that we observed in different frequency ranges, our results are less consistent with the more specific idea of a deficit in “rapid acoustic processing” as previously framed by Tallal (1980). Rather, our results suggest that the left auditory cortex of dyslexic people may be less responsive to modulations at very specific frequencies that are optimal for phonemic analysis (30 Hz), while responding normally or even supranormally to higher frequencies, potentially to the detriment of verbal short-term memory abilities (Ahissar, 2007). These results do not offer direct support for the recent hypothesis of impaired slow auditory sampling in dyslexia (Goswami, 2011) but they are compatible with this idea if we conjecture that a deficit in speech rise time perception reflects a failure to reset gamma activity by a stimulus onset theta burst (Schroeder et al., 2010). Finally, we provide evidence for the intriguing idea that different patterns of cortical reorganization based either on the left or on the right hemisphere may lead to different cognitive profiles in adults with dyslexia. These findings are important because they provide critical clues to genetic studies of dyslexia by narrowing down the phenotype to disorders of local connectivity that are able to increase the rate of oscillatory activity in auditory cortices.

EXPERIMENTAL PROCEDURES

Participants

Forty-four normal-hearing volunteers participated in a MEG study (local ethics committee approval; biomedical protocol C08-39). Twenty-three participants reported a history of reading disability and scored at or below the expected level for ninth graders in a standardized reading test. The remaining 21 participants were normal readers (C) matching dyslexic (D) participants with respect to age, gender, handedness, and nonverbal IQ, but scored above the ninth grade reading level. Demographic and psychometric data, as well as the results of a large battery (Soroli et al., 2010) of literacy and phonological tests are reported in Table S1.

Behavioral Test Battery

The behavioral test battery is fully described in Soroli et al. (2010). Nonverbal intelligence was assessed in all participants using Raven's matrices (Raven et al., 1998). Their receptive vocabulary was assessed with the EVIP test (Dunn et al., 1993). They were included on the basis of performance on the Alouette test (Lefavrais, 1967), a meaningless text that assesses both reading accuracy and speed, yielding a composite measure of reading fluency. Additional literacy tests were conducted using the Phonolec battery (Gatignol et al., 2008) that includes tests of word and pseudoword reading, with both accuracy and time measures. Orthographic skills were assessed using a computerized orthographic choice task, and a spelling-to-dictation test. Phonological tests: we used the WAIS digit span as a measure of verbal working memory (Wechsler, 2000). Verbal short-term memory was tested with a computerized nonword repetition test including 3, 5, and 7 syllables nonwords. Phonological awareness was assessed using computerized spoonerism tasks, where participants heard pairs of words, and had to produce them with the initial phonemes swapped. Finally, rapid automatized naming was assessed using the object and digit sheets from the PhAB (Frederickson et al., 1997) and two custom-made color sheets. The dependent variable is the total time taken to name all items on each sheet, irrespective of errors.

Stimulus, MEG, MRI Recording, and Preprocessing Details

Auditory steady state responses (ASSR) were induced using an amplitude-modulated white noise presented binaurally at 65 dB SPL. The sound modulation rate linearly increased from 10 to 80 Hz in 5.4 s (Poulsen et al., 2007) (Figures 1A and 1B). The sound was surrounded by 0.3 s of unmodulated white noise to prevent onset and offset effects. This 6 s ($5.4 + 2 \times 0.3$ s) stimulus was presented 80 times (silent interstimuli interval (ISI): 2–4 s) during two sessions of 40 trials each. Participants watched a mute wildlife documentary during the experiment to ensure sustained vigilance (Wilson et al., 2007) and were asked to blink during ISI to prevent artifacts during the stimuli. Data were preprocessed and analyzed using in-house software (<http://cogimage.dsi.cnr.fr/logiciels/>). ASSR were recorded using a CTF Systems MEG device, with 151 radial gradiometers over the scalp and 29 reference gradiometers and magnetometers for ambient field correction (1,250 Hz sampling rate; 300 Hz online low pass filter). Trials contaminated with eye movements, blinks, and cardiac or muscular activity were rejected offline (Gratton et al., 1983). Remaining MEG trials were averaged from 0.3 s pre- to 6.3 s poststimulus onset and high-pass filtered at 0.26 Hz. After a baseline adjustment on the 300 ms prestimulus period, the averaged signal was used to compute cortical current maps with BrainStorm (<http://neuroimage.usc.edu/brainstorm>) using the weighted minimum-norm estimation approach. We estimated 15,000 cortically distributed current dipoles, whose locations (but not orientations) were constrained onto the gray matter surface of either the individual brain images when available or the BrainStorm generic brain model built from the standard brain of the Montreal Neurological Institute (MNI colin27). Individual structural MRI could be acquired (Tim-Trio, Siemens; 7 min anatomical T1-weighted magnetization-prepared rapid acquisition gradient echo sequence, 176 slices, field of view = 256, voxel size = $1 \times 1 \times 1$ mm) in 29 participants (14 controls/15 dyslexics: subjects 1–9, 11, 12, 14–18, 20–22, 25–35, and 38; see green frame in Figure S1). Head and cortex meshes were extracted with BrainVISA version 4.0 (<http://brainvisa.info/>). When individual MRI images could be used, source estimates were in a second step projected onto the standard MNI colin27: after realignment and deformation of the subject cortex surface to the Colin cortex surface, the sources amplitudes are interpolated from the subject surface to the Colin surface using Shepard's method (weighted combination of a few nearest neighbors). This was important in order to have the same template for all subjects and enable grand mean average and statistics within and between groups on the whole cortical map. To spatially delineate the auditory response, the time course of all sources in each subject was averaged around the auditory M100, i.e., between 70 and 130 ms following stimulus onset. The grand average of these cortical current maps was used to delimit in each hemisphere 650 contiguous vertices where auditory responses were maximal (Figure 2).

Time-Frequency Analyses

ASSR Localization

Precise ASSR source localization was determined by calculating for each vertex of both 650 vertices regions the correlation between time-frequency

(TF) matrices of the averaged brain activity during the presentation of the modulated noises and the envelope of this modulated sound (5.4 s). TF wavelet transform were applied to the signals using a family of complex Morlet wavelets ($m = 40$), from 10 to 80 Hz (step = 0.5 Hz). The 5.4 s time bins of TF matrices were downsampled in time to obtain a square time-frequency matrix: 141×141 (Figure 1; Figure S1). As ASSR power differs between frequencies (Ross et al., 2000), we applied a Z-score correction to the TF matrices at each frequency bin using the whole corresponding time course response as a baseline. t tests were used to identify the vertices where correlation was significant across all subjects. Four regions of interest of 30 vertices each were selected according to these results. Because of interindividual variability, for each subject and each region of interest, only the five contiguous vertices with highest individual correlation values were used for the following analyses, i.e., ASSR profile by group and hemisphere.

ASSR Profile Analyses. Within each region of interest, a TF wavelet transform was applied to the signal at each vertex ($m = 20$, 10 to 80 Hz, step of 0.5 Hz), and resulting matrices were downsampled in time to obtain a square time-frequency matrix: 141×141 . To enhance the ASSR (centered on the diagonal of the matrix), a Z-score correction was applied to the downsampled TF matrices, using an unbiased baseline that did not contain the ASSR, i.e., taken outside the diagonal. The unbiased baseline included all values except those along the diagonal ± 6 bins, and outside the diagonal those above the mean $+ 2 \times \text{SD}$. Corrected matrices were then averaged over the five contiguous vertices and compared with parametric statistics within and between groups. Unpaired and paired t tests were used to compare at each time and frequency bin the resulting maps between groups and hemispheres. To correct our results for multiple comparisons we used cluster-level statistics (Maris and Oostenveld, 2007) within our hypothesized window of interest 25–35 Hz (sound, S)/25–35 Hz (response, R) probing left-dominant phonemic sampling, and for frequencies above 50 Hz (oversampling hypothesis). Clusters were defined by grouping contiguous bins that exceeded a certain t value (e.g., contiguous positive values below $p = 0.1$). This method is particularly adapted to time-frequency analyses where contiguous bins are correlated to each other (Maris and Oostenveld, 2007). We finally performed TF analyses of whole current maps at frequencies highlighted by the above-mentioned statistics. Unpaired t tests were used to compare the resulting maps between groups at each time bin.

Behavior/ASSR Correlations

Correlations between behavioral and physiological measures (TF values) were computed within each group using Pearson's correlation coefficient. We used a univariate general linear model in which each relevant behavioral measure was entered as a dependant variable and the physiological measure as a covariate, while group, sex, and handedness were modeled as fixed factors. Main effects and interactions were considered significant at $p < 0.05$. All statistical analyses were performed with MATLAB (The Mathworks, Natick, MA) and SPSS (IBM Company, France).

SUPPLEMENTAL INFORMATION

Supplemental Material includes four figures and one table and can be found online at doi:10.1016/j.neuron.2011.11.002.

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Supplemental Figures, Legends, and Table

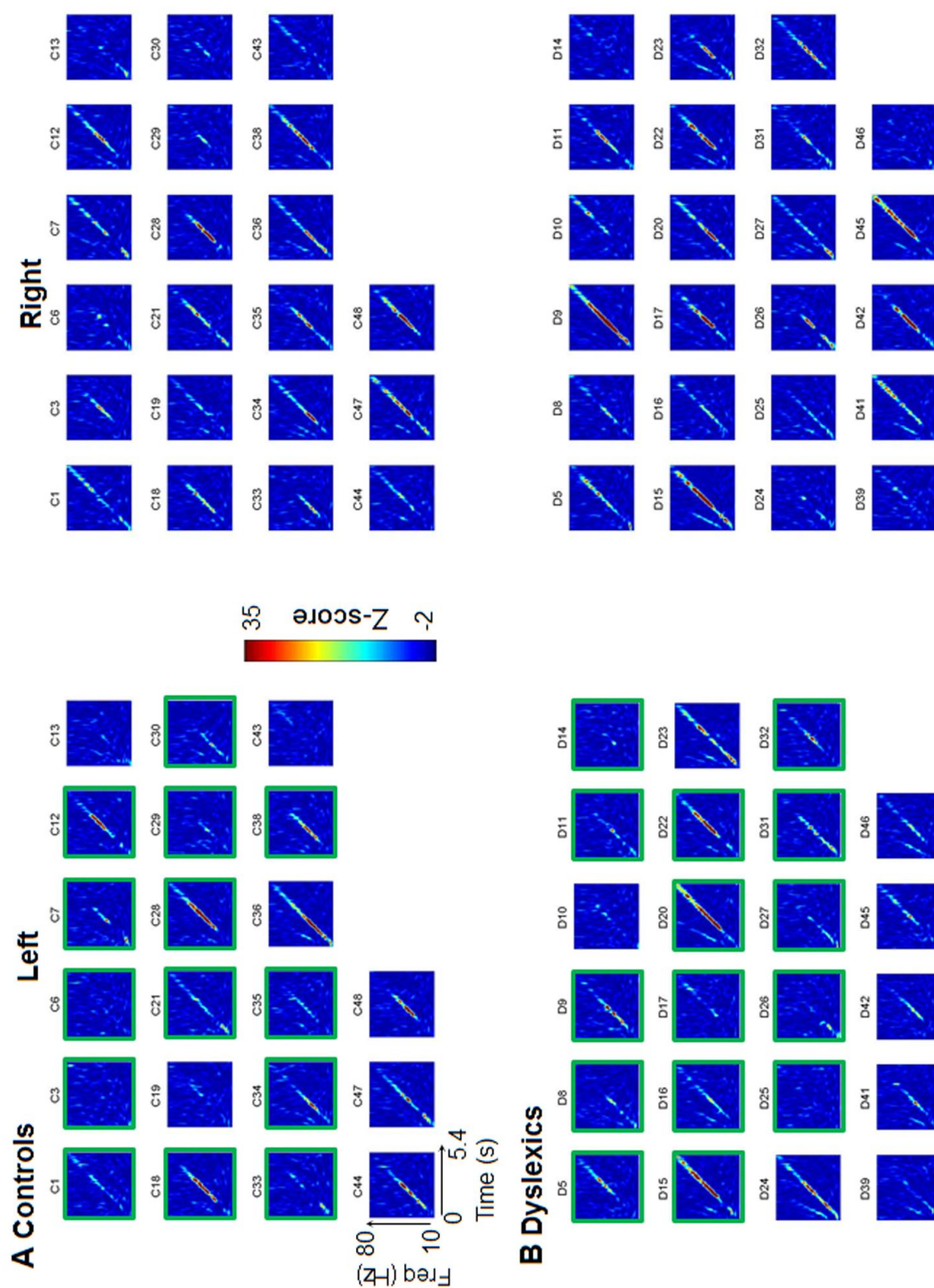


Figure S1, related to Figure 1: Individual raw time-frequency data in A. controls and B. dyslexics in left (left panels) and right (right panels) *planum temporale*. Please

note stronger responses for high frequencies in dyslexics.

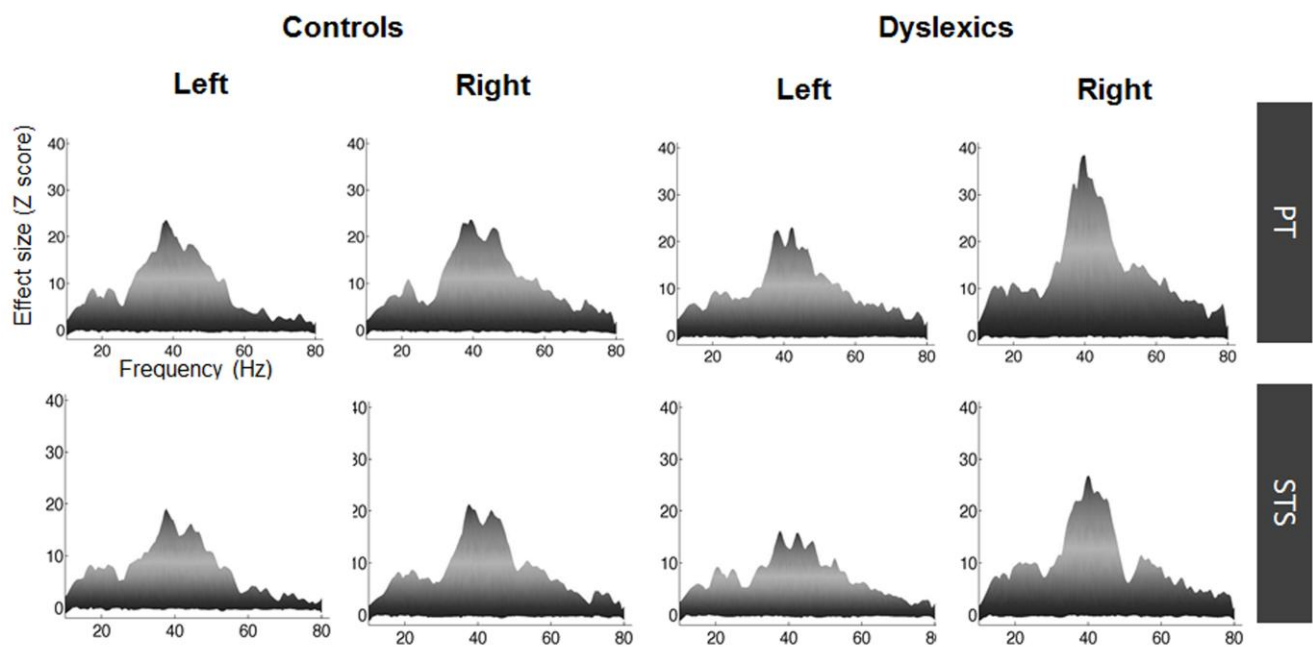


Figure S2, related to Figure 2: Spectrum of ASSR in the 10 to 80 Hz amplitude modulation range in both groups and both auditory cortex locations.

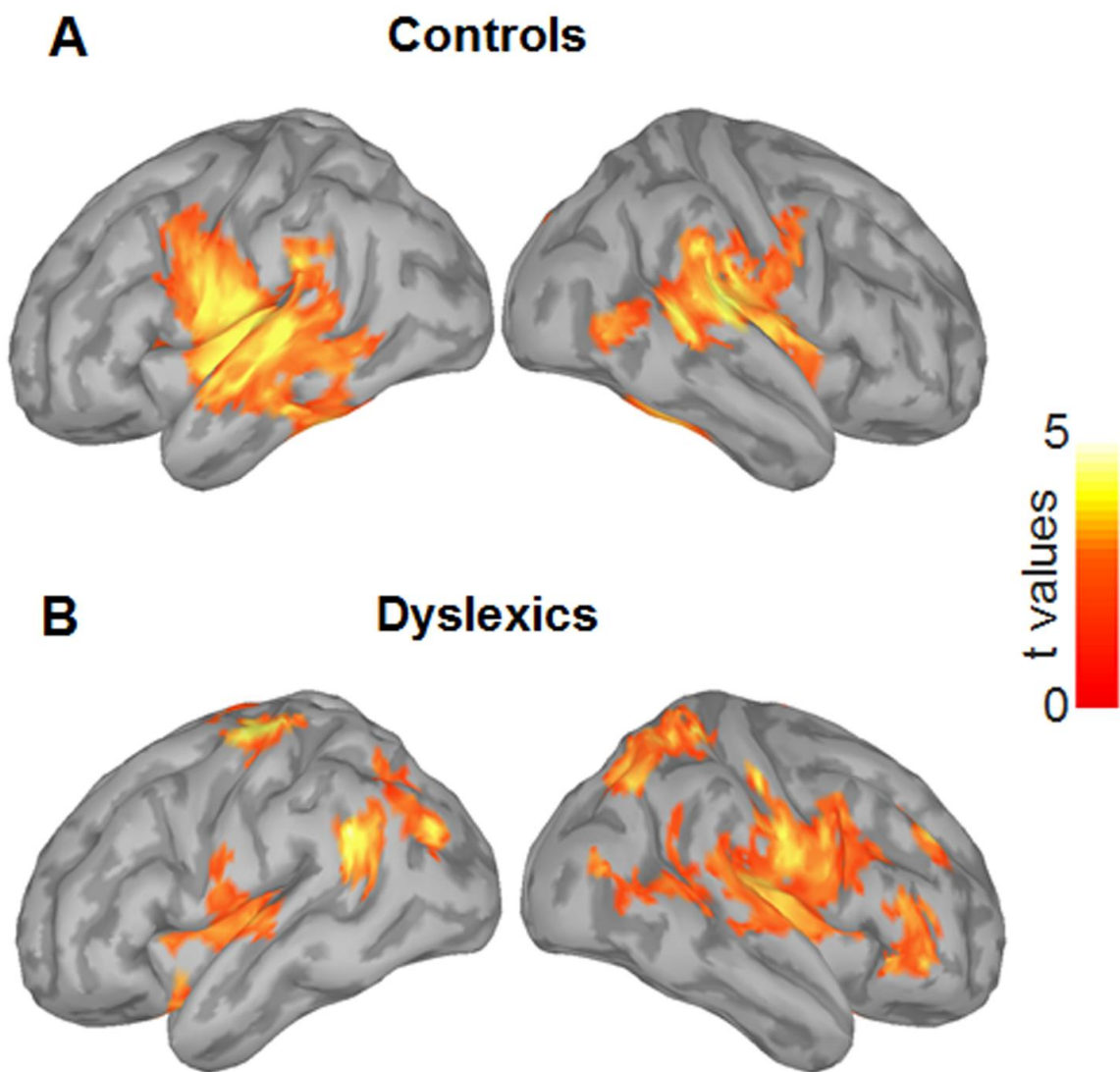


Figure S3, related to Figure 3: Cortical surface rendering of the ASSR at 30 Hz in controls (A) and in dyslexics (B), representation of t values (one tailed, $p < 0.025$, minimum cluster size=40).

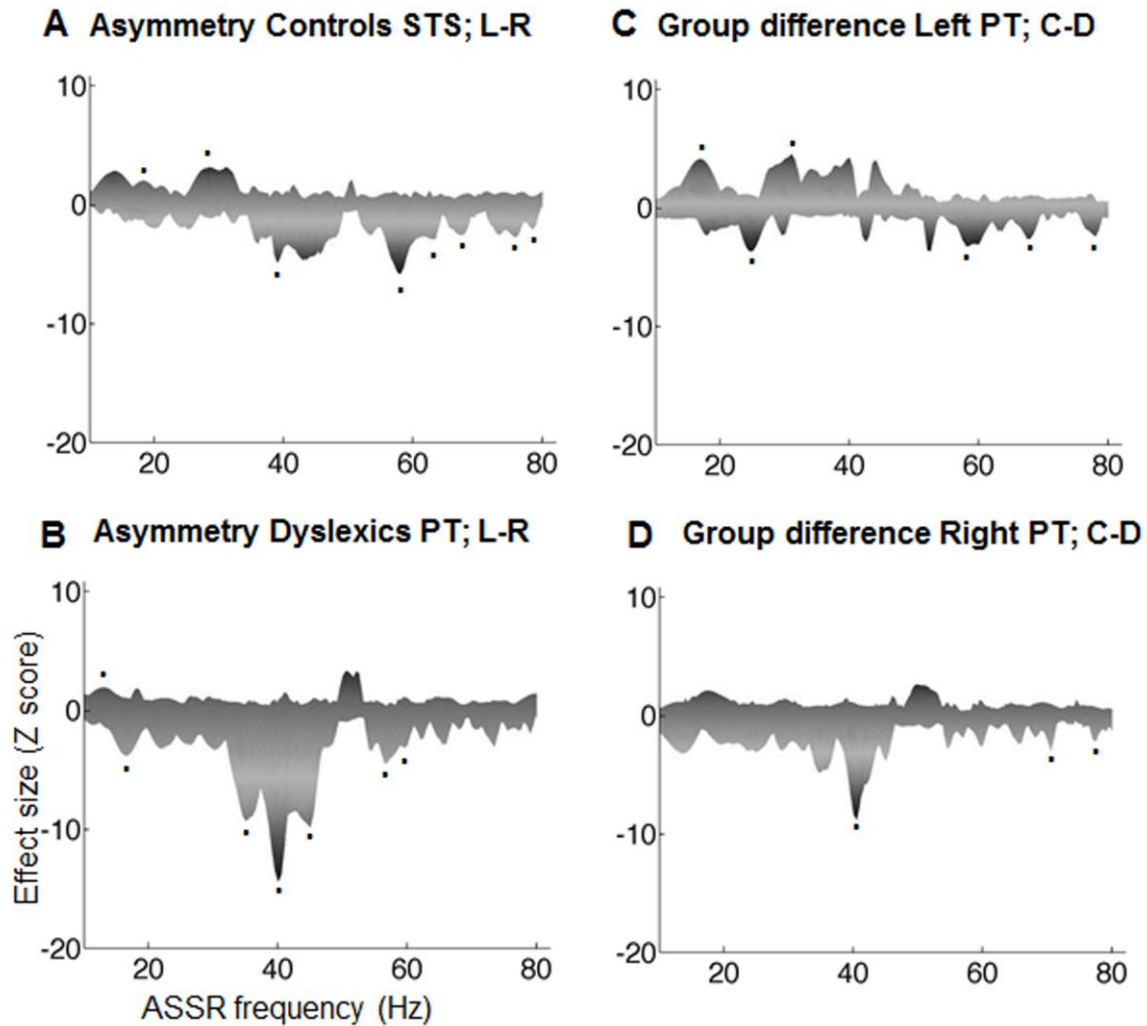


Figure S4, related to Figure 5: Cortical entrainment (ASSR) to 10-80 Hz amplitude modulated noise in the STS: A. ASSRs (left-right) in controls show a left dominance around 30 Hz, and a right dominance to AM frequencies above 55 Hz. B. Left dominance around 30 Hz is absent in dyslexics. C. Controls show significantly stronger 30 Hz entrainment than dyslexics and dyslexics display significantly stronger responses above 40 Hz. D. Dyslexics display stronger responses in the right STS. Points indicate significant local values (two-tailed t-test, $p < 0.05$ uncorrected).

Supplemental Table

Table S1, related to Table 1: Summary of behavioral tests

	Controls (21 subjects)			Dyslexics (23 subjects)		
	n	mean	sd	n	mean	sd
Males	11			14		
Right handed	16			18		
Age	21	24.38	3.85	23	24.61	4.57
Non verbal IQ	21	112.62	12.62	23	109.26	10.45
Reading fluency (nb of correct words / min)	21	194.95	32.38	23	114.09	22.81
RAN of objects (sec) ***	21	61.67	9.04	23	77.06	16.27
RAN of digits (sec) ***	21	30.95	6.17	23	42.80	11.49
RAN of colors (sec) ***	21	54.71	8.98	23	68.59	16.77
Spooner accuracy ***	21	74.14	11.75	20	51.6	26.76
Digit span (%) ***	21	10.52	2.58	22	7.18	2.54
Non word repetition (%) *	21	68.24	8.62	20	60.00	15.73
Spelling (%) ***	21	94.43	4.98	17	79.76	9.57
Orthographic choice accuracy (%)	20	90.75	21.94	22	84.05	20.82
EVIP Vocabulary **	21	123.24	3.43	20	119.55	5.42
Word reading time (sec) ***	21	12.07	1.90	17	16.44	3.57
Word reading accuracy (%)	21	99.76	0.77	14	90.64	26.31

Sec: seconds

RAN: Random Automatized Naming

PHONO: composite measure of phonology

Stars indicated significant differences between controls and dyslexics (unpaired *t*-test, * for $p < 0.05$, ** for $p < 0.01$, *** for $p < 0.001$, uncorrected)