8 **This article is a commentary of the following paper:** Valdes-Hernandez, PA., Polk, R., Horta,
9 M., Frazier, I., Perez, E., Ojeda, Porges E., Cruz-Almeida Y., Feifel D., Ebner, NC. (2021). Chronic
10 oxytocin administration in older men modulates functional connectivity during animacy per-
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1 Oxytocin's dynamic role across the 2 lifespan

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12
13 **Abstract** Older adults have been neglected in biobehavioral oxytocin research. Emerging
14 research indicates that oxytocin signaling activity fluctuates over the lifespan, which suggests that
15 results from studies investigating youth and young adults cannot be easily generalized to older
16 adults. The recruitment of a wider age range of research participants using a variety of research
17 tools is required to uncover the role of the oxytocin signaling system over the lifespan and may
18 reveal novel treatment target candidates in older adults, beyond social cognition and behavior.

19
20 Oxytocin is a neuropeptide primarily synthesized in the hypothalamus that helps coordinate a
21 broad range of physiological processes (Jurek and Neumann, 2018). Oxytocin was discovered over
22 a century ago for its role in childbirth and lactation, but more recently it has received considerable
23 research attention for its role in social cognition and behavior (Leng and Leng, 2021). Human oxy-
24 tocin research in the biobehavioral sciences has mostly involved youth and young adults, with very
25 little work in older adult populations. This is a remarkable situation considering that older adults
26 are the fastest growing population in industrialized nations (UN, 2017) and that increasing age is
27 associated with a decline in social cognition (Olderbak et al., 2019).

28 To help remedy this situation, a recent study by Valdes-Hernandez and colleagues (2021) in-
29 vestigated the effects of chronic intranasal oxytocin administration in 31 older adults [mean age
30 (SD) = 69 (6)] on brain mechanisms underlying animacy perception, which is the tendency to at-
31 tribute motivation and meaning of living things to non-living or inanimate objects based on their
32 motion. Animacy perception was assessed with the Heider-Simmel test (Heider and Simmel, 1944),
33 in which participants watch video clips of simple moving geometric shapes. The test includes a
34 social condition, where the shapes' movements suggest goal-directed behavior, and a non-social
35 condition where movements seem random and non-goal-directed. Previous work using young
36 adult samples found that intranasal oxytocin administration enhances the anthropomorphizing of
37 moving shapes that suggest a "social story", but not for random motion (Scheele et al., 2015), and
38 an increased tendency to interpret social movement as "friendly social interactions" (Hecht et al.,
39 2017).

40 Using fMRI, Valdes-Hernandez and colleagues (2021) did not observe any effects of oxytocin

Figure 1. Oxytocin receptor gene expression is increased in both early childhood and older adulthood across the brain. This lifespan oxytocin receptor expression pattern was derived from Rokicki and colleagues (2021), who used genome-wide exon-level transcriptome data from 57 donors across 16 brain regions.

on brain activity in the social vs. random condition of the Heider-Simmel test. However, they did observe that the pre-to-post intervention change in the social-random difference in functional connectivity was higher in the oxytocin group compared to the placebo group in occipital, temporal, and parietal brain regions, as well as the superior temporal sulcus, a key structure in animacy perception. The authors interpret these findings to suggest that while chronic oxytocin administration does not modulate fMRI activation, it *does* modulate functional connectivity of brain regions involved in social perception in older adults. These observations are consistent with neuroplastic modification by chronic oxytocin administration, which adds to our understanding of oxytocin's effects on brain function and the therapeutic potential of chronic administration. But perhaps more importantly, this study also provides a greater insight into the role of the oxytocin system in older adults.

We currently lack a comprehensive understanding of how oxytocin signaling changes throughout the human lifespan and how these dynamics impact health, cognition, and behavior. As noted by Valdes-Hernandez and colleagues (2021), a limitation of their study was that it did not include a comparison with a younger sample. While Horta and co-workers (2020) have put forward a compelling call to better understand the role of oxytocin across the lifespan via longitudinal and cross-sectional intranasal oxytocin studies across a range of age groups, other methods can be used to complement such investigations. Genetic approaches can be particularly informative, but this line of work generally focuses on how oxytocin receptor gene (*OXTR*) single nucleotide polymorphisms (SNPs) influence cognition and behavior over the lifespan. An alternative to the SNP approach is to evaluate how *OXTR* expression levels in the brain shift over the lifespan. As *OXTR* expression levels in the brain influence behavior (Keebaugh and Young, 2011), identifying *OXTR* expression dynamics in the brain across the lifespan and genes with similar spatiotemporal expression profiles can help identify critical lifespan periods for oxytocin signaling and the functional relevance of these fluctuations.

Recent cross-sectional research using human brain samples from 57 donors revealed a distinct *OXTR* expression pattern across the lifespan (Rokicki et al., 2021). Specifically, *OXTR* expression was shown to first peak during childhood, which is a critical period for social learning. Following this lifespan period, *OXTR* expression across brain reduced during early adulthood, and then peaked again in late adulthood (Figure 1). Increased oxytocin receptor expression in late adulthood was especially pronounced in the cerebellar cortex, which coordinates goal-directed movement and cognition (Strick et al., 2009). We speculate that this late life increase in *OXTR* expression could be a compensatory mechanism to stave off cognitive declines due to the age-related deterioration of

cognitive circuitry in the brain. Rokicki and colleagues (2021) also reported that the genes with the strongest spatiotemporal correlation in the brain with the oxytocin receptor gene are associated with learning (*DRD2*), bone regeneration (*DIRAS3*), and energy homeostasis (*INHBB*), which points to a strong interplay between these genes and *OXT*. Intriguingly, research has found that oxytocin administration in animals can reverse bone deterioration (Beranger et al., 2015). Furthermore, individuals with autism spectrum disorder, a neurodevelopmental disorder characterized by social cognitive- and behavioral impairments, are also reportedly at increased risk for fracture and lower bone density compared to healthy controls (Ekhlaspour et al., 2016). Such results highlight how future research on oxytocin across the lifespan should not only focus on cognition, but also extend to somatic processes, such as bone density and energy regulation, and how these relate to cognition and behavior (Quintana and Guastella, 2020). The data also suggest that results from oxytocin studies including younger adults, which is the bulk of the existing research, cannot easily be generalized to other ages when considering how oxytocin signaling activity fluctuates over the lifespan.

Despite early promising results for oxytocin's effects on social cognition and behavior, more recent evidence has been mixed (Mierop et al., 2020) and generally associated with small effects (Quintana, 2020). While researchers have long recognized the role of individual differences in the response to oxytocin treatment (Bartz et al., 2011), the focus of these differences have tended to be psychological in nature (e.g., personality), with comparatively little consideration of the impact of age (Ebner et al., 2015), which is especially relevant considering *OXT* expression fluctuations across the human lifespan. With the average age of industrialized populations on the rise, research on the needs and interests of older individuals is required where the focus should not only be on living longer, but also living better. Given the emerging research indicating the fluctuating role of the oxytocin system across the lifespan in both cognitive and somatic processes, treatments targeting the oxytocin system are a promising avenue to help address the health needs of aging populations. The neglect of oxytocin research in older populations also represents a missed opportunity, as evaluating the neurobiological mechanisms underpinning the decline of social cognition in healthy aging may help researchers better understand oxytocin's role in social cognition difficulties in younger people with neurodevelopmental disorders. Altogether, pairing longitudinal and cross-sectional studies with genetics and neurobiology can help triangulate evidence (Munafò and Davey Smith, 2018), which can lead to more robust conclusions on the impact of age on oxytocin signaling and how manipulating the oxytocin system might improve health and wellbeing across the lifespan.

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