# Between persistence and flexibility: the neuromodulation of cognitive control

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# Chapter 9

General discussion

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The current thesis addresses the question of why people differ in their capacities for cognitive control and how state-related changes can mediate such control. The final chapter provides an overview of the main findings from each chapter, and explains how they fit into the wider Metacontrol State Model (MSM; Hommel, 2015). Additionally, the chapter offers key takeaways, practical implications, and suggestions for future research.

## Theoretical framework

Cognitive control can be loosely defined as a brain process that guides behaviour according to internally generated goals and plans. The first sections **(Chapter 1 - 2)** of this dissertation address the question of how cognitive control emerges and how sub-processes implicated in cognitive control give rise to higher-order functions such as human creativity. The evidence summarized in **Chapter 2** suggests that the tendency to select automatic or less common associations and actions is governed by cognitive control policies. Specifically, the Metacontrol State Model, (MSM) (Hommel, 2015) proposes that differences in action selection arise from two competing control states, one of which is characterised by strong top-down control promoting persistence, and another, associated with weak top-down control promoting flexibility. A bias toward flexibility increases parallel processing and, thus also the probability of accessing non-dominant representations and behavioural means to reach one's goal. On the other hand, bias toward persistence shields processing from interference allowing one to reach a goal more effectively but perhaps less creatively. Moreover, **Chapter 2** presented a body of evidence suggesting that state-related changes induced by altered states of consciousness (ASC) can mediate such biases in metacontrol and, in turn, affect the interplay between so-called intentional and automatic processes. To test this theoretical model, we conducted five empirical studies (**Chapters 3 - 7**) assessing the extent to which state-related changes induced by experimental manipulations bias metacontrol balance and performance on subsequent behavioural tasks.

**Summary of empirical studies**

In the first empirical study (**Chapter 3),** we implemented Focused Attention Meditation (FAM) and Open Monitoring meditation (OMM) designed to bias an individual's metacontrol state towards persistence and flexibility, respectively. We hypothesized that bias toward persistence induced by FAM would render the retrieval of event files more selective, while bias towards flexibility induced by OMM would reduce the selectivity of irrelevant feature retrieval in the Event-file paradigm. The results of the first experiment provided support for this hypothesis by showing that engaging in OMM, as compared to FAM, produces larger partial-repetition costs in irrelevant stimulus feature binding (color and the response). This effect was mainly driven by OMM, as indicated in the second experiment, and ultimately suggested that engaging in OMM leads to a more flexible and inclusive processing style. Overall, it fits well with the theoretical claims of MSM (Hommel, 2015), suggesting that state-related changes induced by distinct meditation manipulation can have a systematic impact on metacontrol policies and hence influence the balance of relevant and irrelevant information processing (Hommel & Colzato et al., 2017).

The following chapters mark the transition from non-invasive priming manipulation to more invasive psychopharmacological manipulation of metacontrol. Specifically, the next four chapters **(Chapters 4** - **6)**, presented empirical research exploring the effect of serotonergic psychedelics on cognitive control and related sub-processes.

In **Chapter 4,** we investigated the effect of small amounts of psychedelics (i.e., microdosing) on convergent and divergent creativity in an open-label study. During the study, 36 participants completed convergent and divergent creativity tasks before and during the acute effects of a psychedelic microdose. Interestingly, the results indicated that both divergent and convergent thinking performance was improved after microdose. These findings could be interpreted in light of previous psychedelics trials with large doses, which suggested an increase in reversal learning (Bari et al., 2010; Boulougouris et al., 2007), associative learning (Harvey 1995, 2003), and hippocampal neurogenesis (Catlow et al. 2016) during intoxication, which could be theoretically linked to cognitive flexibility (Prochazkova et al., 2018). Such findings are conceptually congruent with our observation of increased divergent quality after microdosing, which was previously linked to cognitive flexibility (Carhart-Harris & Nutt 2017). On the one hand, we would anticipate that convergent thinking would be

impaired by microdosing considering the shift in control policies towards flexibility (Hommel, 2015). Moreover, the study was conducted within an open-label design, and thus the possibility that observed effects were driven by placebo effects could not be eliminated.

In **Chapter 5,** we assessed the effects of microdosing on convergent and divergent creativity in a placebo-controlled design. To this end, we presented results from 3 double-blind placebo-controlled longitudinal trials conducted across 175 subjects. The study's design was unique considering the legal status of psychedelic truffles in the Netherlands, permitting us to combine a well-controlled laboratory assessment with a naturalistic dosing protocol. We found that active microdosing increased performance on divergent thinking (i.e., indicated by a higher number of original answers in the Alternative Uses task) as compared to placebo, while convergent thinking (in the Picture concept task) was unaffected by drug manipulation. This observation was in line with the idea that psychedelics may shift cognitive control balance towards flexibility. This result was also consistent with previous psychedelic trials assessing the effects of large psychedelic doses on creativity. Specifically, large doses were shown to increase divergent originality several days after intoxication, while convergent thinking performance remained unaffected (Frecska et al., 2012; Masson et al., 2019; Masson et al., 2021). Overall, this study provided support for MSM by showing that state-related changes induced by psychedelics mediate distinct sub-processes implicated in creativity. This finding is further significant as previous empirical discussions were mainly concerned with the role of dopamine (DA) in the persistence/flexibility balance (Cools & D'Esposito, 2011; Cools, 2015), and the role of serotonin (5-HT) in cognitive control remains relatively unexplored.

In **Chapter 6,** we presented findings from two double-blind placebo-controlled longitudinal trials (with N = 69 and N = 67, respectively) examining the effect of microdosing on different aspects of cognition and well-being. Contrary to our expectations, microdosing manipulation showed no significant impact on either behavioural paradigms or subjective measures. While some aspects of social cognition, mood, and self-reported flexibility were initially found these effects were rendered insignificant after multiple comparison corrections. The null results contributed to a small number of existing placebo-controlled trials which also indicated highly mixed findings. Specifically, several controlled trials reported significant effects on mental health, cognition and brain function in microdosing (Hutten et al., 2020,

Hutten et al., 2021, Yanakieva et al., 2019, Bershad et al., 2020); other research indicated null effects of microdosing on mood, emotional processing and cognition (Family et al., 2020, Berchard et al., 2018; Marshall et al., 2021). Such discrepancy across findings could be accounted for by low sample sizes of existing microdosing trials, high methodological variability or low experimental sensitivity (Szigeti et al., 2021). Overall, while the null results provide no evidence for the existence of the expected effect, it does not test as evidence of the absence of such effects. For instance, it is possible that implementing different doses, measures or population samples may lead to different results. These findings further highlight the need for well-powered research and future replication. It also signifies the importance of considering methodological heterogeneity in order to offer more parsimonious interpretations of results.

In **Chapter 7,** we move away from the mild serotonergic alterations via microdosing and focus on the post-acute effect of large doses of psychedelics. Specifically, we assessed the sub-acute and long-term effects of inhaling 5-MeO-DMT in 87 subjects on cognitive flexibility and different aspects of mental health. The result indicated that ritualistically use of 5-MeO-DMT increased psychological flexibility and decreased psychological inflexibility even at a one-month follow-up. Relevantly, changes in cognitive flexibility positively correlated with significant changes in life satisfaction and mental resilience. Overall, the study provided support for the hypothesis that psychedelics may bias cognition towards increased flexibility (Carhart-Harris & Nutt 2017). Moreover, the positive associations between change in psychological flexibility and well-being supported the notion that psychological flexibility may function as the underlying mechanism of change in psychedelics (Rastelli et al., 2022; Wießner et al., 2022). Finally, considering the previously reported null findings of microdosing on mental health and cognition (Chapter 5), the results may indicate that larger psychedelic doses might be necessary to reliably facilitate long-lasting cognitive and mental-health changes.

In the last empirical chapter (**Chapter 8**) we examined individual differences in metacontrol “trait-biases” (i.e., bias towards flexibility or persistence) and their relation to transdiagnostic constructs of impulsivity and compulsivity (IMP-COMP). Here we hypothesized that biases in metacontrol (i.e., bias towards flexibility or persistence) could serve as an improved trans-diagnostic model. As anticipated, the results indicated that individual differences (N=33) in metacontrol defaults significantly

predicted individual differences in the IMP-COMP spectrum. Furthermore, as predicted metacontrol bias towards flexibility was positively associated with impulsivity while a persistence bias was associated with compulsivity. Taken together this study provided the first empirical support for the idea that individual differences in metacontrol may be associated with mental atypicality (Colzato, Beste & Hommel, 2022).

**Integration of main findings**

This dissertation aimed to provide empirical evidence for the MSM (Hommel, 2015) that suggests that cognitive control emerges from the dynamic interplay between persistence and flexibility, which balance is further mediated by "state-related" and "trait-related" factors.

After integrating the key findings, the MSM framework was supported in several ways:

(1) The metacontrol balance was influenced by state-related changes (i.e., changes in psychopharmacology, changes in attention) as indicated by the alteration of automatic responses on multiple cognitive tasks.

(2) We demonstrate that the metacontrol balance can be invasively and non-invasively manipulated by psychedelics and meditation practices, respectively.

(3) We showed that specific types of manipulations have a distinct effect on metacontrol biases (e.g., bias towards persistence or bias toward flexibility), and mostly corroborated with the MSM predictions.

(4) Apart from state-related biases, we captured inter-individual differences in metacontrol defaults which further predicted mental atypicality according to MSM.

Together, these finding supports the MSM (Hommel, 2015), which indicates that state-related changes and trait-related predisposition may steer metacontrol towards a specific processing style. Furthermore, the current thesis points toward several practical implications that should be considered in future research and clinical practice. For instance, in the first empirical study (**Chapter 3),** we showed that meditation effects were driven mainly by the OMM manipulation (compared to FAM) in meditation naïve subjects. This implies that OMM may be more suitable cognitive enhancement technique in naïve meditators which can have practical implication in future clinical and sub-clinical intervention design. However, the OMM effect was restricted to the

first session in a within-subject design. This suggests that meditation priming on metacontrol is relatively subtle and short-lasting. Hence, future research would benefit from recruiting expert meditators to test if a repetitive experience of a certain style of meditation may have more pronounced and long-lasting effects on people's cognition. Furthermore, the use of neuro-imaging and electrophysiological measurements in future research would be helpful, as these measures are likely to be more sensitive to meditation priming (Kühn et al., 2011) and could further solidify our understanding of the impact of FAM and OMM on information processing.

Secondly, in cognitive neuroscience research, pharmacological manipulation is a common practice. However, to this date, no reliable method has been discovered for manipulating cognitive flexibility. Since much anecdotal evidence suggested that microdoses of psychedelics could improve people's creativity, to this end, we carried out several microdosing psychedelic studies. The results showed that in two out of three studies (**Chapter 4** & **Chapter 5**), active microdosing increased divergent thinking performance. Such evidence supported the MSM by showing that state-related changes induced by psychedelics are likely to mediate distinct sub-processes implicated in creativity. Thus, overall, these findings aligned with the idea that psychedelics may enhance cognitive control balance towards flexibility.

Nevertheless, in **Chapter 6** microdosing manipulation did not significantly impact performance on any other behavioural paradigms, nor on subjective measures. This implicated that the effects of microdosing on cognition are more subtle and nuanced than initially anticipated. A possible explanation for the discrepancy across the microdosing findings could be related to relatively low sample sizes in the second longitudinal study (**Chapter 6**) when compared to the previous chapter (**Chapter 5**). Secondly, we speculated that microdosing effects may only be detected on specific tasks which involve minimal information processing (Hutten et al., 2020). Clarifying under what circumstances microdosing effects occur and their reliability requires comparing different experimental paradigms in the future.

Importantly, the MSM further proposes that the balance in control policies emerges from the interplay between inter- and intraindividual biases. Considering that people differ in genetics, neurological and learned predispositions (Hommel & Colzato et al., 2017b), such interplay would explain why some interventions may be beneficial for some individuals but detrimental for others (Mekern et al., 2019). Indeed, we observed high inter-individual differences in response to psychedelics.

Specifically, we detected inter-individual variations in response to 5-MeO-DMT. In this large-dose psychedelic study, a small proportion of participants reported severe and prolonged symptoms after intoxication that lasted even at a one-month follow-up. Moreover, we observed that baseline differences tended to interact with the acute effects of microdosing. Specifically, participants with previous experience with psychedelics were significantly more susceptible to placebo effects and reported overall higher psychoactive effects in microdosing compared to naïve participants.

These findings suggest that not-one-fits-all interventions are applicable for the optimization of cognitive control functions. It is currently unknown whether microdosing would benefit participants with cognitive impairment (such as depression, social anxiety, and ADHD/ADD) to a similar degree as healthy participants, as current research has only involved healthy participants.

**Future direction**

In sum, this dissertation examined the underlying mechanisms of cognitive control and its potential enhancement strategies. In order to effectively treat maladaptive behaviours, it is important to have a better understanding of cognitive sub-processes in cognitive control. To achieve this, future research should use more direct neuro-imaging techniques to reveal the biological processes associated with metacontrol biases. Understanding these processes could provide valuable insight into why some individuals respond better to treatments than others. Additionally, further research could help answer important questions, such as: what are the neurological mechanisms that allow some people to benefit from psychedelic interventions but not others? Which inter-individual differences should be considered as contra-indications for a given treatment? Moreover, future research should determine to what degree individual differences in baseline traits (determined by genetic, pharmacological and cultural background) affect subsequent interaction with treatment intervention. Finally, future research investigating the application of MSM in transdiagnostic methods could hold promise for the field of translational psychiatry and clinical treatment.

**Conclusions**

To conclude, this dissertation aimed to provide empirical evidence for the MSM (Hommel, 2015) and test potential enhancement strategies for better cognitive control.

The results suggest that the balance in control policies (flexibility and persistence) is likely the result of a combination between inter- and intraindividual biases (i.e., trait and state differences). The current findings also signify the potential use of OMM and psychedelics (microdoses and macro-doses) in cognitive control optimization. By doing so, the current research provides a stepping stone for further clinical and cognitive enhancement studies. Still, due to inconsistencies in the results (e.g., long-term-short-term effects or effect specificity), more well-powered and methodologically consistent research is needed to support these important yet preliminary findings. Overall, this thesis concludes that successful intervention must follow theoretically guided criteria to select the best-suited intervention technique in the future.

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To conclude, this dissertation aimed to provide empirical evidence for the MSM (Hommel, 2015) and test potential enhancement strategies for better cognitive control. The results suggest that the balance in control policies (flexibility and persistence) is likely the result of a combination between inter- and intraindividual biases (i.e., trait and state differences). The current findings also signify the potential use of OMM and psychedelics (microdoses and macro-doses) in cognitive control optimization. By doing so, the current research provides a stepping stone for further clinical and cognitive enhancement studies. Still, due to inconsistencies in the results (e.g., long-term-short-term effects or effect specificity), more well-powered and methodologically consistent research is needed to support these important yet preliminary findings. Overall, this thesis concludes that successful intervention must follow theoretically guided criteria to select the best-suited intervention.