

## Supplementary descriptive results

### tDCS results for OCD

#### Pre-SMA/SMA

One randomised trial implemented polarity as the randomized aspect without a sham control [1]: if symptoms deteriorated from the randomized condition of anodal (A) or cathodal (C), polarity was switched (A-C or C-A), otherwise the condition was repeated (A-A or C-C). Two patients received A-A and improved by 6.6% on average, two received A-C due to deterioration from A, and then improved by 15% on average. All five patients randomized to cathodal received C-C and had a 20% improvement on average. Cathodal tDCS of the SMA in an open label cohort study led to 17% improvement and 15% response rate [2]. Cathodal tDCS of the pre-SMA led to either a 17% or 0% change in two patients [3].

A RCT of anodal tDCS over the pre-SMA led to improvement of 22% vs 12% from sham and a response rate of 33% vs 9% in sham [4]. An additional five sessions (open label) were provided for non-responders; those who entered from sham (n=11) did not improve further, and those from active (n=7) had a further statistically significant improvement, but there were no additional responders. Anodal tDCS over the pre-SMA and SMA led to individual symptom improvements of 40%, 46.7%, 69.5% [5,6]; one patient deteriorated by 12% and switching polarity to cathodal led to partial response with 29% improvement and 32% improvement at three month follow-up [7].

#### DLPFC

The open label trial of cathodal tDCS of bilateral DLPFC led to 65% improvement [8]. After five and ten days of treatment, mean improvements were 27% and 51% respectively, with further improvement to 81% at three-month follow-up. A case report showed 9% change from cathodal tDCS over the left DLPFC in a blinded and sham controlled protocol [9]. Anodal stimulation of the left DLPFC and cathodal over the right DLPFC led to 22% improvement in a single patient [10].

## OFC

An open label study of five patients used cathodal stimulation of the right OFC and anodal of the left DLPFC. There was an initial 23% improvement in OC symptoms but a 2% deterioration was noted at one month follow-up, yet improvements in depression (31%) remained [11].

Cathodal tDCS of the left OFC assessed in a RCT led to 5% improvement and 2% deterioration in sham, and response in 20% vs 9% in sham [12]. The same montage within an open label study, was associated with a 22% improvement and 26.5% response rate, which increased to 38% at three-month follow-up [13]. Cathodal stimulation of the left OFC and anodal stimulation of the right OFC has been investigated in two case studies, with one patient recording no response immediately following treatment, and a partial response (26%) two weeks later [14]; the other had a 56% improvement in symptoms post-treatment, and 65% two weeks later [15].

## tDCS results for TS

### Motor targets

tDCS targeting the pre-SMA led to individual improvement of 41% (partial response of 23% was reached after just 5 days of therapy), and efficacy was maintained six-months later [16]. tDCS of the SMA in two patients led to improvements of 34% and 20.5%, which increased to 43% and 29% at three-month follow-up [17]. When tDCS was applied to both the pre-SMA and SMA, YGTSS score improvements of 34%, 13% and 5% occurred in three patients, yet tic counts increased in all patients by up to 200% in one of them [18]. tDCS of the primary motor cortex in two patients within a randomized controlled protocol led to 30% and 11% vs 5% and 5% from sham [19].

## TMS results for OCD

### DLPFC

Two RCTs targeted bilateral DLPFC, with HF active rTMS being associated with 37% and 27% symptom improvement when administered prior to, and following sham, respectively; sham led to no change, and 3% deterioration when administered prior to and following active stimulation, respectively [20].

Also, alpha guided frequency rTMS of bilateral DLPFC led to improvement of 32% vs 15% with sham; response rates were 36% vs 0% [21]. When laterality of HF rTMS of DLPFC was examined in an RCT, improvements of 26% from left and 37% from right rTMS were achieved with a comparable response rate of 33% [22].

A RCT of LF rTMS targeting left DLPFC showed improvements of 24% vs 16% with sham, yet at two-week follow-up 28% change from baseline was found in both groups [23]. The pre-treatment severity scores were significantly higher in the active group, such that the absolute but not relative change was greater in those patients. A case report achieved response from LF rTMS of the left DLPFC, but the degree of change was not reported [24].

A RCT of HF rTMS of the left DLPFC led to response in 30% vs 25% in sham. All patients received an extra 10 sessions (open label) with 33% of the entire sample achieving response [25]. Badawy and colleagues performed a non-randomised trial with three arms; medication naïve, and medicated (but SSRI resistant) patients both received HF active rTMS targeting the left DLPFC, while medication naïve patients received sham [26]. Response was achieved in 55% of those who received rTMS combined with SSRI treatment, 25% who received rTMS and were un-medicated, and 5% who were delivered sham; mean change was 20%, 8%, and 5% respectively.

Three RCTs administered LF rTMS of the right DLPFC. Response rates following active and sham were 20% vs 12.5% [27], 50% vs 23% [28], and 20 vs 20% when combined with LF rTMS of SMA [29]. Mean symptom improvements were 14% in active, 1% in sham [27]; 8.6% in active, 6.8% in sham [29], or 11 points in active and 4 points in sham [28]. In a single patient, 10 sessions (4 weeks) of continuous TBS

of the right DLPFC led to a 58% improvement, but subsequent intermittent TBS led to no further improvement in OC symptoms [30].

A RCT of HF rTMS of the right DLPFC led to response rates of 31% vs 14% in sham [31]. The same montage in a single blind non-randomised, sham-control trial led to improvements of 9.4% vs 7.3% from sham, which increased to 19.4% and 17.6% at one-month [32].

When frequency of the right DLPFC was examined within a RCT, symptom improvement reached 45% for LF, 27% for HF and 5.6% for sham conditions; at three-month follow-up, respective improvements from baseline were 41%, 10% and 8% [33].

#### Pre-SMA/SMA

RCTs achieved response rates from active and sham of 22% and 11% [34], 42% and 12% [35], 80% and 8.3% [36], 10% and 20% [37], and 32% and 18% [38]. Mean symptom changes associated with active and sham were 25% and 12% [34], 42% and 16% [35], 40% and 6% [36], 8% and 10% [37], 23% and 16% [38]. Mantovani (2010) showed that an additional 20 rTMS sessions (open label) following 20 closed label active sessions within a subgroup of four patients, achieved an overall symptom improvement of 49% and all four met response criteria, maintained at three-month follow-up.

LF rTMS targeting the SMA was compared to treatment as usual (TAU) in a randomised open label trial, and led to response in 68% vs 24% from TAU, with symptom change of 30% and 19%, respectively [39]. Open label investigations of the SMA reported response in 60% [40], and mean improvement of 34% [41], and 17% [42]. Case studies of pre-SMA stimulation showed improvements of 27%, 35% and 54% [43-45]; and 76% from right SMA stimulation [43].

In an open label trial, LF rTMS study, the SMA was targeted for OCD symptoms and right DLPFC for comorbid MDD (in 22/25 patients), achieving a response rate of 83% with mean symptom improvement of 42% [46].

One RCT investigated continuous TBS of the pre-SMA, with response in 29% vs 36% in sham; symptom improvements were 13% and 17%, respectively [47].

### OFC

Left OFC treatment led to response in 25% vs 0% in sham, and symptom improvement of 19% vs 7% in sham [48]. At 10-week follow-up, improvements were 21% and 8% in sham. Right OFC treatment using deep TMS led to improvements of 19% vs 6% in sham, but improvements had abated at one-month follow-up [49]. A retrospective investigation of left OFC showed response in 44%, and mean symptom improvement of 24%, which were maintained at one-month follow-up [50].

A large retrospective report used LF rTMS to target the SMA (n=46) or OFC (n=33), with the choice of target resting with the patient. Across the whole cohort, 27% improvement and 41% response was reached; there was no statistical effect of target, with 39% response from SMA, and 43% response from OFC [51].

### Other frontal targets

Randomised controlled investigations of HF deep TMS targeting the medial PFC and ACC led to response in 44% vs 7% in sham [52] and 45% vs 12% in sham [53]. Open label applications of LF rTMS of the medial PFC led to mean symptom improvement of 39% [54] whilst 40% improvement was achieved in a study of HF rTMS of the dorsal medial PFC [55]. There was no effect of LF rTMS of the primary motor cortex in a single patient who received rTMS and tDCS treatment [9].

## TMS results for TS

### SMA

Response for active and sham conditions within RCTs were 50% vs 50% using TBS [56], and 33% vs 18% with rTMS [57]. In the latter study, an additional 15 sessions (open label) were administered to 7 participants from the active condition, of which 71% responded; and 9 patients from the sham condition, 44% responded [57]. Open label investigations showed improvements of 34%, 30% and 4.6% [58-60]; in the two former studies, efficacy was sustained at three and six months.

Two case series of LF rTMS of the SMA reported mean improvement of 67% in four patients [40], with individual improvements of 36% and 68% [61]. The patient with 36% improvement relapsed and required additional treatments for efficacy to be maintained one-month later, and the patient with 68% improvement sustained 57% improvement at four month follow-up. Another patient improved by 18% from two rTMS sessions of the pre-SMA [62].

### Motor cortex

A small RCT of five patients [63] applied two LF treatments to the pre-motor cortex; bilateral or left stimulation did not affect OC symptoms ( $\leq 2.5\%$  change). Another pilot RCT applied a different protocol each day to assess high and low frequency treatment of the motor cortex, or PFC [64]: high frequency stimulation of the PFC showed superiority, with 29% improvement. However, sham led to 22% improvement.

## TMS results for OCD

One RCT investigated LF rTMS of the pre-SMA for skin picking, symptom improvement of 36% was achieved, but two of the five patients in the active group were lost to follow-up and the remaining three worsened between 70-110% at three-month follow-up [65]. A case study of LF rTMS of right DLPFC achieved a 30% symptom improvement for one patient with hoarding disorder, that maintained at two-month follow-up [66].

## DBS results for OCD

### Multiple targets within a cohort

Once RCT systematically compared two targets within six patients by implanting leads in the VC/VS and amSTN; the stimulation target was the control rather than a sham condition [67]. DBS of the VC/VS led to 53% improvement and 83% response rate; DBS of the amSTN led to 45% improvement and 50% response rate; and DBS of both the VC/VS and amSTN led to 60% improvement and 83% response rate.

Open label comparison of NAc or BNST DBS within a cohort led to 12% and 39% improvement at six months, respectively [68], and in a different cohort there was 23% and 24% improvement at long term (8-54 months) follow-up [69].

### NAc

Randomised controlled investigations led to improvements of 13% vs 3% from sham [70], and 51% vs 25% from sham [71]. The most recent RCT achieved 85% response, yet response from sham was not reported [71]. Outcomes of one RCT are addressed in the Discussion, as adjunct CBT was involved; rather the open label outcomes are reported here.

Across three cohorts, follow-up improvements reached 12% (6-months), 21% (6-months), 25% (8-months) and 33% (12-months) [70,72,73]. Response rates of 40% (70% partial) and 10% (50% partial) were achieved from 12 months of DBS [70,73].

Case reports of three patients led to individual improvements of 69% at 8 months, 34% and 42% at 24 months [74,75]. Another patient cycled through periods of no change and deterioration by 13% across 30 months [76]. No studies reported that patients had DBS explanted or switched off.

### ALIC

Closed label treatment led to improvements of 43% vs 8% with sham, response in 75% vs 0% with sham [77], also improvements of 20% vs 11% with sham, response in 25% vs 0% with sham [78].

Staggered switch on, at 30- or 60-days following surgery did not affect 12-month outcomes and led to 50% response [79].

Long-term outcomes showed improvements of 43%, 53% (12-months), 56% (21-months) and response in 58%, 67% (12-months) and 67% (6-9 years) across three cohorts [77,79-81]. When the best outcome was reported in the cohort of Abelson (2005) between 4-23-months, 30% mean change was achieved. Case reports showed individual improvements of 19%, 68% and 79% after 12-months [82,83].

Out of 19 patients, two had their devices explanted at 4 and 15-months following surgery, one had their device switched off (timing not reported), and one patient completed suicide 9-months following surgery [77,78,80].

### VC/VS

The multi-site RCT originally targeted the ALIC, and the first few implants are reported in Nuttin (2003) within the ALIC outcomes outlined above. Across implants the target was refined and shifted more posterior, targeting the VC/VS. The closed label phase with these latter implants led to improvements of 42% vs 11% from sham, and response in 70% vs 26% from sham [84]. Other reports of the same cohort as Luyten (2016) showed improvements of 28% (n=10) at three-months, 36% (n=10) and 39% (n=26) at three-years [85,86]. Across the entire cohort, 28% reached response at one-month, and 62% reached response at three-years [86].

Four patients showed mean improvement of 33% at 15-months [87], and in a separate study all four participants achieved response, with a mean improvement of 60% at two-years [88]. An additional patient had 31% improvement at one-year yet developed compulsive picking around the battery eventuating in re-implantation; eight-months later, improvement from initial pre-op baseline, was 11% [89].

Out of 41 patients, six were no longer receiving DBS at four-years within the Luyten (2016) cohort, three had their DBS switched off, and three had DBS explanted and subsequently underwent capsulotomy. Out of these six patients, 50% had chronic active contacts within the ALIC and 20% had chronic contacts within the BNST.



## amSTN

In the closed label phase, there was a median improvement of 25% vs 4% with sham, and response rates of 75% vs 38% with sham [90]. There was a significant order effect, active-sham conditions led to 37% improvement and then 8% deterioration; and sham-active conditions led to 16% improvement, then an additional 14% improvement. At 16 and 48-months follow-up mean improvements were 35% and 51%, respectively [91], the response rate was comparable to closed label phase (75%); however, the criterion increased from 25% to 35% YBOCS reduction between the open and closed label phases. Within this study, two patients withdrew due to lack of efficacy [91].

## Other targets

Investigations of BNST DBS encompassed one RCT, in which closed label treatment was associated with 43% improvement (50% response), but sham outcomes were not reported [92]. Investigations of ITP DBS involved one open label trial, in which 12-months of treatment led to 52% improvement and all 5 patients were considered responders [93]. One patient had the DBS electrodes explanted despite 51% improvement. The superolateral MFB was targeted in two patients, with 33% and 50% improvements at 12 months [94]. The thalamus (medial dorsal and ventral anterior nucleus) was targeted in four patients: outcomes for one patient were not reported; one had no symptom change and the device was explanted at 6-months; and the other two did not reach response (11% and 17% improvement) [95].

## DBS results for TS

### Multiple targets within a cohort

Within a cohort, midline thalamic nuclei DBS achieved mean improvement of 45% (n=4), pv-GPi DBS achieved mean improvement of 32% (n=2), and DBS implanted in both targets achieved mean improvement of 36% (n=2) [96]. There were 37.5% responders, all of whom had been implanted in the thalamus; follow-up periods varied between 6 and 95-months.

A randomised controlled case series targeted the CM-Pf thalamus, GPi, and both targets, each leading to 45%, 78%, and 60% improvement respectively; sham outcomes were not reported [97]. Similarly, in

one patient, DBS of the CM-Pf thalamus, amGPi, and both targets achieved 62%, 59%, and 63% improvement respectively, and 21% deterioration from sham [98].

Four patients were implanted with both GPi and lateral STN DBS and improved by 15-49% at six-months, although one patient withdrew due to limited efficacy [99]. Lastly, one patient implanted with CM-Pf thalamic and NAc DBS led to 84% improvement at 1-year [100].

## Thalamus

*(Centromedian (CM) thalamus; centromedian-parafascicular complex (CM-Pfc) thalamic nuclei; centromedian nucleus- substantia periventricularis - nucleus-ventro-oralis (CM- SP- VOA); centromedian-parafascicular and ventralis oralis complex (CM-Pf- VOA)*

The RCT showed CM-SP-VOA thalamic DBS led to improvements of 40% vs 3% with sham, and response in 66% vs 0% sham [101].

Open label CM-Pf thalamic DBS led to improvement of 44% and response in 60% (3 out of 5) patients at three-months [102,103]. CM thalamic DBS led to improvement of 19% and no responders at 6-months [103]. Another investigation of ventral anterior and ventrolateral thalamic DBS led to improvement of 55% at 6-months, which was maintained at 12-months [104].

A long-term investigation of CM-Pf-VOA thalamic DBS showed improvements of 52% at two-years, increasing to 73% at 5-6 years [105-107]. Two-years of CM thalamic DBS led to 30% improvements and 40% response in a pilot study [108]. The RCT targeting the CM-SP-VOA achieved 49% improvements at one-year, with response in all 6 patients [101]. Two retrospective reports of CM-Pfc thalamic DBS led to 30% improvement and 60% response at one-year [109], and 54% improvement and 63% response at last follow-up (2-91 months, mean 26-months) in another cohort [110].

Case studies showed that seven out of eight patients reached response, with long term improvements (8-months to 35-months) ranging from 49% to 81% [111-115]. Overall, of the 76 patients, three had the DBS switched off, one had additional leads implanted within the GPi, and one had initial leads placed within the ALIC and re-implanted in the thalamus [106,111].

## Globus pallidus internus

*(anterior globus pallidus internus (a-GPi); anterio-medial globus pallidus internus (am-GPi);*

*posterolateral globus pallidus internus (pl-GPi); posteroventral globus pallidus internus (pv-GPi)).*

Randomised controlled investigations of a-GPi DBS (including two patients with comorbid dystonia who instead received pv-GPi DBS) showed mean improvement of 22% vs 8% with sham [116]. Another investigation led to 10% improvement vs deterioration of 4% from sham, and response in 29% compared to 22% in sham, although the response criterion (25% improvement) was relatively liberal [117].

Open label am-GPi DBS led to 47% and 50% improvement at one and three-months respectively, and response in 55% [118]. When follow-up outcomes were reported in the same cohort with an additional six patients, improvements reached 44% at six-months and 54% at last follow-up (8-46-months) with 71% responders [119]. Two cohorts who received 12 months of a-GPi DBS achieved 63% [120] and 40% improvements [117]; the latter cohort reached 48% improvement and 75% response at 30 months [121]. A retrospective report of pl-GPi DBS led to 14% and 55% improvement at 6 and 36-months, respectively, and response in 69% [122].

Across 11 case reports 20 patients were included; with the exception of five patients from two sites [123,124] all achieved response, and improvements were between 47%-95%. Non-responders had implants within the posterior or anterior GPi.

Out of 87 patients, one was explanted at one week, one had DBS switched off following repositioning, two withdrew prior to switch on, three withdrew prior to the closed label phase, and one underwent repositioning at 18 months due to limited efficacy [116,117,124].

## Other targets

One patient was implanted with globus pallidus externus (GPe) DBS; at three-months 58% improvement was achieved, which increased to 71% at six-months [125]. The battery depleted at a year, with the patient experiencing a partial relapse (to 38% improvement from baseline).

One patient achieved 25% symptom reduction after 18 months of ALIC DBS [126]. Another patient achieved 41% improvement and remission from 30-months of NAc DBS, but short term outcomes were not reported [127]. amSTN was targeted in one patient, in whom three-months of therapy led to 29% improvement; after three-years, 92% improvement was reached [128].

## DBS results for BDD

One BDD patient received VC/Vs DBS, and 21% improvement was reached after three-months. Leads were replaced at six-months due to inflammation, and three-months after re-implantation improvement relative to initial baseline was recorded as 35% [129].

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