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Review

On sex/gender related similarities and differences in fMRI language research

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ABSTRACT

Again and again, attempts have been made to find correlates of sex/gender differences in the human brain. Despite the insistence with which differences have been stated, empirical results have not been unequivocal: evidence for and against the influence of sex in the makeup of men's and women's brains has been presented. This article focuses on the relevance of sex/gender related differences in fMRI research, especially with regard to language processing. By discussing some crucial criteria from fMRI examinations, we demonstrate the existence of paradigmatic, methodological and statistical defaults that interfere with assessing the presence or absence of sex/gender differences. These criteria are, among others, the use of contrast analyses, the function of the variable sex/gender as a co-item and the “publication bias”. It is argued that dealing with the sex/gender variable will, at least to some degree, inevitably lead to the detection of differences rather than to the detection of similarities.

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1. Preface

Gender studies claim that a clear-cut distinction between a biological sex and a social gender does not exist (Butler, 1990; Fausto-Sterling, 2000). In this view, sex is not a pure bodily and material fact, but is deeply interwoven with social and cultural constructions of gender. In brain research as well, it is becoming increasingly evident that biological components of reported differences in brain structures and functions cannot be separated from social experience. Most neuroscientists nowadays endorse the concept of neuronal plasticity, i.e. that experience drives the development of the brain during childhood and adolescence and, in addition, continues to shape the brain and its networks well into senescence. Neuronal plasticity can help to explain the close interrelation between sex and gender in each individual brain. To highlight this socio-biological intertwinement, when speaking of women's and men's brains, we use the double term *sex/gender* wherever applicable.

2. Introduction

Is the brain “the most important sexual organ” (Dennis, 2004, p. 390)? Not only as a “sex organ” (Boghi et al., 2006, p. 999), but certainly as a *sexed* organ, the brain plays a central role in the debate surrounding the differences and similarities of women and men (Hines, 2004). Indeed, our mental organ is a crucial mediator in sexed/gendered characteristics such as genes (Reisert and Pilgrim, 1991; Arnold, 2004), hormones (Wisniewski, 1998; Hausmann and Güntürkün, 2000; Hulshoff Pol et al., 2006; Korol 2004), sexual orientation (LeVay, 1991; Swaab, 2004; Hulshoff Pol et al., 2006), as well as in cognition (Kimura, 1992; Thomsen et al., 2000; Lüders et al., 2008). From its structure to its function, at the macroscopic and microscopic level, from the single nerve cell to multimodal networks, the brain has been subject to attempted sex/gender differentiations for decades. Nevertheless, the possible differences between women's and men's behavioural faculties (Hyde, 2005) and brains continue to attract ongoing interest, as well as controversy (Vidal, 2005; Cahill, 2006; Cosgrove et al., 2007).

Determining the volume of the female and male brain has been on the agenda for the last 150 years. As early as 1861, Paul Broca reported that women's brains are smaller than men's (Broca, 1861a), and concluded that this difference in volume corresponded to a slight difference in intelligence, favouring men (Vidal, 2005). At that time, only post mortem studies of the brain were possible. Thus, examinations were restricted to the quantification of size or weight of the brain and its single parts.

From the late 1970s onward, research on sex/gender differences in cognitive functions and their relation to brain

structure has considered three variables in particular: *a/symmetries* between the left and right hemisphere in anatomy and function (McGlone, 1978; Voyer, 1996), the size of the *corpus callosum* (Holloway and de Lacoste, 1986; Steinmetz et al., 1995), and the *extent* of defined brain areas (Gur et al., 2002). Although results have never been both conclusive and unchallenged (Bishop and Wahlsten, 1997; Sommer et al., 2004; Schmitz, 2006), the notion of dissimilarities between the sexes/genders, as opposed to similarities, has continued to dominate neuroscientific concepts. What could be the reason for this preconceived bias?

In 1979, Susan Leigh Star pointed out methodological limitations to the dichotomisation of the brain with respect to sex differences (Star, 1979). She did this by illustrating that hemispheric *asymmetry* and *lateralisation* were not solely a factor for sex/gender differentiation, but emerged partially during the empiric process pursuant to measurement techniques. About a decade later, neurobiologist Ruth Bleier and colleagues, using structural MRI, demonstrated that the splenial part of the corpus callosum does not predict sex/gender (Byne et al., 1988); however, other studies employing basically the same technique did show evidence for sex/gender related callosal asymmetry (McGlone, 1980; de Lacoste-Utamsing and Holloway, 1982).

Further, anatomical sex/gender differences have been examined in relation to different sized brains. Results showed that most regional neuroanatomical variations between women and men can be explained by brain size and volume differences (Jäncke et al., 1997; Leonard et al., 2008). With regard to grey matter, too, it was demonstrated that smaller brains have more grey matter, i.e. that size rather than sex/gender is the variable of significance (Lüders et al., 2002; Leonard et al., 2008). However, others demonstrated that women, but not men, with higher cerebral volume have proportionally more gray matter (Gur et al., 1999). In line with this, Lüders et al. (2004) when quantifying the spatial frequency of gyrification and fissuration of the brain surface, found greater gyrification in frontal and parietal regions in women. This increase in cortical complexity was considered to account for behavioural gender differences (Lüders et al., 2004).

In the 1990s, with the advent of functional imaging research and fMRI, the question of differences between the female and male brain continued to be studied with considerable interest. An analysis of the number of fMRI studies reveals that research on differences between women's and men's brains has grown in parallel with the increased number of fMRI publications (Table 1). Numerous experiments on higher cognition as well as on tasks related to defined cognitive skills have been carried out by means of fMRI in men and in women. Results vary; similarities as well as differences have been demonstrated in a great number of cortical and subcortical regions (Table 2).

Table 1 – Total number of fMRI studies and number of fMRI publications on sex/gender during the last 15 years.

Year	fMRI studies total	fMRI studies on sex/gender
1992	4	
1993	11	
1994	40	
1995	120	1 (0.8%)
1996	175	2 (1.1%)
1997	240	0 (0%)
1998	382	7 (1.8%)
1999	532	9 (1.7%)
2000	693	13 (1.9%)
2001	843	21 (2.5%)
2002	950	23 (2.4%)
2003	1228	29 (2.4%)
2004	1495	35 (2.3%)
2005	1931	64 (3.3%)
2006	2177	77 (3.4%)
2007	2554	68 (2.7%)
2008	2714	77 (2.8%)

The total number of fMRI publications and those on the topic of sex/gender per year are both growing continuously, with a manifest augment for fMRI articles on sex/gender from 2004 to 2005. The relation fMRI total vs. fMRI studies on sex/gender shows a increase over the years. Search strategy was conducted by systematic pubmed-search on keywords, titles, and abstracts (keywords: “functional Magnetic Resonance Imaging” or “fMRI” or “functional MRI” and “sex”). Only English publications from international journals were selected.

In this paper, we will focus on the sex/gender variable in the framework of neurocognitive research, and we will concentrate on the issue of the emergence of sex/gender differences as detected with fMRI. Within the field of cognitive processing, we will pinpoint the highly sexed/gendered ability of *language processing*, regarded to be one of the areas of most pronounced sex/gender differentiation.

The process for selecting fMRI based neurocognitive and neuropsychological literature used in this study consisted of a systematic pubmed-search of key words, titles, and abstracts (keywords: “functional Magnetic Resonance Imaging” or “fMRI” or “functional MRI” and “sex”). Only peer-reviewed English-language studies from international journals published between the years 1995 and 2008 (December) were selected (Table 1). For the detailed analysis of sex/gender related differences in language processing detected with fMRI, we only selected (a) language processing articles based on an experimental task considering phonological and/or syntactical and/or semantic processing of words, pseudowords, sentences or narratives, presented by visual or auditory stimuli, (b) studies of healthy women and men, i.e. no clinical articles, and (c) studies that primarily and explicitly focus on the sex/gender variable, on the basis of a clear a priori hypothesis.

3. Sex/gender differences in language processing

Language processing is considered a highly sexed/gendered variable: women are said to learn and speak new languages

more easily than men. In psycholinguistic research, a female advantage in language production and verbal fluency is proposed (Halpern, 1992), while men are stated to be superior in the comprehension of verbal analogy (Hyde and Linn, 1988). In particular, behavioural language research has shown a prevalence of preverbal skills (Rome-Flanders and Cronk, 1995) and spontaneous language (Craig and Washington, 2002; Jackson and Roberts, 2001) among small girls. Correspondingly, for adults, female dominance has been detected in spelling, language ability, and grammatical usage (Kimura, 1999) as well as in verbal memory — for specific lists of unrelated words, digits, or paragraph content (Heaton et al., 1996; Kimura, 1999). Furthermore, sex/gender differences have been reported in phonological processing such as speeded matching and word reading (Majeres, 1999) and in visual influence on heard speech (Irwin et al., 2006). However, no differences were detected in the average number of words spoken per day by men as compared to women: both uttered around 16,000 words daily (Mehl et al., 2007). A recent meta-analysis of language abilities and their anatomical basis in healthy subjects as well as in patients did not find a clear-cut sex/gender effect (Wallentin, 2009).

Language research by means of fMRI was first directed at sex/gender differences in non-clinical populations in 1995 (Shaywitz et al.). From the very beginning, research concentrated on *bi-/lateralisation* as the main criterion of difference. In agreement with clinical studies in aphasics (McGlone, 1977; Kimura, 1983; Hier et al., 1994), women were found predominantly to activate on both sides of the brain, whereas men showed activation in left-hemispheric language regions only. Strikingly, these findings fit the widely held stereotype that at the behavioural level women have “networking” characteristics and men are more “focused” or “analytical”. However, this hypothesis of congruence between brain activation and social abilities has never been subjected to a critical test.

In the field of language-related fMRI studies, there are 19 direct investigations of sex differences based on a clear a priori hypothesis for the period of 1995 until today (March 2009). Direct investigations are defined either by the topic's appearing in the title/abstract or the paper's being structured around this question. Most of these studies that focus primarily on the question of sex/gender differences found differences (Shaywitz et al., 1995; Pugh et al., 1996; Schlösser et al., 1998, Kansaku et al., 2000; Gur et al., 2000; Phillips et al., 2001; Baxter et al., 2003; Kocak et al., 2005; Clements et al., 2006; Chen et al., 2007; Kaiser et al., 2007; Dong et al. 2008). Fewer direct investigations explicitly reported the absence of differences as a main result of the study (Frost et al., 1999; Weiss et al., 2003; Sommer et al., 2004; Plante et al., 2006; Haut and Barch, 2006). Finally, the two most recent direct studies explicitly highlight procedures and methods of differentiating between groups (Harrington and Farias, 2008; Ihnen et al., 2009). Other studies that do not address the sex/gender question as a main factor of research, i.e. indirect studies, observed no differences and reported on these aspects briefly in passing (Pujol et al., 1999; Billingsley et al., 2001; Szaflarski et al., 2002).

fMRI studies report sex/gender related differences in language production (Schlösser et al., 1998; Weiss et al., 2003; Kaiser et al., 2007) as well as in language perception (Pugh et al., 1996; Frost et al., 1999; Kansaku et al., 2000;

Table 2 – Topics of differentiation between women and men in brain research.

Topic	Example (year)	Journal	Similarities, differences and contrasts	Sample size: W vs. M
Cognition:				
Language	Baxter et al. (2003)	Brain Lang.	F: bilateral STG, L IFG M: L IFG, L STG, cingulate regions	19: 10 vs. 9
Spatial skills	Jordan et al. (2002)	Neuropsychologia	F: bilaterally in IPS, SPL, IPL, ITG, PMcd M: R POS, L intrapariet. sulc., L SPL, L mot. cort.	24: 14 vs. 10
Planning	Boghi et al. (2006)	Neuroimage	F: bilateral fronto-pariet.: DLPFC, R pariet. cort. M: bilateral fronto-pariet.: precuneus	18: 9 vs. 9
Memory	Piefke et al. (2005)	Hum Brain Mapp.	F and M: bilateral network: med., lat. temp. regions: hippocamp., parahippocamp. structures, post. cingulate, prefront. cort. M>F: L parahippocamp. F>M: R dorsolat. prefront. cort.	20: 10 vs. 10
Perception:				
Facial	Kranz and Isahi (2006)	Curr Biol.	F and M: bilat. face-selective regions in visual cort., limb. system, and prefront. cort. and mdT, OFC	40: 20 vs. 20
Olfactorial	Royet et al. (2003)	NeuroImage	F: bilat. insula, L piriform-amygdala, L OFC M: bilat. insula, L piriform-amygdala	28: 14 vs. 14
Control (vegetative):				
Satiety	Smeets et al. (2006)	Am J Clin Nutr.	F: R precentr. gyr., R sup. temp. gyr., R putamen M: L ventr. striatum, R/L insula, R orbitofrontal and med. orbitofront. cort.	24: 12 vs. 12
Emotions:				
Processing	Hofer et al. (2007)	Psychol Med.	F: L sensorimot. cort., L ang. gyr., L precuneus/post. cingul. M: L sensorimot. cort., R cerebel., L ang. gyr., L parahippocamp. gyrus/hippocamp., retrosplenial, L ling. gyr./cerebel., L mid. front. gyr.	38: 19 vs. 19
Diverse:				
Humor	Azim et al. (2005)	Proc Natl Acad Sci U S A.	M: L STG, L MTG, L IFG, L ITG, L FG F: L FG, L ITG, R Nacc, L lenticular nucleus, L IFG, L MFG and DLPFC, L STG and MTG	20: 10 vs. 10

In the last 5 years, several cognitive and cognition-related tasks have been carried out with respect to the women vs. men dichotomy, demonstrating similarities as well as differences. Examples were chosen from leading experts working on the subject. Not included were fMRI studies on clinical research (for instance Goldstein et al., 2005; Walder et al., 2007), metastudies (for instance Sommer et al. 2004), and studies on sexuality (for instance Hamann et al., 2004) or sexual orientation (for instance Ponseti et al., 2006), all of which also consider the sex/gender question. Abbreviations: F — female, M — male, R — right, L — Left, STG — superior temporal gyrus, MTG — middle temporal gyrus, ITG — inferior temporal gyrus, IFG — inferior frontal gyrus, IPS — interparietal sulcus, SPL — superior parietal lobe, IPL — inferior parietal lobe, PMcd — dorsal premotor cortex, POS — parieto-occipital sulcus, DLPFC — dorsolateral prefrontal cortex, OFC — orbitofrontal cortex, FG — fusiform gyrus, Nacc — nucleus accumbens.

Phillips et al., 2001; Baxter et al., 2003). This is the case for the classical language regions: Broca's area (Broca, 1861b) and Wernicke's area (Wernicke, 1874) where, cytoarchitectonically, Broca's area is defined as Brodmann area (BA) 44 and 45, whereas Wernicke's area is specified as the posterior part of BA 22. The number of brain areas described as being involved in language processing has increased on the basis of fMRI imaging data. For instance, activation in the context of the sex/gender variable was found in the angular gyrus, in prefrontal, thalamocapsular, retrosplenial, and cerebellar regions (Frost et al., 1999), and in the (pre-)cuneus and cingulate areas (Clements et al., 2006). In addition, bi/lateralisation effects due to sex/gender in other than classical language areas were shown in fusiform regions (Chen et al., 2007, and as a follow-up study also Dong et al., 2008).

Language related regional brain activation varies considerably with the nature of the language task. However, for our argument, the question of task specificity is only addressed

marginally (Section 4.5). We are mainly interested in exploring how the variable of sex/gender is dealt with in fMRI paradigms. We aim to reveal that there are some scientific determinants that interfere during the process of exploring for similarities and differences. For a detailed analysis of the tasks tested in fMRI language research, see Clements et al. (2006), Sommer et al. (2004) or Kaiser et al. (2007).

In fMRI, a large variety of data processing procedures are employed. Differences can be described illustratively by demonstrating both the female and the male group activation separately, followed by calculating sex/hemisphere interactions based on ROI-analysis, as was the procedure in most early studies (Shaywitz et al., 1995; Pugh et al., 1996). Statistics have been executed by t-test comparisons based on the number of activated pixels and voxels respectively, thus focusing on the volume rather than on the strength of activation, which would require detailed analyses of the time resolved BOLD-curve (e.g. Marcar et al., 2004; Haller

et al., 2007; Ihnen et al., 2009; Haller and Bartsch, in press). When focusing on the spatial distribution of language-associated activation in women and men, lateralisation indices (LI) are often determined: these give a quantitative estimate for interhemispheric asymmetries and are calculated according to the formula $LI = (L - R) / (L + R)$; where L is the amount of activated voxels within the left hemisphere and R is the amount of activated voxels within the right hemisphere (van der Kallen et al., 1998; Phillips et al., 2001). Positive results thus show left-sided lateralisation, whereas negative results demonstrate right-sided asymmetry. Furthermore and as shown below, in recent years, contrast effects have been used for direct comparison of female and male brain activation (Baxter et al., 2003; Chen et al., 2007). Alternatively, individual frequencies of lateralisation in the total sample of subjects can be calculated (Kaiser et al., 2007) or threshold independent peak percentage activation (Phillips et al., 2001) can be determined to analyse sex/gender distinctions.

Experiments on language processing, especially those concerned with lateralisation effects, generally take handedness into account, as approximately 95% of right-handers and 60–70% of left-handers have a left lateralised dominance for language (Geschwind, 1970; Hughdahl and Davidson, 2002). Often, fMRI studies examining the direction of brain asymmetries (right or left) focus on variables, sex/gender and handedness (van der Kallen et al., 1998; Narr et al., 2007). To avoid biases within the frame of sex/gender related fMRI language experiments, handedness is usually controlled, for instance by the Edinburgh Handedness Test (Oldfield, 1971). Thus, if differences between women and men are found, handedness can be excluded as an interfering factor.

4. Aims in the detection of difference: a critical overview

In the following, we will investigate the process of differentiation itself and the perceived relevance of differences between the sexes/genders with special focus on language processing in fMRI research. By illustrating that sex/gender differences are connected to the body of knowledge of fMRI research, this article will critically describe and provide an overview of some of the paradigmatic, methodological and statistical criteria that come into play during the process of examining the sex/gender variable in fMRI research. We will argue that the differentiation of men from women is enforced by experimental settings, including the way results are reported in publications, and we will hypothesise that differences rather than similarities may tend to emerge in the process of comparing women and men. Most recently, others, too, have examined similar issues highlighting the impact of methodological approaches on the outcome of sex/gender effects in fMRI language studies (Harrington and Farias, 2008) and criticising the unreflective generalisation of the results (Ihnen et al., 2009).

4.1. Differences in performance vs. differences in the brain

The lack of direct control for task performance is a well known problem in language experiments using fMRI (Schlösser et al.,

1998). In neurocognition, fMRI studies are of particular interest due to their potential to visualise the interrelation between performative and neurobiological data. Therefore, most fMRI experiments consist of both the measurement of brain activation and the acquisition of empiric material in task performance. Given this precondition – and only when it is in place – can correlations be made between cognition and neuroanatomy. Whether cognitive processes can ultimately be inferred from neuroimaging data is still under debate (Poldrack and Wagner, 2004; Poldrack, 2006).

Concerning sex/gender related investigations in general, studies may also be driven by the impetus to answer the question of whether *neuroanatomical differences* between women and men determine or, alternatively, result from *differences in performance*. For language processing, the question of whether sex determines neurofunctional predictors is explicitly addressed in the fMRI study by Chen et al. (2007). Can neuroanatomical differences predict differences in performance, or can performative and behavioural differences, such as gendered learning and socialisation, give rise to neuroanatomical variety? Even though such polarised questions do not contribute to the aim of converging human behaviour and brain function (Nichols and Newsome, 1999), they nevertheless depict two general antagonistic views within the broad and interdisciplinary field of neuroscience.

The interaction between performance and neuroanatomical structure is also relevant in language processing. Some fMRI studies do not report behavioural performance data at all (Vikingstad et al., 2000), preventing the determination of whether sex/gender related results were attributable to performance issues or to functional neuroanatomy or to both. In the long period of psycholinguistic research before the advent of brain imaging methods, sex/gender related differences based on performance in language processing were established (Hyde and Linn, 1988; Halpern, 1992; Kimura, 1999). However, sex/gender differences in performance, such as in measurements of reaction time or accuracy with linguistic items, were absent in subjects enrolled in fMRI language processing studies carried out later (Shaywitz et al., 1995; Pugh et al., 1996; Kansaku et al., 2000; Baxter et al., 2003; Clements et al., 2006; Chen et al., 2007). Instead, in these studies, differences were demonstrated in neuroanatomical activation patterns. The question then arises: why were sex/gender differences detected in performance as long as they could not be tested through neuroimaging methods, only to vanish, later on, in fMRI research at the level of behaviour?

4.2. Contrasting women and men

A comparison between women and men in fMRI experiments – in language processing as well as in the study of other cognitive skills – requires an approximately equal number of subjects in each sex/gender group. In second-level fMRI analysis, group-averaged brain activation for the main effect task vs. baseline can be processed separately with two different statistical tests, one for each sex/gender (women vs. baseline and men vs. baseline). Resulting images are often shown descriptively to illustrate the areas of activation. At this point of advanced statistical computing, it is not yet known whether activations

within the sexes/genders are *significantly* different from each other. In the case of separate analysis, a common mistake in interpretation is often made when, for example, a region *x* shows activation in women but not in men. At this stage it cannot be concluded that region *x* is activated to a significantly larger degree in women than in men.

Only by comparing women and men directly with one another within one statistical test can significance be ensured. In the setting of fMRI, this is usually embedded into the framework of a general linear model (GLM) analysis (Friston et al., 1995). This analysis is performed by means of *contrasting*, i.e. by calculating which one of two groups shows significantly more activation than the other. Significant differences are therefore obtained through *F>M* contrasts, i.e. patterns in which women activate more than men, or, respectively, through *M>F* contrasts, i.e. patterns in which men activate more than women. Numerous fMRI language studies claiming to demonstrate differences between women and men have not carried out a contrast analysis. Instead, they show separate images for each sex/gender (Shaywitz et al., 1995; Schlösser et al., 1998; Kansaku et al., 2000; Phillips et al., 2001). This is of serious concern because, independently of the performed statistical analysis, fMRI images have their own expressive impact. Based on their illustrative power, dissimilar images quickly lead to the assumption of differences. For this reason, contrast images should become a central tool of analysis when aiming to elucidate the neuroanatomical basis of the variable sex/gender. This has been the case in more recent studies (Chen et al., 2007; Kaiser et al., 2007; Dong et al., 2008).

4.3. Thresholds and the detection of bi-/lateralisation: an example

Many fMRI language studies operate with uncorrected *p*-levels for second-level group comparisons (Piefke et al., 2005; Clements et al., 2006; Chen et al., 2007), whilst others apply corrected values (Haller et al., 2005, 2007). With respect to sex/gender analysis in language processing, the employed statistical threshold can affect the detection of *bilateralisation* and *lateralisation*, respectively. The chosen statistical threshold can modify lateralisation patterns when comparing the number of active voxels between both hemispheres (Bosch, 2000). For example in their study on auditory language perception, Phillips et al. (2001) detected gender-dependent hemispheric asymmetries and discussed the systematic influence of thresholds on bi- and lateralisation patterns. In other words, voxel-count based lateralisation patterns are not unequivocal, which implies the need for a direct statistical analysis of hemispheric weighting (Bosch, 2000). Another concern in the estimation of lateralisation indices is related to the cerebral anatomy. Most interhemispheric comparisons make the immanent assumption that both hemispheres are mirror symmetric. This is however not necessarily the case. For example, it was demonstrated that the cerebral cortex is thicker in left-hemispheric language areas (Lüders et al., 2006). This means that left-hemispheric language areas will evoke a higher number of active voxels compared to the right hemisphere simply because of an anatomical asymmetry. Consequently, the appropriate choice of corresponding ROIs in both hemispheres is far from trivial, yet it is certain that the use of

perfect homotopic areas for interhemispheric comparison is not adequate for language areas.

In the next paragraph, we address a further peculiarity of the interaction between statistical thresholds and bi-/lateralisation. Empirical data from our own studies were acquired during an fMRI language production task of fluent narration, in which covert language production was contrasted with an auditory attention task. The female to male ratio was 22:22 (for further details see Kaiser et al., 2007).

Figs. 1A and C demonstrates a left lateralised activation in men as well as in women in Broca's area at a significance threshold of $p < 0.05$ (Bonf. corrected). After adjusting the significance threshold to $p < 0.001$ (Bonf. uncorrected) to search for additional activation (Gaab et al., 2003), not only was the expected increase in the size of activated brain regions obtained, but a different pattern emerged, i.e. a difference in lateralisation. At this lower threshold, bilateral activation was revealed in men (B) but not in women (D). This sex/gender difference persisted in the contrast analysis (Kaiser et al., 2007, not shown here). At present, tools are lacking which would allow determination of whether the "reversed sex/gender pattern" – i.e. a bilateral pattern in men and a left lateralised one in women – found here under a specific mode of analysis, has any neurofunctional foundation. Which one of the patterns best describes the neurofunctional situation in the population investigated is completely open for speculation.

4.4. The sex/gender factor as co-or main variable

When categorising by "hard" variables, the dichotomy women/men serves as a natural default. Compared to sample data gathered through complex selection criteria – i.e. *investigating quadrilingual subjects* (Briellmann et al., 2004) – or groups that are classified in highly elaborate categories via biographical examination – e.g. *subjects who had acquired 2 languages before the age of 5 years vs. subjects who had acquired a second language after the age of 7 years* (Mahendra et al., 2003), male/female classifications are seemingly effortless and obvious in brain research.

Against this background, the importance of (co-)measuring sex/gender as an additional variable becomes evident: sex/gender differences are often co-examined, even if other variables are the primary topic of the research. With regard to studies comparing controls with pathological groups, introducing sex/gender as a supplementary factor augments the possibilities for differentiating the groups from each other. In these cases, reported sex/gender differences can be regarded as by-products (Kaiser et al., 2007; Sommer et al., 2008). Leaving this potential source of significant differentiation unconsidered could eventually mean missing out on a proper opportunity to publish.

Furthermore, the manner in which co-examined sex/gender differences are reported within a study also matters. As an example, the primary aim of the *post mortem* study by Harasty et al. (1999) was to determine the topography and degree of atrophy in language-associated cortical areas in patients with Alzheimer's. Concerning the sex/gender variable, the group of patients showed a difference between women and men in the anterior superior temporal gyrus only, i.e. in one out of the nine language-associated areas examined (which were

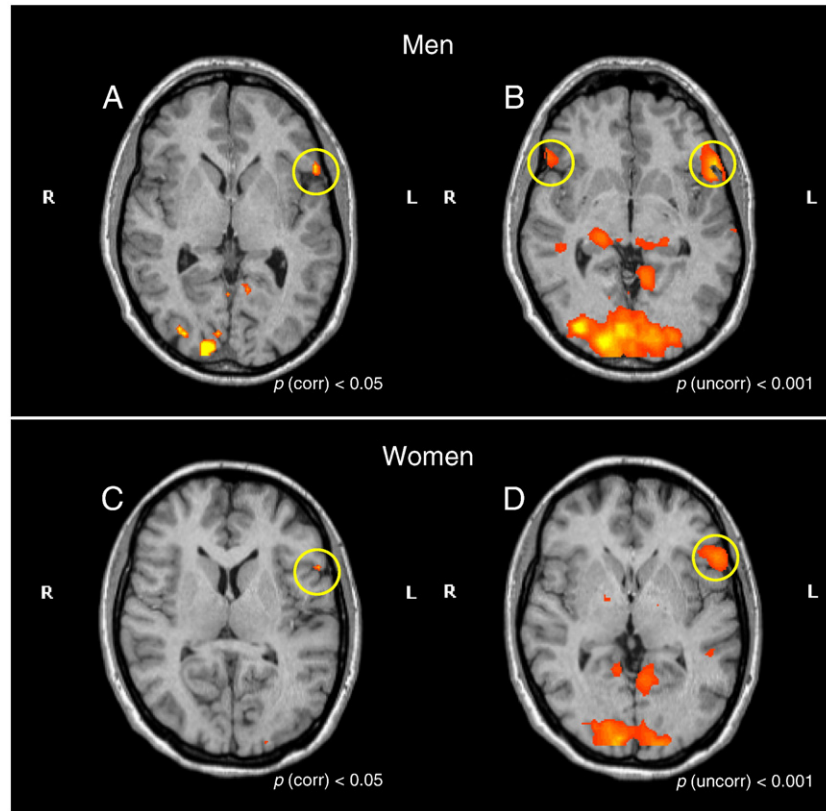


Fig. 1 – Regional cerebral activation in Broca's area (encircled) induced by free narration during a language fMRI task. Random effect analysis at $p(\text{corr}) < 0.05$ and $p(\text{uncorr}) < 0.001$ in both the group of men (top) and women (bottom). Corrected p -values are shown left (A, C) and uncorrected p -values right (B, D). Talairach coordinates: men left: $x = -52, y = 20, z = 3$; men right: $x = -52, y = 22, z = -2$; women left: $x = -55, y = 16, z = 9$; women right: $x = -52, y = 20, z = 2$. Activation at $p(\text{uncorr}) < 0.001$ was found in women in BA 44 while in men activation was more frontal in BA 45. Abbreviations: R — right side, L — left side. Right pictures, top and bottom: from Kaiser et al., *International Journal of Psychophysiology*, 2007 (not coloured).

Broca's area, the inferior, the middle and the anterior superior temporal gyrus, Heschl's gyrus, the planum temporale, the inferior temporal-parieto-occipital junction, as well as the angular gyrus and the supramarginal gyrus). In the anterior superior temporal gyrus, women showed a greater atrophy than men. No differences were found in any of the other regions. However, this minimal dissimilarity is granted space in the abstract of the paper. In this way, the sex/gender variable changes its position from a marginal point within the research setting to a prominent place within the published paper. This leads to an increase in perceived relevance, as the content of the abstract becomes more likely to be included in the cited literature. A single and specific dissimilarity, abstracted and indexed, could henceforth be found in databases as sex/gender difference. An analogous bias can be found in fMRI studies as e.g. in Shaywitz et al.'s (1995) language study (Schmitz, 2006). Although female's bilateral activation was detected only in phonological processing within a battery of tasks measuring brain activity in orthographic, phonological and semantic aspects, the study's title outlines this sex/gender difference as evidence for the sex/gender related organisation of the brain for language. Similarly, Shaywitz et al. (1995) are cited in discussions of this evidence (Gur et al., 2000; Baxter et al., 2003), without reference being made to the phonological result

as only one out of three different measured language criteria, of which the other two under examination do not demonstrate significant sex/gender differences. Going a step further, the institutionalisation of search items like "sex/gender differences" makes it difficult to direct a database search on sex/gender similarities, even if findings demonstrate similarities rather than differences (Jacklin, 1981).

4.5. Task specificity and performance level

In fMRI language research, the sex/gender variable is closely related to the nature of the task: individual language tasks may produce different results with respect to female and male regional activation patterns (Frost et al., 1999; Binder et al., 2000; Phillips et al., 2001). Within the large variety in the operationalisation of language processing in fMRI – such as matching for phonological, orthographic or semantic pairs (Shaywitz et al., 1995; Pugh et al., 1996), classifying words within semantic deduction (Frost et al., 1999), listening to narratives or stories (Kansaku et al., 2000; Phillips et al., 2001), deciding on a semantic category (Baxter et al., 2003), generating words (Weiss et al., 2003), judging nonsense word rhymes (Clements et al., 2006), and learning an artificial language (Chen et al., 2007) – different outcomes are not surprising. As

reported in behavioural studies, there is a general female advantage in language production and verbal fluency (Halpern, 1992) and a general male dominance in tasks of verbal analogy (Hyde and Linn, 1988). Thus, the female dominance in language production may have influenced tasks such as generating words (Weiss et al., 2003), while male advantage in analogy may have interfered with deciding on a semantic category (Baxter et al., 2003). Therefore, it seems necessary to develop fMRI paradigms that specifically test for task dependent sexual differences (Phillips et al., 2001).

Controlling the performance level generally causes a challenge to fMRI that comes into effect for the sex/gender variable, too (Jordan et al., 2002; Weiss et al., 2003). If subjects are not previously matched by the level of performance, a possible bias may emerge when sex/gender is examined. The systematic bias consists of a performance level-dependent regional activation, erroneously thought to be the result of the experimental task. In an exemplary fashion for fMRI research, Unterrainer et al. (2005), in their work on planning strategies, underlined that it was predominantly the subject's performance level rather than his or her sex/gender that influenced regional activation patterns during higher cognition tasks. In this context, problem-solving strategies also have to be studied. Having controlled for overall performance, Jordan et al. (2002) demonstrated that differences in sex/gender dependent strategies can cause different patterns in regional brain activation. In sum, the relation between performance, strategies, and regional brain activation needs to be the topic of future research.

5. Discussion

Brain research data showing sex/gender differences are published more often than data in support of no difference. This is not unique to the sex/gender issue. There seems to be a positive correlation between a paper's demonstration of significant differences and its success in being published. This so-called "publication bias" (Dickersin and Min, 1993; Bishop and Wahlsten, 1997; Gilbody et al., 2000) also influences the notion of sex/gender related neurofunctional differences in language processing: Binder et al. (2000) explicitly stated that there is a publication bias against studies that reveal a null hypothesis and emphasised the possibility that many studies demonstrating an absence of sex/gender effects in language processing may never have been given the chance to be printed in indexed journals. Consequently, this unknown but possibly not negligible volume of unpublished "results" demonstrating sex/gender similarities ought to be taken into account (Knight, 2003).

The number of published fMRI studies reveals that the attention paid in research to differences between women's and men's brains has increased. Considering the fact that 6–7 fMRI studies are published per day (Bandettini, 2007) and many of them are methodological papers, the percentage of 3.4 devoted to sex/gender brain difference in the year 2006 (Table 1) is considerable. Seventy four articles in 2006 amounts to one paper every five days alluding to this topic Table 1 shows that the peak has been reached in 2006.

One principal intention of this article has been to demonstrate that sex/gender differences in the brain cannot merely

be regarded as fact. Rather, they should be seen as a variable of examination in a knowledge production setting, where statements of differences are, due to historical scientific paradigms, received as more relevant than those of similarities. Paradigmatic, methodological, statistical as well as publishing or reception issues are deeply interwoven when, during the fMRI-examination process, men's brains are determined to be different from women's.

So far, concerning sex/gender differences in fMRI language research, the following implications can be made. First, the relation between performance and brain activation needs special attention. We stressed that there may be an experimental predisposition in fMRI language research to find differences in the brain that cannot be detected at a performance level. Second, statistical sex/gender comparisons and illustrations of brain activation can be deceptive: only contrasts analyses allow revealing differences; moreover, brain images have the power to project dissimilarities where there are none. Third, thresholds may influence the representation of asymmetries in language areas. Beyond the fact that the measured asymmetry increases systematically as the threshold increases (Phillips et al., 2001), there may be bilateral patterns that appear after adjusting the chosen significance level — a meaningful emergence for the sex/gender question. Fourth, even if the sex/gender variable is a co-item of examination, it tends to be granted a high degree of perceived relevance in the process of publication. A final consideration concerns task specificity. Potential advantages in verbal tasks for women and men, respectively, make it all the more necessary for fMRI paradigms to be adapted to sexed/gendered dominances. All these factors emphasise the need for a rigorous examination of methods and biases during the examination and interpretation of sex/gender differences in fMRI studies. Still, when talking about sex differences in language lateralisation, the question should not only be whether results have been interpreted in a correct or valid way, but also whether experimental settings based on preconceived determinants have influenced the outcome of the study.

6. Conclusions

In the spirit of looking forward, the concluding remarks are dedicated to the topic of neuronal plasticity. They expand the discussion from methodological aspects to underlying theories of brain-behaviour relations. In fact, neuronal plasticity is a crucial factor in elucidating the question of sex/gender differences in the brain.

If differences between women and men are found in neurocognitive fMRI research, for instance in language processing, it still does not give any indication of whether they are the origin or the result of sex/gender behaviour and experience (Schmitz, 2006; Leonard et al., 2008) nor if they are an immutable, hard-wired condition (Jordan et al., 2002). We alluded to this point specifically when discussing differences in performance vs. differences in the brain (see 4.1). In this regard, the aspect of experience with its profound effect on regional brain activation should be integrated into the fMRI experimental setting. The concept of neuronal plasticity describes the experience-driven modification of neuronal networks. For

functional systems, this has been shown in musicians (Jäncke et al., 1997; Schlaug et al., 1995), jugglers (Draganski et al., 2004) or taxi drivers (Maguire et al., 2000). Neuronal plasticity is defined as an increase in neuronal response strength, as an augmentation in synaptic density, or as an expansion of representation across cortical areas (Jäncke et al., 2001). Based on these assumptions (Jäncke et al., 2001; Münte et al., 2002; Draganski et al., 2004), sex/gender differences, especially with respect to higher cognition, appear as not fixed and immutable in the cerebral organisation but rather open to any kind of experience during life.

Following this line and completing the arc from the beginning of this paper, it can further be argued that, for the case of language processing, potential bilaterality in women and laterality in men are embodied results of language socialisation rather than chromosome-driven structural differences. In other words, sex differences in the brain themselves are not evidence of a pure material dimension, but reflect gendered behaviour as learned and incorporated in a social context. Once incorporated into the brain, gender differences become part of our cerebral biology (Fausto-Sterling, 2000). This is how gender comes into the brain and why it is appropriate to use the term of *sex/gender* rather than *sex* or *gender* in the context of language processing.

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