From methods to meaning in functional neuroimaging

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Outline of the thesis

This thesis focuses on several aspects of functional human brain mapping involving both PET and fMRI experiments. Conclusions drawn from neuroimaging studies are always within the context of the experiment design, the data analysis applied and the subsequent interpretation. Therefore, a basic requirement of functional neuroimaging studies remains methodological refinement. More specifically, using an optimized methodological basis will increase the statistical inference and the validity of the conclusion.

Chapter 3 describes a comparison between an iterative reconstruction algorithm and the standard filtered backprojection reconstruction algorithm, and discusses their effects on the statistical power using SPM of $H_2{}^{15}O$-PET activation studies. The significance of task-induced cerebral blood flow responses depends, among other, on the signal-to-noise ratio (SNR) of the data. Often, PET sinograms of $H_2{}^{15}O$ activation studies are reconstructed using Filtered backprojection (FBP). Alternatively, the acquired data can be reconstructed using an iterative reconstruction procedure. The comparison in chapter 3 between FBP and iterative reconstruction shows that iterative reconstruction has the potential to increase the statistical power in $H_2{}^{15}O$-PET activation studies.

In $H_2{}^{15}O$-PET activation studies, apparent changes in rCBF may be caused by subject inter-scan displacements rather than by actual changes in cognitive state. The research described in chapter 4 explores the impact of these artifacts and assesses whether they can be removed by applying a scan-specific calculated attenuation correction (CAC) instead of the default measured attenuation correction (MAC). The results of this study show that inter-scan displacement induced variance can be prevented by applying a (re)aligned attenuation correction scan, e.g. CAC.

Chapters 5 and 6 present a symptom provocation study in patients with dissociative identity disorder (DID). The results show that specific changes in localized brain activity are consistent with the ability of these patients to function in at least two distinct parts of their personality. In chapter 5 a rather philosophical approach (den Boer, 2003) of DID is presented. This approach reveals different states of self-awareness and consciousness (Putnam, 1994; Edelman and Tononi, 2000). Based on these data, the conclusion is drawn that different brain states exist with distinguishable identities, each with different access to autobiographical memories. This is elaborated further in chapter 6. The results presented in chapter 6 are of general interest to clinicians and research scientists in psychiatry and are especially important for mental health care. As DID is still a controversial diagnosis in psychiatry, this data lends further credibility to the diagnostic validity of this mental illness. Most importantly, this data provides a better insight into and understanding of this specific trauma-related disorder, which, in the end,may benefit patients suffering from DID. Chapter 6 presents the neural correlates and the behavioral aspects of this disorder. The distinguishable identities show different subjective reactions, cardiovascular responses and cerebral activation patterns to trauma-related memory scripts. During exposure to trauma-related memory scripts, the pattern of changes in cerebral blood flow included, among others, a bilateral activation in the amygdala. This is of importance, as the amygdala has been pointed out to be involved in a broad range of psychiatric disorders (e.g. see Liberzon et al., 2003; Rauch et al., 2003).

The amygdala has been found to play a key role in conditioned fear and in the perception and processing of threat-related stimuli (LeDoux, 2000; Davis and Whalen, 2001; Phan et al., 2002; Sander et al., 2003). Chapter 7 offers an investigation into the robustness of fear perception, with additional response exploration in amygdala regions presented in chapter 8. These chapters comprise an fMRI study in healthy volunteers. Chapter 7 presents an investigation in which the robustness of emotionally salient (a neutral or fearful face) information processing, as compared to the processing of non-salient (a house) information, is explored. In this study, the experimental stimulus appeared gradually from dynamically decreasing random visual noise. At a certain point the subjects became aware of the stimulus, i.e., the perceptual pop-out. Information processing was found to be more robust for emotionally salient than for emotionally non-salient stimuli. In addition, the results indicate that salient information processing is mediated by the amygdala. In chapter 8 an additional event-related analysis is presented to address the question whether amygdala activation was already present prior to conscious pop-out and occurred earlier for fearful than for neutral faces. The results indicate the involvement of the subcortical thalamic-hippocampal-amygdala pathway for fast subconscious threat perception. The paradigm used in this study has great potential for application in several groups of patients to explore fear processing in the amygdala.

In this thesis, induced differences in brain activity are analyzed within the concept of functional localization (Frackowiak et al., 1997). Functional localization implies that a function can be localized in a segregated brain area. This is often referred to as functional specialization. Most sensory brain functions are functionally specialized, e.g. vision in the visual cortex or hearing in the auditory cortex. More complex brain functions, for example emotion, may be localized, but they can also be distributed over several segregated brain areas (Phan et al., 2002), which need to interact through a connected neural network to functionally integrate information (Friston, 1994). Emotional information processing can be localized in the amygdala, but can also involve more complex brain functions, like attention (Vuilleumier et al., 2001; Pessoa et al., 2002; Pessoa and Ungerleider, 2004). At the top of the hierarchy of brain functioning are cognition (Dolan, 2002) and consciousness (Tononi and Edelman, 1998; Posner and Rothbart, 1998; Damasio, 2000), implying a broad integration of information through a connected network of brain areas. Possibilities to approach this functional integration in functional neuroimaging data are described in chapter 9, which includes a short review on theoretical connectivity literature. Functional and effective connectivity data analysis moves away from the standard 'hot spot' approach and addresses functional neuroimaging data analysis in terms of functional networks (Petersson et al., 1999; Sporns et al., 2000; Friston et al., 2003). Future perspectives in the context of functional network data analysis methods are given at the end of this thesis, to allow for an approach to assign a functional meaning to biological neuronal networks (Tononi et al., 1999; Laughlini and Sejnowski, 2003), which embody the human brain.

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