Valorization Addendum
The work presented in the current dissertation aimed to investigate borderline personality disorder (BPD) uniqueness of neural correlates of emotional sensitivity, emotion regulation and impulsivity, especially with regard to stimulus category specificity and diagnosis specificity. This valorization addendum focuses on a broader societal and economic context, it discusses the societal and economic relevance, gives an overview of the target groups for whom our research findings might be relevant, discusses possible activities and services, and innovative aspects resulting from the research.

**Societal and Economic relevance**

BPD is a common mental disorder that is associated with negative consequences from societal and economic points of view. BPD imposes a substantial impact on those suffering from BPD, their friends and families (including possible children), the public health systems and society. Apart from the severe functional impairments, BPD is considered to be difficult to treat and requires more treatment than patients with other disorders. Despite that effective treatments are available now, not every patient recovers fully, and treatments are lengthy and costly. Therefore, BPD is considered to be one of the most expensive psychiatric disorders. This economic burden of BPD is due to direct costs including all medical costs (e.g. hospital days, emergency room visits and psychotherapy), and indirect costs that occur secondary to the disorder (e.g. production loss and work absence). The overall annual societal costs in the Dutch population were estimated at 16,852 euro (price level 2000) per patient (van Asselt, Dirksen, Arntz & Severens, 2007), of which more than 50% were indirect costs. Although the current dissertation does not directly contribute to decreasing costs it contributes to increasing insight into underlying mechanisms of emotional sensitivity, emotion regulation and impulsivity and point towards new targets for treatment. For example, the dorsolateral prefrontal cortex is considered to play an important role in top-down control and might be a potential target for real-time fMRI neurofeedback and transcranial magnetic stimulation, both potential tools to improve cognitive control. Furthermore, the effect of psychotherapy might be mediated by changes in brain activity. Therefore, understanding how brain activity is associated with (successful) psychotherapy (treatment response predication), and identify changes of brain activity after psychotherapy (treatment mechanism) is of great relevance. Next, specific components can be added or removed to make the treatment more efficient and effective. A forthcoming series of studies from our lab that will contribute to this aim investigates changes of brain activity over the course of schema therapy and treatment-as-usual. Finally, cost-effectiveness of individual schema therapy has been demonstrated previously in the Netherlands in borderline and other personality disorders (Bamelis, Arntz, Wetzelaer, Verdoorn & Evers, 2015; van Asselt, 2008). The BPD patients included in the studies of the current dissertation were recruited in the context of an international multicenter randomized control trial investigating the clinical
effectiveness, cost-effectiveness and cost-utility of group schema therapy as compared to treatment-as-usual (Wetzelaer et al., 2014).

**Target groups for whom our findings might be relevant**

The findings of this dissertation might be relevant for several target groups: 1) researchers in the field of BPD to verify and refine theoretical models, 2) health care professionals as the gained knowledge might provide new leads to effective treatment, 3) patients suffering from BPD and their family and friends, and 4) society to reduce the economic costs. Together, to strive for better understanding of BPD and psychotherapy with their possible underlying mechanisms of change, we might be able to bridge existing gaps between research and theory on the one hand and clinical practice on the other hand.

**Activities and services**

This dissertation is driven by the motivation to understand and help BPD patients more effectively. Ultimately validation of clinical theories and insight in the underlying mechanisms might be used to improve treatment outcomes and novel treatment techniques. One can train emotion regulation strategies or control and alter patterns of brain activity, using for instance real-time fMRI neurofeedback and transcranial magnetic stimulation. When successful, these techniques might be integrated in treatment modules. However, to date it is too premature for workshops (in the context of scientific conferences) and training programs to teach health care professionals specific techniques.

**Innovation**

Abnormalities in the regulation of emotions or inhibition of impulses in BPD have been linked to altered fronto-limbic brain responses. Therefore empirical knowledge on BPD uniqueness of neural correlates of emotional sensitivity, emotion regulation and impulsivity can inform us about the underlying mechanisms and possible targets for treatment. Chapter 2 sheds a critical light on the methodology and important unanswered issues of fMRI studies involving emotional sensitivity, emotion regulation and impulsivity in BPD. In order to improve our understanding of BPD the studies conducted in chapters 3 and 4 address novel research questions build upon a couple of the issues pointed out in the critical review of chapter 2. More specifically, we extended previous research by adding positive and erotic stimuli to the traditional negative and neutral stimuli to examine stimulus category specificity across stimuli differing in their emotional content. As previous research mostly involves negative stimuli it is unclear whether emotional reactivity also holds for positive stimuli, pointing to a general emotional reactivity. Additionally, given high rates of childhood sexual traumatization and relationship problems are often reported in BPD, erotic
stimuli were added. Furthermore, because of high rates of comorbid Axis I and II disorders within BPD it remains unclear whether findings are BPD diagnosis specific or characteristic of psychopathology in general. By adding a clinical control group of Cluster-C personality disorder patients we examined diagnosis specificity compared to other personality disorders. Finally, the statistical power was increased, compared to previous studies, by increasing the sample size by recruiting participants from multiple international centers. In chapter 5 we included repeated resting-state enabling the investigation of post-task brain changes. Besides the studies showing altered amygdala-prefrontal functional connectivity during induction of negative emotions and task-free resting-state, this is the first study to examine the enduring effects of an emotion regulation task on amygdala resting-state functional connectivity. An objective for future research will be the use of longitudinal designs predicting clinical outcomes.

Although not an immediate consequence for treatment these findings do contribute to a better clinical understanding of BPD, and how BPD compares to other personality disorders. The results relating to stimulus category specificity indicate a general emotional sensitivity as they were also present for positive stimuli, whereas emotion regulation was specific for negative stimuli. The latter however makes sense, considering that regulation of positive emotions is in most cases undesirable. The findings concerning response inhibition showed a general responsivity across stimulus categories in the inferior parietal lobule, while effects in the frontal eye fields were specific for negative stimuli. This might suggest that if top-down modulation does not work on the perceptual input channel at the level of the inferior parietal lobule, in BPD this must happen in the output channel of the frontal eye fields.

Furthermore, no significant differences regarding emotion generation and emotion regulation brain areas and impulse control of social emotional stimuli were found for the comparison BPD patients versus Cluster-C personality disorder patients, indicating that these results were not diagnosis specific for BPD. Linearity analyses showed responses of the Cluster-C personality disorder patients in-between the non-patients and BPD patients. This supports the notion of a dimensional approach rather than a categorical approach, in which Cluster-C personality disorder patients exhibit emotional and interpersonal features in common with BPD, yet weaker.

**Schedule and implementation**

This work has been conducted in the program “Open Research Area in the Social Sciences”, in which participants were recruited in two sites in the Netherlands (Maastricht and Heerlen) and three sites in Germany (Freiburg, Lübeck, and Hamburg). Therefore to perform the present international multicenter fMRI studies, our research group developed international relationships with Freiburg and Lübeck.
The outcome of the studies described in this dissertation will be communicated within scientific community by international peer-reviewed journal publications and conference presentations. Communication of the findings outside the scientific field will be done through the media.

References


