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Short communication

2D:4D and spatial abilities: From rats to humans

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ABSTRACT

Variance in spatial abilities are thought to be determined by in utero levels of testosterone and oestrogen, measurable in adults by the length ratio of the 2nd and 4th digit (2D:4D). We confirmed the relationship between 2D:4D and spatial performance using rats in two different tasks (paired-associate task and watermaze) and replicated this in humans. We further clarified anatomical and functional brain correlates of the association between 2D:4D and spatial performance in humans.

Many factors can influence performance on memory tasks and induce intrinsic between subject variability that by increasing the noise in the data can lead to lower statistical power for the main question. For example, when investigating memory consolidation via spatial tasks, general spatial abilities will affect how well subjects perform. General spatial ability and preferred spatial strategy is a sexual dimorphic trait, which is thought to be influenced in utero via the testosterone/oestrogen hormone ratio (Valla & Ceci, 2011). This prenatal hormonal ratio does not correlate with sex hormone levels in the adult, making it very difficult to directly measure in memory experiments with adult subjects. Interestingly, studies in rodents showed that this same prenatal hormone ratio also affects the growth of the 4th digit with higher hormone ratios inducing longer 4th digits in comparison to the 2nd digit (Zheng & Cohn, 2011). More specifically, androgen receptor (AR) and estrogen receptor α (ER-α) are more prevalent in digit 4 than in digit 2. Inactivation of AR or activation of ER- α decreases growth of digit 4, which causes a higher 2D:4D ratio; whereas inactivation of ER-α or activation of AR increases growth of digit 4, which leads to a lower 2D:4D ratio. Intriguingly, several genes identified by Zheng et al to be responsible for the 2D:4D ratio also have roles in development of the brain (Andersson et al., 2008). Thus the ratio between these digits (2D:4D) is an indicator for the hormonal ratio in utero, with lower finger ratios indicating higher testosterone to oestrogen.

In a study aimed at investigating memory consolidation effects across different tasks in male animals, we noticed early in training while discussing the current state of performance that we had "smart" and "not so smart" rats across different tasks. And in fact, the correlation between probe trial performance in the Delayed-Match-to-Place version of the watermaze, with daily switching escape locations (Steele & Morris, 1999), and in a flavour-location association task (Tse et al., 2007) in an open field environment (arena) was significant ($n = 20$, $r = 0.53$, $p = 0.015$; Fig. 1A; see supplemental materials), suggesting some factor e.g. general spatial ability confounded the performance in both tasks. To measure memory performance in the watermaze we used % swim time in a zone surrounding the previous location of the platform with no current platform present and in the arena % dig time in the correct sandwell associated to the flavoured cue given in the beginning of an unbaited probe trial. As a negative correlation between the right (but not left) 2D:4D and spatial performance in the watermaze has been demonstrated in humans (Csathó et al., 2003; Nowak & Moffat, 2011), we dissected our rat's front paws post-mortem and measured their 2D:4D. And in fact, the right 2D:4D correlated negatively with the performance in both tasks (2D:4D_arena: $r = -0.46$, $p = 0.044$, 2D:4D_watermaze: $r = -0.50$, $p = 0.024$; Fig. 1B and C). Similar to previous human results, there was no such correlation present using the left 2D:4D (left 2D:4D_arena: $r = -0.94$, $p = 0.694$, left 2D:4D_watermaze: $r = 0.22$, $p = 0.925$). Thus we could translate the prenatal programming effect of sex hormones on cognitive domains to rats, further emphasizing that cognitive sexual dimorphic traits are not solely caused by societal influence but have an inherently biological component.

To investigate the neural basis of the association between 2D:4D

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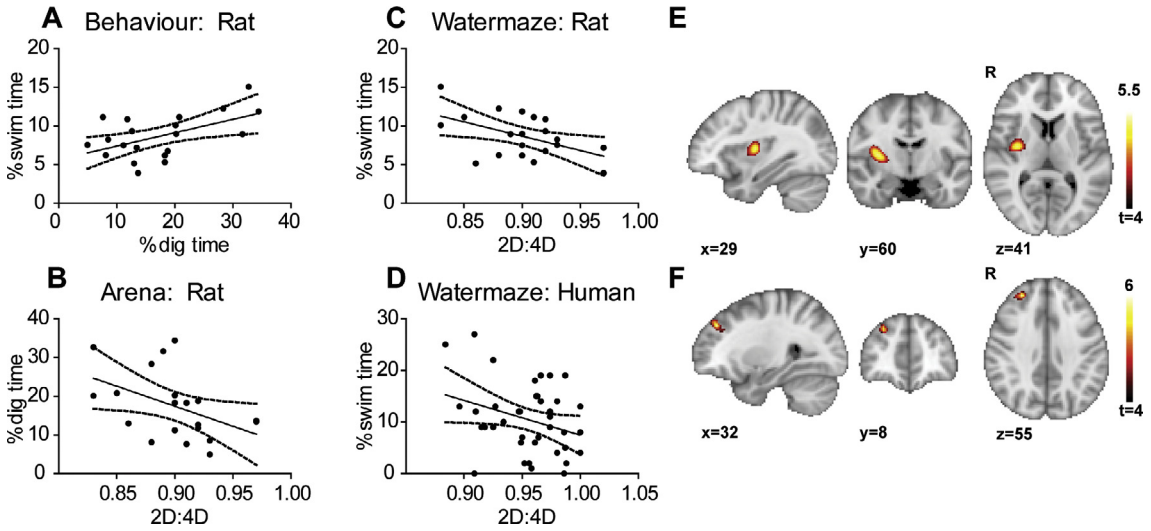

Fig. 1. 2D:4D, Behaviour and Neural Correlate. A. Shown is the performance in the watermaze (y-axis, % swim time in a zone around the previous platform location during a probe trial without platform present) and arena task (x-axis, % dig time in the correct Sandwell during an unbaited probe trial) with significant regression line and 95%CI ($F_{1,18} = 7.2$, $p = 0.015$). The regression analysis for both performance in the arena task and watermaze with 2D:4D was significant (B, arena $F_{1,18} = 4.7$, $p = 0.044$; C, watermaze $F_{1,18} = 6.1$, $p = 0.024$). Also in humans the performance in the watermaze showed a relationship with 2D:4D (D; $F_{1,38} = 3.9$, $p = 0.056$). E. Anatomical analysis (VBM) showed a significant cluster in the right caudate that was positively associated with the 2D:4D ratio ($p_{FWE\text{-whole brain}} < 0.05$). F. Using the caudate cluster from A. as a seed, we could show that functional connectivity during rest between that cluster and a right frontal cortex region predicted the immediate water maze performance ($p_{FWE\text{-whole brain}} < 0.01$).

and spatial ability, we turned to human subjects. Human behavioural data was collected for the purpose of this study after the hypothesis was generated and already verified in rats. We replicated our finding in rats that performance in the watermaze correlated with 2D:4D in a similar all male, human sample (n = 40) using a virtual reality version of the watermaze. Performance in a probe trial after four learning trials correlated significantly with the right 2D:4D ratio ($r = -0.30$, $p = 0.056$; Fig. 1D). Further, we acquired structural as well as functional resting-state scans using MRI (see supplemental materials). We found a cluster including the right caudate nucleus and insula that showed a positive correlation with 2D:4D in the structural analysis (VBM, Fig. 1E); an area previously already identified as sexual dimorphic in humans (Ruigrok et al., 2014). Interestingly, the positive correlation indicated that smaller 2D:4D (reflecting higher testosterone levels in utero) was associated to smaller size of this cluster. Further, including this anatomical cluster as a region of interest in the functional resting state analysis together with immediate watermaze performance as regressor, we found a significant cluster in the prefrontal cortex ($p_{FWE\_whole\ brain} < 0.01$); thus the higher the resting state functional connectivity of the cluster found in the anatomical 2D:4D analysis with the prefrontal cortex cluster, the better the subjects performed in the watermaze, most likely indicating a more efficient spatial memory network Fig. 1F). Watermaze performance has been associated with a brain-wide memory network including the striatum, caudate, prefrontal cortex and hippocampus (Woolley et al., 2013; Korthauer, Nowak, Frahmand, & Driscoll, 2016). Further, in contrast to many other dry-land spatial tasks, watermaze performance remains hippocampal dependent despite longer time-intervals and even though systems consolidation effects are seen in the prefrontal cortex (Squire, Genzel, Wixted, & Morris et al., 2015; Genzel et al., 2017). The continued involvement of the hippocampus may be due to navigation in water, which needs constant path calculations since stopping or tight turns are not possible (Squire et al., 2015).

With this study, we are the first to confirm the association between fetal sex hormones measured indirectly via 2D:4D and cognitive abilities in rats, reported previously in humans (Nowak & Moffat, 2011; Genzel et al., 2012). The testosterone/oestrogen balance in utero was shown previously to causally influence 2D:4D growth in mice via genes also present during development in the brain (Zheng & Cohn, 2011; Andersson et al., 2008). The testosterone levels in utero seem to be determined by the mother's hormone production levels as well as testosterone produced by the fetus itself (Ventura, Gomes, Pita, Neto, & Taylor, 2013). As shown here and previously in humans (Nowak & Moffat, 2011; Genzel et al., 2012) these hormone levels seem to "pre-program" the brain to be either more adept in "male" tasks (e.g. spatial ability) or "female" tasks (e.g. verbal, recognition and fine motor skills; not tested here) by influencing brain maturation (i.e. anatomical and functional effects seen in Fig. 1E and F).

The implications of this study are twofold. Firstly, it provides evidence for the biological and not solely social basis of "male" and "female" memory and cognition (Valla & Ceci, 2011; Korthauer et al., 2017) and emphasizes that sex matters in neuroscience (Cahill, 2006). Sex and sex hormones influence and can confound seemingly unrelated research and the 2D:4D is a possible marker to control for the influence of fetal hormonal influences. Studies using 2D:4D to investigate prenatal programming effects of sex hormones on behavior and disease are increasing. For example, in humans prostate and breast cancer were found to be associated with 2D:4D (Waters et al., 2013). In summary, our study could show an association and neural correlate between spatial task performance and 2D:4D in rats and humans, providing further evidence for the biological nature of sex hormone effects on cognition (Valla & Ceci, 2011). These findings should be followed up with interventional approaches investigating how sex hormones affect brain development and subsequent spatial abilities.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.nlm.2018.04.012.

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