More GABA, less distraction: A neurochemical predictor of motor decision speed.

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People vary markedly in the efficiency with which they can resolve competitive action decisions, even simple ones like shifting gaze to one stimulus rather than another. We find that an individual's ability to rapidly resolve such competition is predicted by the concentration of GABA – the main inhibitory neurotransmitter – in a region of frontal cortex relevant for eye movements, but not in a control region (occipital cortex).

Action decisions are widely believed to be the product of resolving a competition between different potential action commands. Such competition has been most studied with eye movements (saccades), and one well established phenomenon is the distractor effect, in which saccades to simple visual targets are delayed when an irrelevant stimulus appears elsewhere in the visual field 1. The presence of a visual distractor is thought to automatically produce a signal in neurons of the superior colliculus and frontal eye fields (FEF) 2, and this activity competes with the activity generated by the target stimulus [3, 4]. In order to reach a goal-directed decision, inhibitory mechanisms are thought to suppress the distractor activity in favour of target activity 5. Individual differences in this inhibition would strongly influence the time taken to resolve the competition, and thus could potentially explain fundamental differences in people's susceptibility to distraction.

The majority of inhibitory synapses in mammals employ the neurotransmitter GABA (gamma-aminobutyric acid), and disrupting its normal operation in saccade-related brain areas in monkeys disrupts eye movement control [6, 7]. However, being able to artificially disrupt a process is different to knowing what causes natural variation. We therefore tested whether the small differences in GABA concentration that naturally occur in humans play a role in explaining basic differences in behaviour.

We located the FEF individually in twelve participants using anatomical landmarks and functional MRI (Fig 1 and supplementary material), and we obtained measures of GABA concentration from a $(3\ cm)^3$ voxel around the FEF using magnetic resonance spectroscopy (MRS) 8-10. In a separate laboratory session, we assessed each participant's susceptibility to saccade distraction by measuring how much suddenly appearing distractors prolonged the time taken to initiate a saccade to a target stimulus11 (Fig 1d,e and supplementary material). This varied from 5% to 36% across participants and is a stable trait (supplementary material).

The amplitude of the distractor effect correlated strikingly with GABA concentration measured by MRS in the region around FEF (Figure 2a; r=–.76, p=.004, 95% CI r=–.48 to –.91). We confirmed this by replicating the correlation in a separate cohort of nine participants (Figure 2a inset; r=–.65, p=.03 1–tailed, , 95% CI r=–.28 to –.95), and at the same time ruled out any influence of the FEF localising procedure on the MRS measure (supplementary material). Importantly, the correlations do not simply arise from differences in grey matter volume in the GABA voxel measured: there was no correlation between measured GABA concentration and percentage of grey matter in the voxel in either experiment (r<.1), nor between grey matter percentage and saccade distraction (r=–.2 expt 1, r=–.3 expt 2, r=.03 overall). Additionally, the correlation does not arise from the age of the participants: there was no significant correlation between age and GABA concentration in our samples (r=.19) and when controlling for age, the correlations between GABA concentration and saccade distraction remain strong (r=–.77, r=–.61).

As a control site, we also measured GABA in the visual cortex (supplementary methods). Perhaps surprisingly, GABA concentration in the visual cortex region did not correlate at all with GABA concentration in the region around FEF (Figure 2b; r=.003). This being the case, while GABA in the frontal region predicts saccade distractibility, visual cortex GABA would not be expected to. This was indeed what we found (Figure 2c; r=.3, p=.35). Thus individual differences in eye movement control appear to be attributable to differences in neurotransmitter concentration in a region that includes a brain area known to be a major contributor to eye movements, but not in a different region. More widely, these results indicate that GABA concentration appears to be regionally specific, and demonstrate that it is possible to study non-invasively in humans the relationships between neurotransmitter concentration in specific brain regions and basic behavioural variation.

The exact source of the relationship we find between GABA in the frontal voxel and the resolution of competitive eye movement decisions remains undetermined. Anatomically, it is

most likely to arise from the grey matter, which contains GABAergic synapses. Within the grey matter, we consider the FEF to be the most likely driver of this relationship because it has been repeatedly associated with eye movement control[3, 6], while the adjacent area has not, but the voxel size we used to ensure good quality individual MRS data precludes us from being able to state this categorically. In functional terms, it appears that higher GABA levels are associated with more efficient suppression of the influence of distractors specifically, rather than more general inhibition or caution, which would also be expected to influence overall response time and error rate, neither of which correlated with GABA (r=.08, r=–.06).

In physiological terms, naturally occurring individual differences in GABA may reflect differences in the number of GABA interneurons in certain regions, the number of synapses per neuron or simply differences in GABA concentration per synapse. Thus we should not expect natural variation to mimic the effects of pharmacological agents, which tend to manipulate the efficacy of GABA at the synapse rather than changing overall concentration, synapse density or cell numbers. We expect future research to clarify the relationship between natural variation and induced modulation of GABA, but we already have a hint that they are different: injections of the GABA antagonist bicuculline in monkey FEF produced greater variance in saccade latency 7, but in our data, although some participants were more variable in their response times than others, this did not correlate with natural differences in GABA concentration (r=.12). Studying naturally occurring GABA differences in restricted brain regions thus promises to offer different insights from studying the consequences of artificially manipulating GABA signalling in humans or animals.

More broadly, the reasons why humans differ from each other, even in basic mechanisms of sensory-motor behaviour, is crucial to our understanding of normal brain function, but it also has important implications for many clinical disorders where there appears to be a spectrum from “normal” to “pathological” without any clear boundary in between. GABA-mediated inhibition (interacting with other neurotransmitters, such as dopamine) has been implicated in many such disorders, including schizophrenia, epilepsy, anxiety, depression, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), autism and Tourette’s syndrome [7, 12, 13]. Furthermore, in many of these disorders there appear to be deficits or differences in basic motor or oculomotor behaviour14. In schizophrenia in particular, deficits of eye movement competition and inhibition have been reliably measured over two decades15, which, on the basis of our current findings, we predict may correlate with regionally specific GABA concentration.

In sum, we have demonstrated a link between individual variability in action control and neurotransmitter levels in a specific brain region. Moreover, our finding that GABA concentration may be regionally specific in the brain – an individual with low GABA in one brain area does not necessarily have low GABA in another area – is of crucial importance for the associations between GABA transmission and clinical disorders.

Figure 1. Methodology (example data from one individual). The bilateral activation of FEF revealed by fMRI (**a**,**b** red/yellow, see scale bar for t value) is used to locate the MRS voxel (green, 3x3x3cm^3), which was also aligned with the brain surface and remained anterior to the central sulcus. Edited MR spectra (**c**) allow the quantification of GABA concentration[8, 10] (glutamine/glutamate, Glx, and N-acetyl-aspartate, NAA, peaks are also marked). In the saccade distractor paradigm, **d,** targets (black) occur either alone or accompanied by distractors (light grey), which could appear at various delays before (as illustrated) or after target onset. **b** shows the characteristic rise and fall in the distractor effect as distractor onset time varies relative to target onset. The peak distractor effect for this individual (red star and dotted line) is extracted by fitting a Gaussian curve to the data 11. See supplementary information and supplementary figures S1–S4 for all participants.

Figure 2. GABA in the frontal region correlates with saccade distraction. Higher GABA concentration in the region around human FEF predicts smaller distractor effects across individuals (**a**). This result was replicated in a second cohort (inset). There was no correlation between the frontal GABA concentration and the control, occipital GABA concentration (**b)**, and GABA concentration in visual cortex did not correlate with the distractor effect (**c**).

Acknowledgements

This work was supported by the ESRC, the Wellcome Trust, the Wales Institute of Cognitive Neuroscience (WICN), and the Schools of Psychology, Biosciences and Chemistry at Cardiff University. CUBRIC was established with support from the UK Department of Trade and Industry, Cardiff University and the Welsh Assembly government. RAEE held an RCUK fellowship and acknowledges pulse programming advice from Gareth Barker and Dikoma Shungu. We thank also Fred Boy, Suresh Muthukumaraswamy, Benedict Taud, Masud Husain, Chris Chambers, Tom Freeman, Rob Honey and Laurence Wilkinson.

Author contributions

PS, RAEE and KDS conceived and planned the experimental study. RAEE, PS and CJE carried out and analysed the MR while PS and AB performed and analysed the behavioural experiments. All authors contributed to interpretation and presentation.

Competing interests statement: None.

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Journal: Nature Neuroscience

Article Title:	More GABA, less distraction: A neurochemical predictor of motor decision speed.
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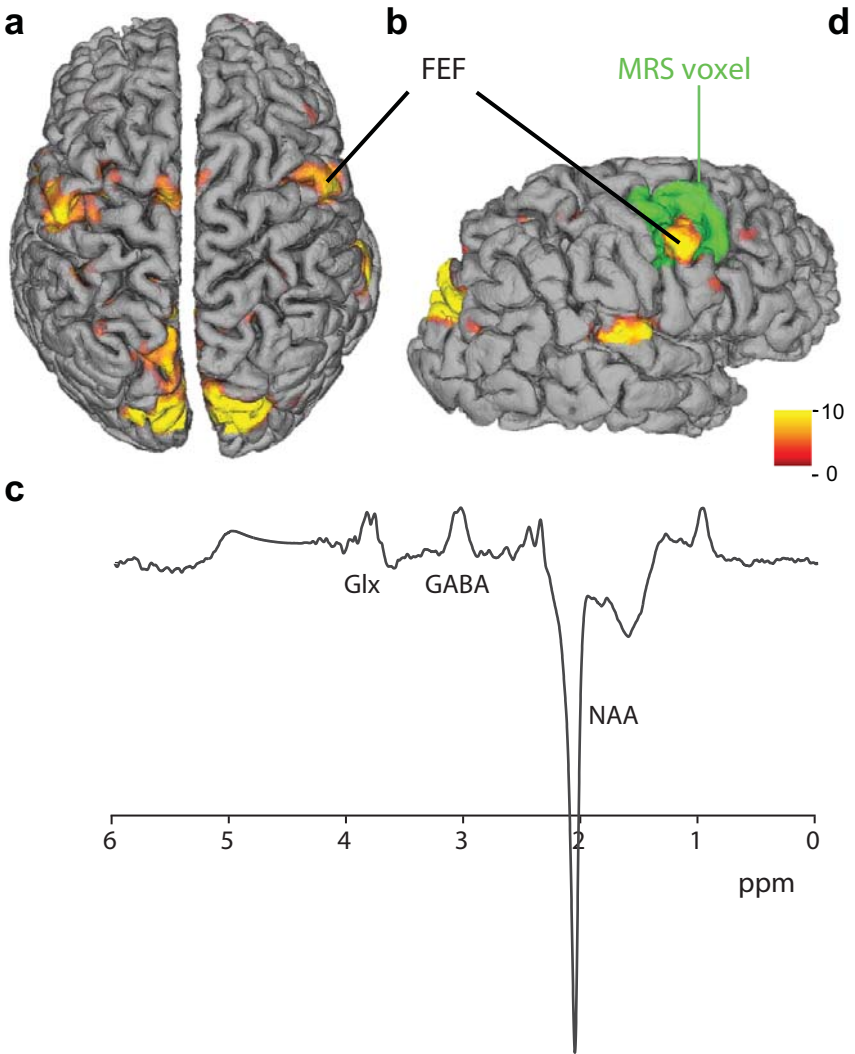
Supplementary Item & Number **(add rows as necessary)**	Title or Caption
Supplementary Figure 1	**MEGA-PRESS spectra robustly detect GABA in the frontal region.**
Supplementary Figure 2	**Individual spectra for experiment 2.**
Supplementary Figure 3	**Distractor effects for each participant (experiment 1).**
Supplementary Figure 4	**Distractor effects for each participant (experiment 2).**
Supplementary Figure 5	**Errors and latency.**
Supplementary Methods (or Discussion or Data or Note)	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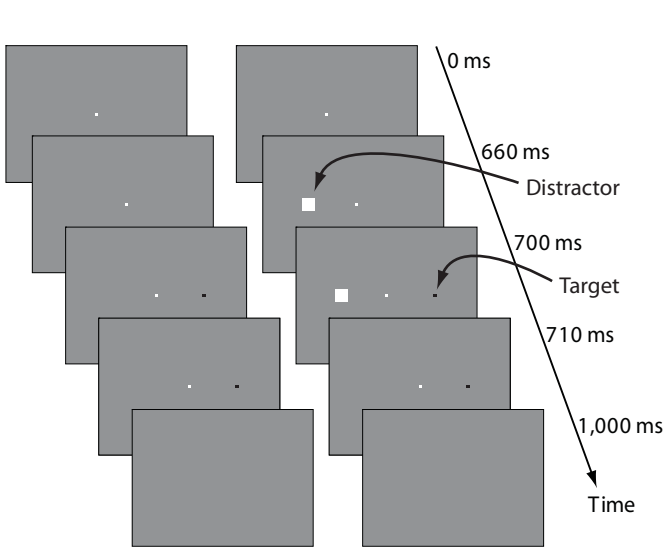
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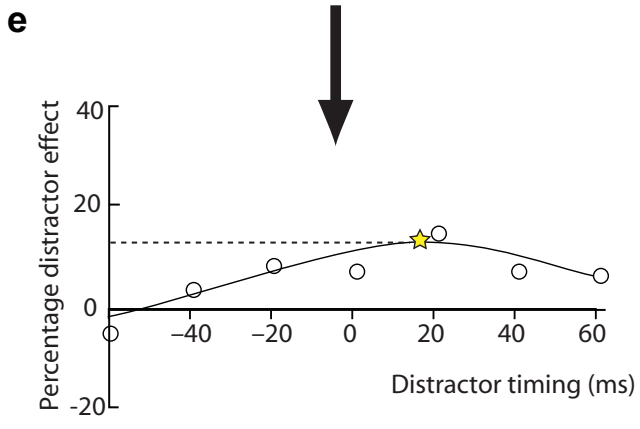
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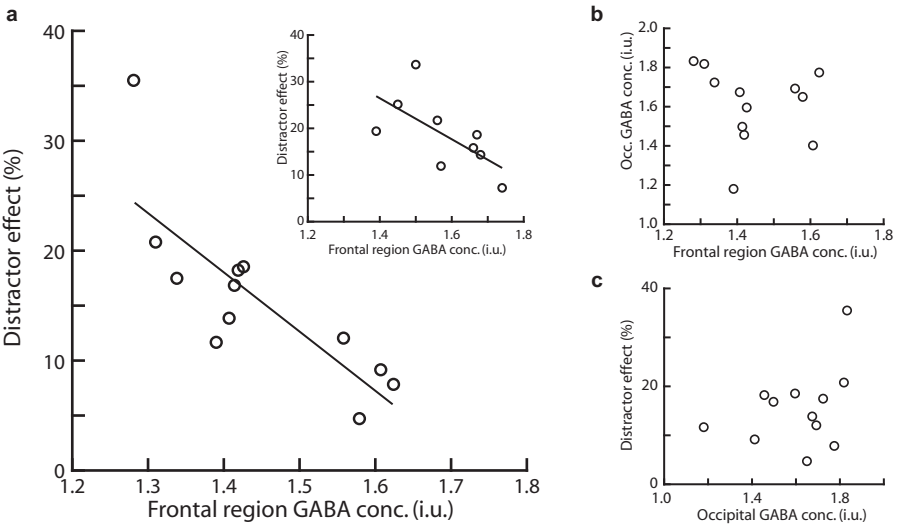
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Distractor effect (%)
Frontal region GABA conc. (i.u.)
Distractor effect (%)
Frontal region GABA conc. (i.u.)
b
Occ. GABA conc. (i.u.)
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c
Distractor effect (%)
Occipital GABA conc. (i.u.)