Dancing in the (B)rain

Valorization

As a scientist it is important to contribute not only to science, but also to society. This entails reflecting on your own work and the possible implications your work may have on society as a whole. The ministry of Education, culture and science uses the following definition: "valorization is the process of creating value from knowledge by making knowledge suitable and/or available for economic and/or societal use and translating that knowledge into products, services, processes and/or entrepreneurial activity"[1]. Examples of neuroscientific knowledge finding its way in the field of psychiatry could be the development of new medicines, non-pharmacological treatments, diagnostic procedures, and guidelines. Valorization is an essential objective of a good scientist. You have a responsibility towards society to inspire, share your knowledge and to bridge the gap between science and society. There are several ways to achieve this goal. This chapter is an attempt to explore potential influences of the work described in this thesis on society. Besides writing this chapter, I have been involved in several other activities related to valorization in the past four years, as highlighted in my CV and the personal portfolio at the end of this thesis. A range of topics are important when discussing the potential societal benefit(s) of science in general and the work in this thesis specifically, and some major points are addressed below.

Implications for patients and their families

A clear societal impact of the research described in this thesis is the potential implications for the clinical practice of people with mental disorders in general and with the 22q11.2 deletion syndrome (22q11DS) specifically. An important aim when investigating clinical populations is to reduce any suffering caused by the disorder and to gain insights that can be useful for potential treatment options for patients. Knowledge about underlying neurobiological systems related to the psychiatric symptoms in 22q11DS and mental disorders in general, can influence decisions by policy makers, insurance companies and other professionals in the future as well.

During the data collection of this PhD project I was fortunate to meet a lot of different people with 22q11DS and their families. One place especially made an impact on me due to the dedicated care of a family for their son with 22q11DS, encouraging them to open a housing facility for people with intellectual disabilities. A housing community for people in need of extra care and support in their day-to-day life. During one of my home visits I met Lucas (this case is anonymized) who had been living in this housing facility already for a number of years. He felt happy and accepted in that environment. He participated in my PhD studies because he wanted to contribute to more awareness, knowledge and insight into 22q11DS, thereby ultimately helping other people suffering from the syndrome.

To other people with 22q11DS he wanted to say: “interact with people you can trust, who understand you and who care for you”. Another boy with 22q11DS and past psychotic episodes also lived at the facility and was eager to participate in my research, aiming to help increase the awareness for 22q11DS in society. To other people with 22q11DS he wanted to say: “accept who you are, don’t demand too much from yourself. Listen to your disabilities and don’t care too much about the opinion of others.”

Besides these two examples, many of the other participants and especially their families and peers told us that one of their primary reasons to participate in the research was to increase awareness for 22q11DS in society and amongst clinicians. Therefore, we hope that also the work described in this thesis will contribute to more awareness for 22q11DS in society.

Despite 22q11DS being one of the most common genetic syndromes in the world with a prevalence of 1 in 2000 to 4000 births[2], it is still highly unknown. Patients and their families have to deal with a lot of misunderstanding of 22q11DS in society. This was one of the main frustrations and challenges the caretakers, family and patients shared with me during my visits in their daily life situations. The general lack of awareness of the syndrome sometimes decreased their ability of getting the right treatment, support and care they were looking for. When a syndrome and its characteristics are unknown, it is harder to be acknowledged, have access to sufficient treatment, suitable education, feasible jobs and also to generally feel accepted in society. More awareness and acceptance are therefore of great importance to improving the quality of life of the patients and their environments. “VG netwerken” and “Stichting Steun 22q11[3]” have done a great job in raising more awareness in society, with their slogan “unknown leads to misunderstanding”. However, awareness still remains a huge challenge and more scientific research and evidence, like described in this thesis, is therefore necessary to explain why 22q11DS increases risk for several symptoms and why having this syndrome can severely impact your daily life.

The work described in this thesis is part of the research conducted in the “22q11DS international Brain and Behavior Consortium”[2] in which scientists from all over the world collaborate to gain more insights into mental disorders and cognitive problems related to the syndrome. By combining the expertise of different international scientific departments, it is expected to better understand why some people (with 22q11DS) do- and others do not - develop mental disorders. Our results are believed to add a valuable piece to the complex puzzle of causal factors leading to mental disorders, including aberrant reward and stress processing in 22q11DS (chapters 1,2,3,5 and 6), which might ultimately lead to new treatment methods and an improved quality of life of patients and their families.

The work in this thesis could also have implications for patients without 22q11DS with mental disorders including psychotic disorders. To increase prevention and the success of treatment, it is useful to improve the understanding of underlying

neurobiological mechanisms in 22q11DS, a population at high genetic risk for developing psychotic disorders.

We can speculate about the clinical relevance of the findings in each individual chapter of this thesis. Reward and reinforcement learning impairments in 22q11DS, described in chapters 1 and 2, could imply a decreased hedonic component of reward anticipation and potentially aberrant reward sensitivity. It could be speculated that people with 22q11DS need other (more) rewarding stimuli in order to feel motivated, compared to people without 22q11DS. This should be taken in to account when professionals (deciding about suitable treatment options) and other people in the direct living situation (e.g. family, school, work situations) want to create the best possible environment for individuals with 22q11DS to flourish. More research is necessary to decide what kind of rewarding and motivational incentives would most appropriate and important to individuals with 22q11DS.

The results described in chapter 4 show that pre-pulse inhibition (PPI) is a valuable method to investigate specific endophenotypes related to information processing and brain functioning in 22q11DS, given the lack of invasiveness. Results of studies using this method could potentially be valuable in the clinical settings as well, however more research is currently necessary to relate the findings on information processing to societal impact for 22q11DS.

Our findings of both chapters 3 and chapter 5, suggest a frontal hyperdopaminergic state and hypocortisolism in adults with 22q11DS, which could have (clinical) implications for people with 22q11DS. The results suggest that the 22q11.2 deletion could cause over-activation, sensitization or even exhaustion of the catecholamine and endocrine systems (e.g. the hypothalamic-pituitary-adrenal-gland (HPA)-axis) throughout the developmental trajectories in 22q11DS, which could lead to dysfunction of these systems later in life. We therefore propose that 22q11DS should be seen as a developmental syndrome that can severely disrupt these systems over time, potentially related to the increased risk for mental disorders in individuals with 22q11DS. A genetically programmed abnormal dopamine (DA) and stress system could perhaps precede psychopathology in 22q11DS. The sensitization of the stress system could for example result in different stress reactivity in 22q11DS. Minor daily life challenges (or unexpected events) might be experienced more stressful (traumatic), potentially associated to the high levels of chronic stress and anxiety in (children with) 22q11DS. Our results on altered cortisol functioning add valuable new evidence for the endocrine impairments in 22q11DS which should be taken in to account when (new) treatment guidelines are designed.

Our experience sampling results in chapter 6 show that in general adults with 22q11DS report more negative mood throughout the day, which could have implications for guidelines and day-to-day interaction in society. This negative mood could be related to the high rates (especially the negative symptoms) of psychotic disorder, anxiety and mood disorders reported in 22q11DS[4,5]. More research is necessary to indicate if a

relationship between abnormal stress reactivity and psychiatric symptoms is present in 22q11DS, as it is in other populations with (a risk of) psychiatric disorders. It is additionally interesting to explore clinical intervention possibilities in 22q11DS. These interventions could either focus on the reduction of stressful events in the environment of people with 22q11DS, or on modifying emotional reactivity to stress, in order to improve resilience and coping strategies, for instance using acceptance and commitment therapy, or mindfulness-based stress reduction.

Summarizing, the key points to take away from the results described in this thesis, related to treatment possibilities are that:

- Individuals with 22q11DS might experience an emotional or sensory overload, possibly resulting in, or resulting from, an oversensitive HPA-axis, frontal hypodopaminergic functioning, aberrant reward sensitivity and aberrant stress reactivity.
- Our results indicate:
  - a mismatch between stressful events, the emotional- and the biological response (HPA-axis functioning) to (minor) stressful daily activities.
  - a mismatch between rewarding stimuli and the biological response (reward-network activation and DA release) to these rewarding events in the environment.
- Minor daily life challenges (or unexpected events) may be experienced as more stressful and the general appraisal of daily life experiences could be more negative and/or less rewarding
- The results in this thesis could potentially be associated to the high levels of mood disorders, psychotic disorder, chronic stress and anxiety in 22q11DS and should therefore be considered when designing treatment options.

References

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