Point-to-point reply

Sobanski and Wagner: Functional Neuroanatomy of Panic Disorder – Status Quo of the Research

Reviewers' comments:

We would like to thank both reviewers for their helpful and constructive comments. We feel that suggested changes led to a substantial improvement of the manuscript.

Reviewer # 02445281:

"Functional Neuroanatomy in Panic Disorder – Status Quo of the Research" Comment. This is a wide, very nice review. The document is very well written and documented. Surely, it must be of interest for WJP readers. I have only two observations. 1. Check the manuscript, there are some typewriting mistakes, e.g., patter (p. 16), fasculi (p. 18). 2. Please, reduce abbreviations to a minimum. In many parts of the manuscript abbreviations are used a couple of times in the same paragraph, making some sections hard to follow.

Reply: We thank reviewer # 02445281 for the careful reading of the manuscript and for her/his kind words. The manuscript was thoroughly read by both authors and additionally by a native speaker. We corrected the typewriting mistakes and unclear sentences as well as reduced the abbreviations to a minimum, as suggested.

Reviewer # 02445261:

We thank reviewer # 02445261 for the careful reading and helpful and constructive comments.

This is, in summary, an interesting review manuscript aimed to provide a detailed and comprehensive overview of the current research in the functional neuroanatomy of panic disorder. The authors mainly focused on recent neurofunctional, neurostructural, and neurochemical studies about the specified topic. They concluded that it is conceivable that new research advances may lead in the near future to the development of clinically useful tools like predictive biomarkers or novel treatment options. The authors may find as follows my comments/suggestions.

First, throughout the Introduction section when the authors stated that antipanic drugs such as tricyclic antidepressants or MAO inhibitors block brainstem-provoked panic attacks, that other treatments like benzodiazepines and relaxation training reduce anticipatory anxiety via the limbic system, and desensitization and cognitive therapies relieve phobic avoidance by influencing functions of the prefrontal cortex, they could also report that recent antidepressant medications seem to be able to enhance neuroplasticity mechanisms and adult neurogenesis in the hippocampus and prefrontal cortex.

Reply: We thank the reviewer # 02445261 for the interesting suggestion to modify the introduction section according to suggested articles. We accordingly modified the introduction section in the revised version of the manuscript.

In the revised version, we added the following paragraph to the introduction section on page 9:

"With regards to drug therapy in PD, Gorman et al[1] not only stated that antidepressants exbit their antipanic effects via the brainstem, as proposed in their original model[2], but also that therapy with SSRIs might act directly on the limbic system (in particular on the central and lateral nuclei of the amygdala; please see section "The role of serotonin")[1]. In light of the above, it is intriguing that recent antidepressant medications seem to be able to enhance neuroplasticity mechanisms and adult neurogenesis in the hippocampus and even in the prefrontal cortex[3]."

In addition, most of the commonly available antidepressants lacked efficacy and tolerability for patients with major depressive disorder. Among all antidepressant drugs predominantly acting through monoaminergic mechanisms, some recent psychoactive compounds are of particular interest due to another alternative mechanism of action able to enhance neuroplasticity mechanisms. For this purpose, I suggest to cite the paper of Pompili and colleagues which was published on World Journal of Biological Psychiatry in 2013.

Reply: As suggested, we cited the highly interesting paper of Pompili et al. (2013) in the revised version of the manuscript and added two sentences about the role of the novel antidepressant agomelatine in treatment of panic disorder (p. 9).

"Therefore, due to its unique characteristics, the novel antidepressant agomelatine might also be effective in PD. Preliminary studies have provided encouraging results regarding effectiveness and tolerability of this substance, although it has to be noted that agomelatine is not yet approved for the treatment of PD[4, 5]."

Moreover, there are statements within the same section such as "many patients with PD suffer from anticipatory anxiety and maladaptive changes in cognition and behavior resulting in phobic avoidance" or "different treatments for panic disorder and agoraphobia not only affect different parts of the illness but also different parts of the brain" or "by today there are numerous neurofunctional, neurostructural, and neurochemical studies, which have demonstrated the significant role of certain structures in the fear network" that need to be supported by adequate references.

Reply: As suggested by the reviewer # 02445261, the references supporting the highlighted statements are now provided in the revised version of the manuscript.

On page 7: "*Besides panic attacks, many patients with PD suffer from anticipatory anxiety and maladaptive changes in cognition and behavior resulting in phobic avoidance[6].*"

On page 7-8: ***"Hence, according to Gorman et al[2] different treatments for panic disorder and agoraphobia not only affect different symptoms of the illness but also different parts of the brain."***

On page 9: ***"Today, there are numerous neurofunctional, neurostructural, and neurochemical studies that have demonstrated the significant role of certain structures in the fear network[7-10]"***

In addition, within the Methods section, there are some missing details/information that should be more clearly elucidated. For instance, how many and which key words have been specified by the authors during their search is a matter of debate. In addition, how many articles have been first screened, selected, and finally included into their search needs to be specified. The inclusion of the Systematic Reviews and Meta-Analyses" (PRISMA) guidelines summarizing the most relevant results of the search strategy (identification, screening, eligibility, and inclusion process) used for selecting studies and aimed to achieve a high standard of reporting would significantly ameliorate this section.

Reply: We thank the reviewer # 02445261 for this very valuable comment. We modified the methods section accordingly and described every step of the literature search in the revised version of the manuscript as follows:

Page 10:

"We searched the electronic database PubMed for neurostructural, neurofunctional, and neurochemical studies on PD that were published in the period between January 2012 and April 2016. The search was conducted using the following search terminology: "(PANIC DISORDER) AND (F/MRI OR DTI OR PET OR SPECT OR MRS OR NIRS OR IMAGING GENETICS OR SEROTONIN OR NOREPINEPHRINE OR NORADRENALINE OR LOCUS COERULEUS OR DOPAMINE OR HPA AXIS OR INSULA)". The total number of publications found by the PubMed research was 457 (f/MRI: 94; DTI: 2; PET: 5; SPECT: 5; MRS: 11; NIRS: 2; Imaging genetics: 21; Serotonin: 137; Norepinephrine: 19; Noradrenaline: 28; Locus coeruleus: 3; Dopamine: 8; HPA axis: 23 Insula: 99). The total number of publications

after screening for topic was reduced to 281 (fMRI: 88; DTI: 2; PET: 3; SPECT: 1; MRS: 8; NIRS: 1; Imaging genetics: 17; Serotonin: 106; Norepinephrine: 11; Noradrenaline: 4; Locus coeruleus: 2; Dopamine: 2; HPA axis: 16; Insula: 20). The remaining 281 studies were screened for duplicates and finally evaluated for eligibility. Subsequently, a secondary search was conducted that involved a broad review of potential neuroimaging studies by carefully perusing through the citation lists of the retrieved articles. Thereafter, a final screening of the retrieved articles was performed to ensure that the focus of the articles was within the scope of the present review. The literature search was conducted both jointly and independently by the authors (TS, GW). Finally, 76 studies published between January 2012 and April 2016 were included in this review."

Overall, the Results section is, in my opinion, too long and difficult to follow for the general readership, thus I sincerely suggest to insert one/more Tables throughout the main text in order to enhance its readability.

Reply: We thank the reviewer for her/his suggestion to insert some tables. Due to the considerable length of the present manuscript, we have decided to add brief summaries to each section of the results chapter. We believe that these summaries are an appropriate tool to help the reader through the manuscript. Inserting tables would mean that parts of the information are presented in a threefold manner (in the text, in the brief summaries, as well as in the tables). We hope that reviewer # 02445261 will agree with this answer.

Nevertheless, if it appears to be necessary to the editors to additionally have tables in the review, we will be pleased to follow the suggestion of the review # 02445261 and will provide the required tables.

In addition, throughout the first lines of the Discussion section, the authors do not need to report for another time what is the main aim of the manuscript (this has been already specified before).

Reply: As suggested, we removed this first paragraph from the discussion section.

Lastly, what is the final take-home message? The authors should insert some conclusive remarks and a general summary of their wide overview about the main topic. This would be highly appreciated by the general readership.

Reply: We thank the reviewer # 02445261 for this very helpful comment. We now added a conclusion section in the revised version of the manuscript to provide a general summary and final take-home message.

On pages 50-51:

"This review discusses the recently published neurofunctional, neurostructural and neurochemical alterations in panic disorder.

However, the premise that PD is a single phenotype, might not be accurate. Studies on abnormal brain structure in PD revealed a relatively large heterogeneity of significant findings, which makes it difficult to relate specific regions or tracts with aberrant gray or white matter to PD. Additionally, the application of functional MRI did not reduce the heterogeneity of reported findings, even if the brain's salience network, mainly composed of the amygdala, insula and anterior cingulate cortex becomes increasingly important for the understanding of panic attacks.

On the other hand, the new era of imaging genetics provided first insights into the potential etiological heterogeneity of PD. Imaging genetic studies have not only confirmed the importance of serotonergic and noradrenergic transmission in the etiology of PD, but also indicated the significance of neuropeptide S receptor and CRH receptor gene variants. These new insights reveal possible targets for the development of drugs for personalized anxiolytic treatment. Furthermore, appropriate imaging genetics studies may lead to a better understanding of non-response to psychotherapy, e.g due to the variability of top-down control that the prefrontal/anterior cortex exerts on the amygdala/hippocampus, as well as on the brainstem in PD[154]. In the future the imaging genetics approach will be of major importance for the further development of the

neuroanatomical model, because genetic risk variants may significantly influence fear network activity in PD[15]. Therefore, imaging genetic consortia are necessary to accumulate a sufficient number of functional and structural brain scans, which may allow researchers to detect genome-wide significant loci affecting brain function and structure in panic disorder."

References:

1 **Gorman JM**, Kent JM, Sullivan GM, and Coplan JD, Neuroanatomical hypothesis of panic disorder, revised. *Am J Psychiatry* 2000; **157**: 493-505 [PMID: 10739407 DOI: 10.1176/foc.2.3.426]

2 **Gorman JM**, Liebowitz MR, Fyer AJ, and Stein J, A neuroanatomical hypothesis for panic disorder. *Am J Psychiatry* 1989; **146**: 148-61 [PMID: 2643361, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2643361]

3 **Pompili M**, Serafini G, Innamorati M, Venturini P, Fusar-Poli P, Sher L, Amore M, and Girardi P, Agomelatine, a novel intriguing antidepressant option enhancing neuroplasticity: a critical review. *World J Biol Psychiatry* 2013; **14**: 412-31 [PMID: 23530731 DOI: 10.3109/15622975.2013.765593]

4 **Levitan MN**, Papelbaum M, Soares G, Simoes P, Zugliani M, Freire RC, Mochcovitch M, and Nardi AE, Agomelatine in Panic Disorder: A 6-Week Follow-Up Case Series. *J Clin Psychopharmacol* 2016; **36**: 395-6 [PMID: 27285660 DOI: 10.1097/JCP.0000000000000524]

5 **Huijbregts KM**, Batelaan NM, Schonenberg J, Veen G, and van Balkom AJ, Agomelatine as a novel treatment option in panic disorder, results from an 8-week open-label trial. *J Clin Psychopharmacol* 2015; **35**: 336-8 [PMID: 25856784 DOI: 10.1097/JCP.0000000000000313]

6 **Cox BJ**, The nature and assessment of catastrophic thoughts in panic disorder. *Behaviour research and therapy* 1996; **34**: 363-74 [PMID: 8871370, http://www.ncbi.nlm.nih.gov/pubmed/8871370]

7 **Dresler T**, Guhn A, Tupak SV, Ehlis AC, Herrmann MJ, Fallgatter AJ, Deckert J, and Domschke K, Revise the revised? New dimensions of the neuroanatomical hypothesis of panic disorder. *J Neural Transm (Vienna)* 2013; **120**: 3-29 [PMID: 22692647 DOI: 10.1007/s00702-012-0811-1]

8 **Holzschneider K** and Mulert C, Neuroimaging in anxiety disorders. *Dialogues Clin Neurosci* 2011; **13**: 453-61 [PMID: 22275850, http://www.ncbi.nlm.nih.gov/pubmed/22275850]

9 **Pannekoek JN**, van der Werff SJ, Stein DJ, and van der Wee NJ, Advances in the neuroimaging of panic disorder. *Hum Psychopharmacol* 2013; **28**: 608-11 [PMID: 24038132 DOI: 10.1002/hup.2349]

10 **Paul ED**, Johnson PL, Shekhar A, and Lowry CA, The Deakin/Graeff hypothesis: focus on serotonergic inhibition of panic. *Neurosci Biobehav Rev* 2014; **46 Pt 3**: 379-96 [PMID: 24661986 DOI: 10.1016/j.neubiorev.2014.03.010]