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Precuneus: A key on the road to translation

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Ramping up in the late 2000s, the road from “bench to bedside” has been active. Primary deliverables have included acknowledgement by the scientific community that there is something truly unique and valuable gained by integrating neuroimaging into the investigation of mechanisms underlying behavioral treatment response (Gabrieli, 2018). This awakening has not only been seen in the field of addiction, but has also increasingly gained traction in other fields as well, as an avenue to localize and identify factors that are likely to be impactful in determining who does (and does not) respond to specific psychosocial interventions (McAdams, 2017; Pfeifer & Allen, 2016). This is critical because behavioral interventions remain the *most utilized treatment approach for addictions*. Thus, understanding how the brain responds to widely disseminated evidence-based psychosocial addiction treatments and how that brain response is linked to behavior change, is critical to elucidating which aspects of psychosocial treatment work best, and for whom.

Grodin and colleagues (2019) do a fantastic job of elegantly asking three critical questions in the domain of behavioral treatment response, and of relevance – they ask these important questions within the context of non-treatment-seeking individuals. Arguably, targeting non-treatment-seeking heavy drinkers is among the highest of public health priorities given low rates of treatment utilization due, in part, to the inherent reticence of this population to seek alcohol treatment (Schmidt, 2016). Opportunistic interventions, such as the one offered by Grodin and colleagues, maximize highly salient “teachable moments” to facilitate behavior change with individuals who would be unlikely to seek or receive treatment otherwise. More specifically, Grodin’s team first evaluated the extent to which non-treatment seeking drinkers responded to a brief alcohol intervention; second, they examined how behavioral treatment immediately impacted neural response on an alcohol cue task; and third, they determined how these two factors (the brief behavioral treatment and the neuroimaging alcohol cue response) corresponded with reductions in drinking behavior one month later.

In terms of the degree to which non-treatment seeking drinkers showed a reduction in drinking following their brief intervention (1 session), in Grodin’s study, there was no statistically significant difference between the intervention and attention control conditions. Importantly, their sample sizes were quite small; of relevance, the authors note their limited

power, and its likely impact on the detection of significant treatment group differences (n=22 in the intervention condition, n=24 in the attention control condition). While the intervention group showed a 53.3% reduction in heavy drinking days from baseline to 1-month follow-up, the attention control condition showed a 37.4% reduction ($d = -.182$ for Percent Heavy Drinking Days and $d = -.203$ for average drinks per week). Grodin and colleagues interpreted the control group's reduction in heavy drinking days in terms of possible reactivity to completing the comprehensive baseline assessment battery. Indeed, assessment reactivity is a domain that has been shown to be impactful on behavior change. Further, it is important to note that even though the intervention did not hit the threshold of statistical significance, Grodin et al's intervention condition still achieved a 53.3% reduction in heavy drinking days, thus representing *clinically* significant behavior change, based on their "halving" of substance-related symptoms (Miller & Manuel, 2008). Finally, the absence of a statistically significant difference in the reduction in heavy drinking days at 1-month follow-up between the two treatment groups, reflects some of the true challenges in this arena – including the challenges inherent to conducting well-powered translational studies with non-treatment seeking samples – this is precisely one of the domains where we hope to see more work in the future.

The brief intervention was based on motivational interviewing (MI) and FRAMES principles, which are often inadvertently collapsed together, but notably, are not the same (Miller & Rollnick, 2009). One distinguishing factor is that MI can include, but does not require, development of a change plan; the requirement of which, in MI, has been found to operate against behavior change in large studies of drinkers, in effect operating to decrease the likelihood of behavior change, if implemented in a manner not aligned with participant readiness (Amrhein, Miller, Yahne, Palmer, & Fulcher, 2003). Further, MI-based interventions have been increasingly showing mixed effects when used in opportunistic settings for a variety of substances of abuse (Bogenschutz et al., 2014; Saitz et al., 2014), with some MI studies reflecting better impact on behavior with longer (2-session, rather than 1 session) interventions.

One question that Dr. Feldstein Ewing's lab has been asking revolves around which components of brief behavioral interventions, such as the one utilized within the Grodin et al. (2019) study, may be truly driving observed treatment outcomes. It is likely the case that some degree of non-specific elements is relevant in treatment outcomes. Moreover, these types of questions can be obscured by the nature of current practices in clinician training, particularly in brief interventions for alcohol use and addiction, which tend to highlight and encourage a handful of therapist approaches to help facilitate patient behavior change, but do not consistently elucidate how and why each therapist behavior is important, and to what degree each therapist behavior may impact behavior change. As an example, in the training of MI, therapists are trained to interact with participants using OARS (open-ended questions, affirmations, reflective listening, summary statements).

Arguably, some of these therapist behaviors have more therapeutic impact (e.g., reflective listening>provision of summary statements); however, in the field of motivational interviewing, dismantling studies determining degrees of relative impact of certain recommended therapist behaviors (e.g., use of summary statements) over others (e.g., use of

reflective listening) have not yet been completely conclusive. The challenge is that use of behavioral-only metrics (e.g., self-report; verbal coding) - on their own - continue to hit roadblocks. As exemplified by a recent excellent study conducted by Gaume et al. (2019), behavioral-only metrics did not replicate the relationship between even widely-agreed upon therapist factors in the MI relationship (therapist empathy) and behavior change. In turn, without creative solutions that allow a deeper dive into potentially impactful therapeutic mechanisms, much of our therapeutic training is unable to avail itself of translational science that is vital to guide and advance the field on which therapist behaviors truly elicit behavior change, and to what degree they impact behavior.

Without a careful test using more sensitive metrics, such as neuroimaging, to disaggregate which of these therapeutic behaviors impacts treatment response (and to what degree), we cannot identify what, where, and how psychosocial therapeutic factors are activating the brain. These neural data are requisite to optimize treatment to maximize the intervention's impact, particularly in settings where we only have a brief window with our patients, such as with the otherwise non-treatment seeking participants in the Grodin et al. (2019) study. Dr. Feldstein Ewing's lab is carefully examining actual therapist statements in the neuroimaging environment to answer precisely these questions, so we can see which therapist approaches actually impact and sustain behavior change in the context of alcohol use, and which pieces do not advance behavior change (Feldstein Ewing et al., 2016). Our goal is to determine how best to optimize and maximize treatment delivery via utilization of the pieces of psychotherapy that actually contribute to brain and behavior change, and to discontinue therapist practices that do not advance treatment response and/or behavior change. Ultimately, we aim to generate optimal avenues to deliver the most impactful approaches to help facilitate behavior change within our brief encounters with non-treatment seeking clients, such as the individuals in the Grodin et al (2019) study.

Regarding the finding that the brief intervention, relative to the attention control condition, was not associated with differential neural cue reactivity. It is worthwhile to note that in the design examined herein, the imaging session was conducted immediately after the intervention. It is possible that perhaps this timing did not allow for optimal processing of the treatment elements; it might be the case that cue response associated with intervention effects is not apparent immediately post-treatment. Most studies, including those by Feldstein Ewing et al. (e.g., Feldstein Ewing, Filbey, Sabbineni, & Hutchison, 2011), delivered the cue response paradigm a week following the first session, perhaps allowing participants to have more time to percolate on behavior change, and to detect treatment response. Further, most of the Feldstein Ewing et al. studies also included an appetitive control (such as lychee juice) rather than water. Grodin and colleagues (2019) also note that they used an abbreviated version of the alcohol taste cue task, while recently validated, may not have recruited reward response as robustly as the original version. The degree to which differences in methods limited detection of treatment effects on neural cue reactivity in the Grodin et al. study (2019) warrants further investigation by both labs.

Finally, in terms of the neural response to the alcohol taste cue task, it was fascinating to see the role of the precuneus in predicting reductions in drinking behavior at 1-month follow-up across both brief intervention and attention control conditions. Notably, this finding is

similar to prior work in this area (Feldstein Ewing et al., 2013), which found that greater precuneus activation was associated with reductions in cannabis use at 1-month. When examined across disciplines and domains, the precuneus not only emerges as salient in studies of addiction (Starcke, Antons, Trotzke, & Brand, 2018), but also in higher order cognition, learning/memory, and socioemotional decision making, factors highly relevant in the context of psychotherapy, and ideally, during the cognitive processes requisite to truly achieve and maintain sustained behavior change (Ashar, Andrews-Hanna, Dimidjian, & Wager, 2017; Cosme, Mobasser, Zeithamova, Berkman, & Pfeifer, 2018; Plis et al., 2018; van Schie, Chiu, Rombouts, Heiser, & Elzinga, in press). Increasing the sample size, and augmenting the treatment condition (e.g., perhaps expanding to two sessions) could improve the Grodin team's capacity to detect, and likely, observe greater evidence of significant treatment outcomes.

The precuneus and prefrontal cortex are highly interconnected, and the strength of their connectivity has been hypothesized to reflect a state of heightened self-awareness (Kjaer & Lou, 2000). The precuneus is a salient aspect of the default mode network (Raichle, 2015), and together with structures such as the medial prefrontal and mid-parietal cortex, support mental representation of self and self-awareness (Cavanna & Trimble, 2006). As discussed by Grodin et al. (2019), the ability to activate self-related cognitions, particularly in relation to alcohol-related cues following an intervention, may signal an individual's response to treatment, i.e., the extent to which intervention content might impact self-related cognitive processing that has a downstream effect on reducing drinking.

Ultimately, neuroimaging offers one window into what might be happening under the clinical veil. Neuroimaging is a sensitive metric for examining the brain systems that fundamentally drive treatment response. Few have examined these relationships in a prospective design – this is one strength of the Grodin et al. (2019) study. A second is the public health relevance of examining an opportunistic intervention with a non-treatment seeking population of heavy drinkers, given the large number of affected individuals and consequence of high unmet treatment need in this community (Schmidt, 2016). The third contribution of the Grodin team's study, includes the highlighting of the role of the precuneus as an important hub in psychosocial interventions, specifically in terms of dynamic self-related cognitive processing critical to successful behavior change.

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