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Intrusive Thinking From Molecules to Free Will

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Intrusive thinking has been defined as “any distinct, identifiable cognitive event that is unwanted, unintended, and recurrent. It interrupts the flow of thought, interferes in task performance, is associated with negative affect, and is difficult to control” (Clark 2005:4). Intrusive thinking is ubiquitous: it occurs as random, sometimes annoying daily interruptions but can also be a profoundly disabling symptom in almost all psychiatric disorders. Clinical examples include, but are not limited to, craving in drug addiction, recall of life-threatening events in posttraumatic stress disorder (PTSD), rumination in depression, and hallucinations in schizophrenia. The transdiagnostic nature of intrusive thought in neuropsychiatry points to the importance of understanding the genesis of the intrusions and how they can be therapeutically monitored and regulated. The neuroplasticity and circuitry that underpin intrusive thinking need to be clearly characterized in order to identify sensitive biomarkers and targets useful for translation into novel pharmacological and psychosocial treatments.

This 30th Ernst Strüngmann Forum brought together experts from a wide range of scientific disciplines to evaluate the current state of research into intrusive thinking and to define the boundaries of what is known and unknown about this perplexing and ubiquitous phenomenon. Using a dynamic cross-fertilization strategy of discovery (for more information, see the Preface), teams of experts from neurobiology, neuropsychiatry, and cognitive neuroscience explored four thematic areas: (a) molecular and circuits, (b) psychological cognitive processes, (c) system approaches and models, and (d) interventions and treatments. Within each working group, discussion centered on advancing research and treatment strategies, on identifying challenges to be addressed by future research, on developing models of intrusive thinking, and on the

social and philosophical implications beyond its relevance for mental health. This volume, organized around the thematic areas of the working groups, synthesizes the multifaceted deliberations that took place in Frankfurt, Germany, from June 14–19, 2019.

Molecular and Circuits

The first section focuses on identifying molecular and circuit approaches to intrusive thinking. In Chapter 2, Paul Phillips and Amy Milton emphasize that although complex, a biological understanding of intrusive thoughts is tractable based on our current knowledge of model-based and model-free systems and their operation. These systems reflect different approaches of how individuals learn about their environments (Daw et al. 2011). Phillips and Milton point out that it is important to appreciate that these circuits are not fixed and immutable, but rather it is likely that they undergo repeated rounds of plasticity and metaplasticity, which may be the source of intrusive events as a consequence of imbalance within the circuit.

Bernard Balleine (Chapter 3) reviews evidence of parallel circuits mediating the distinct forms of control associated with reflexive and volitional actions, and the interactions between these circuits in determining adaptive behavior. He conceptualizes intrusive thoughts and actions not as a failure of habitual or goal-directed control processes, but rather as a failure of the cooperative and competitive interactions between cortical and basal ganglia circuit processes that form the basis of habitual and goal-directed behaviors.

In Chapter 4, Michael Bruchas posits that advances in molecular technologies beyond standard optogenetic and chemogenetic strategies will provide unprecedented precision in understanding synaptic and circuit mechanisms of the thought generation and behavioral actions that characterize intrusive thinking. Using these approaches in animal models can provide an important bridge toward clinical translational of how brain circuits function and adapt. As examples, he highlights closed-loop sensing of neuronal activity (GCaMP or other) and optogenetic (channelrhodopsin-2 or halorhodopsin equivalents) or pharmacological manipulations in a wireless setting. These approaches can yield real-time sensing during behaviors defined to represent “intrusive thoughts” across species and, together with optogenetic and pharmacological control, can establish causality and mechanisms for intrusive thoughts.

Shannon Gourley et al. (Chapter 5) summarize the principal findings from their group’s discussions. They highlight standard animal models, behavioral tests, and outcome measures that could be exploited to shed light on the neurobiological components of intrusive thought. They also propose a conceptual model which captures intrusive thoughts as an emergent property of multiple systems (emotional, cognitive, motor, and autonomic/somatic) that are represented in hubs throughout the brain. Finally, they suggest that when

the choreography between these neural hubs and their corresponding nodes becomes disrupted, this creates a loss of homeostatic and/or cognitive control and leads to maladaptive thought intrusions and inappropriate behaviors.

Psychology and Cognition

In this section, the psychological and cognitive processes important for intrusive thinking are the focal point for discussion. Marie Banich (Chapter 6) begins with a review of different methods that can be used to examine and understand intrusive thought, such as self-report and diary measures, to capture the experience, duration, and intensity of intrusive thoughts. She also discusses self-report measures of the difficulty in controlling such thoughts. Moreover, she identifies a number of behavioral paradigms (e.g., the Think/No-Think paradigm) that specifically address mechanisms of memory retrieval and suppression, and pinpoints a significant challenge that remains; namely, the need to find and validate a method that can be used to corroborate the occurrence of intrusive thinking and its contribution to clinical diagnosis.

In Chapter 7, Marie Monfils and David Buss address the psychological aspects of intrusive thinking, highlighting instances in both clinical and non-clinical contexts. They emphasize the high prevalence of intrusive thinking across the population and the challenges this brings when attempts are made to identify unique meaning behind its occurrence. Further, they suggest that the possible adaptive nature of the phenomenon be accounted for in everyday and clinical contexts, when treatments strategies are considered.

The psychiatric literature is reviewed by Florian Schlagenhauf, Andreas Heinz, and Martin Voss in Chapter 8. They point out that although intrusive thought is part of the diagnostic criteria for PTSD and obsessive-compulsive disorder (OCD), it is also a prominent symptom in other psychiatric conditions, such as drug craving in addiction or rumination in depressive disorders. From a descriptive perspective, intrusive thought must be distinguished from thought insertion, observed in schizophrenia and related psychotic disorders. Schlagenhauf et al. raise issues that remain critically unsolved: Are there similar psychological and neurobiological mechanisms underlying intrusive thinking across diagnostic categories, despite striking phenomenological differences between, for instance, negative verbal thoughts and intrusive visual images and memories?

In Chapter 9, the summary of this working group, Renée Visser et al. begin by revisiting systematically definitions of intrusive thinking, addressing all circumstances in which intrusions might occur as well as their manifestations across health and disorders. The least constrained definition emphasized the interruptive, salient, and experienced nature of intrusive mental events as compared with a common definition that specifies unwanted and conscious as well as interruptive criteria. This process brought them to an alternative, more

inclusive definition of intrusions as “*interruptive, salient, experienced mental events.*” They propose that clinical intrusive thinking differs from its nonclinical form with regard to frequency, intensity, and maladaptive reappraisal, and emphasize that recurrence is an important property, particularly for psychiatric manifestations. Visser et al. explore the neurocognitive processes which underpin intrusive thinking and its control and discuss its relationship to agency, meta-consciousness, and (mal)adaptiveness or desirability.

Systems and Models

To consider intrusive thinking within the framework of systems and models, John Fedota and Elliot Stein (Chapter 10) examine the neuroimaging literature, which shows that specific and related dysfunction in the calculation of salience involved multiple neuroanatomically and functionally linked regions. These regions involve both cerebral cortex and subcortical areas. These authors suggest that bias at each stage of salience attribution leads to both an overrepresentation of potentiated stimuli and an insensitivity to counterfactual evidence that normally signal the need to alter behavior. In addition, they raise questions to be taken up by future research such as: What are the limits of the neurobiological framework for intrusive thinking that is solely centered on cortical-subcortical-thalamic loops?

In comparison, David Badre (Chapter 11) takes a systems approach to address the following questions: Are there one, many, or any networks whose primary function is best described as cognitive control? Do the networks support cognitive control in the brain, and, if so, is their intrinsic and extrinsic organization “hub-like” or “hierarchical”? Are the networks for cognitive control modulatory or transmissive in the pathway from thought to action? Does controllability apply at the level of cognitive function or brain state? Badre proposes that answering these questions will constrain any conception of how intrusive thought can be controlled and lead to the development of novel mechanism-based interventions.

In Chapter 12, Kayuet Liu and Hakwan Lau advocate a framework for how conscious awareness of one’s own intentions and emotions enables the formation of causal narratives about oneself and the world. They argue that these narratives determine one’s sense of agency. Moreover, this sense of agency depends on the extent to which one is capable of forming culturally appropriate narratives. Liu and Lau evaluate different ways to characterize consciousness and focus on one that may prove most useful for the intersection between individual agency and intrusive thinking.

In the report of their discussions (Chapter 13), Angela Roberts et al. suggest a general scheme to identify essential elements of an intrusive experience, and where in this scheme dysregulation could occur to increase the likelihood of an intrusion. They find that computational models of intrusive thinking can be

embedded in a Bayesian model of active inference, integrated with psychological and physiological models of interoception (i.e., the processing of the brain-body relationship), and informed by psychological and neurobiological models of working memory and associative learning. These models can be examined in terms of flexibility and stability of intrusive thinking. Finally, Roberts et al. conceptualize intrusive thinking as emerging from a deficit in the neuromodulatory mechanisms and dynamics that implement the top-down control of attention; namely, its sensory attenuation.

Interventions and Treatments

In this section, directions are explored for the development of interventions and treatments for intrusive thinking within the context of intrusive thinking as a transdiagnostic endophenotype of many psychiatric disorders. In Chapter 14, Emily Holmes and coauthors suggest focusing efforts on core clinical symptoms (i.e., intrusive imagery). They propose that different interventions may interfere with the reconsolidation of a memory on different levels. By looking specifically at intrusive imagery, rather than broad and fuzzy assemblies of symptoms clusters, they propose that one may be able to radically change current treatment approaches in mental health. Moreover, Holmes et al. highlight the need to develop psychological interventions that can prevent involuntary distressful images from intruding into a person's mind, while still enabling the person to recall voluntarily information about the event.

Harriet de Wit and Anya Bershad consider the challenges in studying intrusive thoughts as a unique entity in Chapter 15. They conclude that relatively little is known about the effects of psychiatric medications on intrusive thoughts, both within disorders separate from other symptoms as well as across disorders. In addition, they note that a wide range of medications are used to treat intrusive thoughts and that these target a range of different neurotransmitter systems. Thus, given the uncertainty about intrusive thinking as a singular entity, it is difficult to determine which medications are specifically effective for regulating intrusive thinking.

In Chapter 16, Colleen Hanlon and Lisa McTeague review transcranial magnetic stimulation as a tool to induce causal change in behavior, cortical excitability, and frontostriatal activity, thus providing an overview of the cortical and subcortical areas that are often implicated in intrusive thinking. They propose that interactions between clinical and preclinical neuroscience researchers, with both electrophysiology and pharmacology backgrounds, could further enhance the efficacy of neuromodulatory approaches.

Judson Brewer et al. consider the challenges in defining intrusive thoughts and the difficulty in distinguishing normal processes of cognition and emotion from indicators of dysfunction, from practical, neurobiological, and cultural points of view (Chapter 17). Throughout, they use the term *intrusive events*

to encompass both thoughts and images that become intrusive. Brewer et al. review the behavioral, pharmacological, and emerging electromagnetic brain interventions to target intrusive events. In addition to a discussion of its neuroscientific basis and clinical relevance, they address intrusive events that impact society in multiple ways, and thus can be understood outside of a solely biological or medical perspective.

Summary

Several themes emerged throughout the Forum, which we feel important to highlight, as they could be developed into future programs of scientific and clinical discovery into the phenomenon of intrusive thought. First, all groups wrestled with the definition of intrusive thinking (e.g., whether it represents a singular process) and emphasized the need for bringing operational criteria (tightly related to the underlying neurobiology) to the definition of intrusive thinking. As a consequence, especially when the transdiagnostic nature of thought intrusions are considered, future investigation may aim to develop a psychometrically more refined delineation of intrusive thinking that links closely to the underlying neurobiology. Such an approach may be similar to what has been used across psychopathology (i.e., the use of questionnaires based on item banks) and might substantially reduce subject burden by using an adaptive measurement framework similar to the PROMIS system (Cella et al. 2010).

Second, there is some consensus that intrusive thinking is best understood in terms of a circuit dysfunction. Such circuits exist on a molecular, synaptic, cell, and systems level and may be best understood as dynamical systems, which when perturbed by disruptive events give rise to the intrusion. The precise delineation of these circuits will require sophisticated molecular and systems neuroscience approaches as well as complementary computational models to determine which processes contribute to intrusive thinking.

Third, although phenomenologically related symptoms (e.g., craving, intrusive images, ruminations, hallucinations) exist, it is far from clear whether these dysfunctions have a common neural substrate, involve similar neurochemical circuits, and can be modulated using similar interventions. Thus, future studies need to develop a transdiagnostic framework of intrusive thinking and sophisticated experimental approaches to determine the validity of intrusive thinking components and to assess where the construct converges and diverges.

Finally, intrusive thinking extends beyond psychopathology into everyday life. In a society where individuals are constantly exposed to distractions, it will be important to determine whether intrusive thinking emerges with increased frequency as a consequence. Moreover, the cultural framework of intrusive thinking frequently determines the valence and the urge to resist intrusions,

and the expectation of free will is fundamentally challenged by the existence of unwilled intrusive thinking. Future investigations may need to bring more conceptual clarity to the definition of intrusive thinking in the context of agency, free will, and culture. Taken together, the study of intrusive thinking is fertile ground to delineate an important endophenotype that has thus far been neglected by mainstream basic and clinical neuroscience research but which offers enormous potential in finding interventions that can ease mental suffering.

