What causes tics in Tourette's syndrome?

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Model of focus in striatum discharging to release focal movement via inhibiton of pallidal output and disinhibition of thalamo-cortical projection (after Mink)

Activity time locked to tics is seen in several animal models of Tourette using bicuculline in striatum





A facilitatory, but not obligatory link between BG output and movement

Hikosaka & Wurtz

Fig. 4. Activities of a nigral cell during a delayed gazeorienting task.

Control of tics

- If the removal of inhibitory basal ganglia output does not necessarily produce an obligatory movement....
-then it is easy to see how tics could be suppressed by volitional effort
- It also means that the causes of tics might be separate from mechanisms used to prevent (suppress) tics
 - Should measures of behavioural inhibition correlate with the severity of tics (i.e. causal) or to the ability to suppress tics (i.e. prevention)?

Control of tics: behavioural measures

- Stroop task, flanker task, go-nogo task, stop signal task
- Some studies report a deficit in inhibitory control (Georgiou et al., 1995; Dursun et al., 2000; Ganos et al., 2014), others show no change (Crawford et al., 2005; Roessner et al., 2008; Jung et al., 2013; Fan et al., 2017) and some an enhanced control (Mueller et al., 2006; Jackson et al., 2007, 2011) relative to age-matched, healthy controls (Mazzone et al., 2010; Draper et al., 2014).
- Confused?!
- May not be very relevant if these techniques measure something related to tics suppression rather than tic expression.
- Jahanshahi et al (2015) distinguish between volitional versus automatic mechanisms of inhibition

New study of inhibition (Vishal Rawji)

- 19 patients with primary tic disorder and healthy matched control group
- Examined volitional and automatic inhibition (Jahanshahi et al, NRN 2015)
- Volitional: Conditional stop signal task
 - Measures of proactive and reactive inhibition
 - Drift diffusion modelling of strategy for response
 - TMS study of premovement build-up of corticospinal excitability
- Automatic: Masked priming task
 - Negative and positive compatibility effects
 - Errors

/			YGTSS Score							
	Patient	Age	Motor	Vocal	Severity	Impairment	Total	OCD	ADHD	Medication
	1	26	24	24	48	0	48	No	Yes	Sertraline
	2	43	10	8	18	10	28	Yes	Yes	Clonazepam
	3	59	9	0	9	40	49	Yes	No	None
	4	38	9	0	9	10	19	Yes	No	Melatonin
	5	23	18	18	36	30	66	No	Yes	Sertraline
	6	46	18	13	31	30	61	No	Yes	Paroxetine
	7	32	5	5	10	30	40	No	No	Iron
	8	30	16	16	32	30	62	No	No	None
	9	44	15	13	28	30	58	Yes	Yes	None
	10	48	9	9	18	20	38	Yes	No	Citalopram, Clonazepam
	11	29	8	17	25	20	45	No	No	None
	12	20	17	10	27	30	57	No	Yes	None
	13	20	12	22	34	40	74	Yes	Yes	None
	14	19	15	15	30	20	50	Yes	No	None
	15	36	17	15	32	10	42	No	No	Pimozide
	16	28	14	6	20	10	30	No	No	None
	17	26	14	8	22	20	42	No	No	None
	18	49	16	16	32	30	62	No	No	None
	19	50	9	0	9	10	19	No	No	None



Conditional stop signal task

- When people do not expect to have to stop (i.e. non-critical direction), their RTs are faster than when they have to stop, even in GO trials
 - This is called the response delay effect (RDE)
 - It is used as a measure of proactive inhibition (i.e. suppressing the tendency to respond because you think you will have to stop)

- The stop signal reaction time (SSRT) is the timing when participants can successfully stop on 50% trials
 - It is found by randomizing the timing of the stop signal after the GO



Reaction times in general were slower in the Tourette group

BUT their proactive inhibition (RDE) was the same as normal



It looked initially as if the SSRT was also slower in the Tourette group (i.e. like the GO reaction time)

BUT this effect was driven by 7 of the 19 patients who also had comorbid OCD (known to increase SSRT)

Volitional inhibition: summary

- Our measures of proactive and reactive inhibition were the same in the Tourette group as in the control group
- Combined with the very variable data in the literature, conclude there is not much wrong with volitional inhibition in primary tic disorder
- The ability to control tics is not necessarily related to the severity of tics, especially in adults.
- Hypothesise that volitional inhibition is not an effective way of controlling tics (i.e. preventing a release of inhibition provoking a movement): a better way would be via an automatic mechanism

Automatic inhibition: masked prime task (but see Stenner et al MDJ 2018)

- Participants do not perceive the prime but their responses are biased by it
- If the prime is compatible, then it speeds up the response to the stimulus if the stimulus is presented <100 ms after the mask
- BUT, if the stimulus is presented later, around 100-150 ms, then the response is delayed
- The prime produces an initial period of response facilitation but this is cut short by a period of response suppression
 - These are the positive and negative compatibility effects (PCE, NCE)





Reaction times on compatible (C) and incompatible (IC) trials. The important thing is the difference in RT between C and IC trials at each timing (SOA)



For Tourette there is no negative incompatibility effect at around 100-150ms as there is in the control group. (i.e. when the stimulus is presented 100ms after the mask, the RT is longer if the prime was compatible than if it was incompatible)

In fact, the Tourette are dominated by the positive compatibility effect.

They have a reduced efficiency of automatic inhibition.



Tourette group make more errors overall.

Discrimination errors are when the wrong button is pressed.

This is mainly because the Tourette group are more affected by the prime. Thus, in incompatible trials, they respond in the direction of the prime and make an error.

Motor tic severity correlates with discrimination and speed errors (p = 0.03)

Automatic inhibition: summary

- The Tourette group are more positively influenced by the prime than the control group
 - They fail to show a negative compatibility effect
 - And have a larger positive compatibility effect
- This leads them to respond more often in the direction of the prime even in incompatible trials
 - More discrimination errors in incompatible trials
- Patients fail to control the triggering influence of the prime
- Is the facilitatory action of the prime like the facilitation produced by a "tic discharge" in the striatum?