

# Clinical Neurochemical Implications of Sleep Deprivation's Effects on the Anterior Cingulate of Depressed Responders

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*The antidepressant and cerebral metabolic effects of total sleep deprivation (TSD) or partial sleep deprivation (PSD) for one night has been studied with functional neuroimaging in seven publications from five different groups. Despite the variations in methods and techniques, the over-all findings were relatively consistent. First, before sleep deprivation, responders have significantly elevated metabolism compared with non-responders and normal controls, in the orbital medial prefrontal cortex, and especially the ventral portions of the anterior cingulate*

*cortex. Second, after sleep deprivation, these hyperactive areas normalize in the responders. One functional imaging study suggested that synaptic dopamine release was associated with the antidepressant effects of TSD. The neurochemical implications of these findings are explored. Possible dopaminergic and serotonergic mechanisms are discussed.*

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Sleep deprivation is an effective and rapid antidepressant in a subset of depressed patients (Wu and Bunney 1990). Functional brain imaging studies have consistently found that one of the markers that differentiates depressed responders from depressed nonresponders at baseline is higher cingulate activity in the responders which is decreased with sleep deprivation response. Ebert et al. (1991) first reported this finding in a SPECT scan study of 10 patients (See Table 1). Our group first reported this finding of higher glucose metabolic rate with PET scans in depressed responder back in 1992. This initial finding was subsequently extended to a larger group

of depressed patients (Wu et al. 1999). We reported that depressed responders were higher at baseline in the medial prefrontal cortex, ventral anterior cingulate and posterior subcallosal gyrus than depressed nonresponders.

To summarize all the findings from functional imaging studies (positron emission tomography (PET) or single photon emission computerized tomography (SPECT) with hexamethyl propylene-amine-oxime (HMPAO) (Table 1)), four different groups with a total of five published studies reported that responders had increased relative localized metabolic activity in the general location of the ventral anterior cingulate cortex (ACC) compared with non-responders or normal controls at baseline: (Ebert et al. 1991, 1994a; Volk et al. 1997; Wu et al. 1992, 1999), and Holthoff et al. (1999). (In the two groups which did not report this finding, Volk et al. (1992) did not examine subcortical areas in his study, and Smith et al. (1999) had only six patients and could not compare responders and non-responders at baseline since all the patients tended to improve.) Second, all five studies in which four groups compared patients both pre- and post-sleep deprivation reported that

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**Table 1.** Functional Imaging Shades of Sleep Deprivation

Author	Year	No. of Depressed patients	Depressed Responder	Controls	Imaging	TSD or PSD	Findings
Ebert	1991	10	5	8	spect	tsd	All depressed hypoperfused in lt anterolateral prefrontal cortex before and after sd Resp show hyperperfusion in limbic system at baseline Resp show reduction in limbic region after SD
Volk	1992	20	11		spect	tsd	Resp show sig lt temporal and rt parietal increase after SD
Wu	1992	15	4	15	Pet	tsd	Resp > Nonresp or normal controls in cingulate metabolism Resp showed decrease in cingulate to normal levels after SD
Ebert	1994	20	11		spect	tsd	Resp > Nonresp in rt ant cing and rt and lt ofc perfusion at baseline Resp also hyperperfused in hippocampus at baseline
Ebert	1994	10	5		spect	tsd	Resp show sign decrease of d2 rec occupancy compared to nonresp after SD
Volk	1997	15	9		spect	psd	Resp > Nonrsp in rt ofc/basal ganglia perfusion at baseline Rt ofc/cing perf before psd and left inf temporal perfusion after PSD were accurate predictors of change in Hamilton
Holthoff	1999	14	8		spect	tsd	Resp > nonresp in ant cing perfusion at baseline Resp show decrease in ant cing perfusion to normal levels after SD baseline, all pts show hypoperfusion in left PFC vs. rt responders show normalization upon remission
Smith	1999	6		6	Pet	tsd	Depressed pts show reduction in ant cingulate (BA24) after SD Reduction persist after recovery sleep and after antidepressant tx
Wu	1999	36	12	26	Pet	tsd	Resp > Nonresp in ant cingulate (BA24), medial prefrontal cortex (BA32), and posterior subcallosal gyrus (BA25) at baseline Resp decreases in MPFC (BA32) after SD

TSD = total sleep deprivation

PSD = partial sleep deprivation

clinical improvement was associated with normalization of the increased metabolic activity in the general area of the ventral anterior cingulate/medial prefrontal regions (Wu et al. 1992, 1999; Ebert et al. 1991; Volk et al. 1997; Holthoff et al. 1999). Consistent with this, in the Smith et al. (1999) study, the whole group improved and metabolic rate in the anterior cingulate decreased significantly after sleep deprivation compared with baseline.

In three sleep deprivation studies clinical improvement correlated significantly with metabolic activity in specific areas. Volk et al. (1992) reported that the higher the baseline (HMPAO) perfusion in orbitofrontal region and left temporal cortex prior to PSD, the greater the clinical improvement post-PSD. (Limbic structures were not studied.) Using multiple regression, Volk et al. (1997) reported a somewhat similar finding: the greater the HMPAO activity in the right orbitofrontal cingulate pre-PSD and in the left inferior temporal cortex post-PSD, the greater the clinical improvement post-PSD. Finally, Wu et al. (1999) reported that the greater the reduction in local cerebral glucose metabolic rate (LCGMR) in left medial prefrontal cortex and the greater the increase in the left temporal cortex, the greater the clinical improvement in clinical ratings post-TSD compared with pre-TSD ratings.

In another method, using SPECT with a dopamine 2 receptor ligand (IBZM), Ebert et al. (1994b) reported that responders had significantly greater displacement of D2 ligand after sleep deprivation compared with nonresponders, suggesting that sleep deprivation mobilizes the dopaminergic system in responders.

Some, but not all, functional imaging studies with antidepressant medications have reported similar findings to those with TSD or PSD. Mayberg et al. (1997) reported that metabolic activity in ventral anterior cingulate was elevated before treatment and reduced after clinical improvement in responders to antidepressant medications. Buchsbaum et al. (1997) also noted that the antidepressant benefits of sertraline were decreased cingulate metabolism in depressed patients. Recently, these concepts were confirmed with a new methodology. Pizzagalli et al. (2001) reported that increased EEG theta activity in anterior cingulate during the pretreatment period predicted clinical antidepressant response in 18 patients with major depression following 4–6 months treatment with nortriptyline. Theta activity in anterior cingulate was inferred from topographical cortical EEG sites by a method called low-resolution electromagnetic tomography (LORETA), which computes

the 3-dimensional intracerebral distributions of current density for specific EEG frequency bands. Pre-treatment theta activity in the medial frontal region extending to anterior cingulate gyrus (BA 24 and 32) correlated positively with percent improvement on the Beck Depression Inventory after treatment.

The anterior cingulate has been hypothesized to play a significant role in affect and cognition (Devinsky et al. 1995). The anterior cingulate can be subdivided into several regions including the infralimbic or posterior subcallosal region (BA25) which is considered the cortical center of the autonomic nervous system which may regulate visceral motor response to stressful behavioral or emotional events. Afferents to the infralimbic regions include the amygdala, the hypothalamus and the thalamic paraventricular nucleus.

Reduced neurotransmission of dopamine and serotonin may be responsible for elevated metabolic rate in anterior cingulate in responders compared with nonresponders at baseline. Both neuroanatomical and neurochemical evidence suggest that the anterior cingulate is innervated by both the dopamine and serotonin system. Serotonin transporters, serotonin receptors, serotonin synthetic enzymes, serotonin release, dorsal raphe afferents and functional markers of response to serotonin (e.g. immediate early genes, metabolic PET response to serotonin are present in the anterior cingulate). Benedetti et al. (1999) noted that the long variant of 5HTT-linked polymorphisms was associated with better mood amelioration with sleep deprivation. The long variant is associated with increased density of the 5HT transporter.

Evidence for dopaminergic input into cingulate comes from retrograde tracing studies, dopamine synthetic enzymes, and electron microscopic studies of dopamine axon varicosities in the cingulate. PET evidence of functional dopaminergic response, dopamine receptors, and dopamine transporter presence have also been found in anterior cingulate.

Dopaminergic activity may inhibit absolute metabolic activity in anterior cingulate. Both cocaine and amphetamine administration reduced the rate of cerebral glucose metabolism. If dopaminergic activity is inhibitory, then decreased dopaminergic firing in responders at baseline could disinhibit metabolic rate in the anterior cingulate.

Mobilization of the dopamine and serotonin system could hypothetically be associated with decreased metabolism in the anterior cingulate seen in responders following sleep deprivation. Most metabolite studies, neuronal firing studies, and human pharmacological studies suggest that sleep deprivation enhances the serotonergic system (Asikainen et al. (1997). Serotonergic dorsal raphe neuron activity was increased in cats after sleep deprivation (Gardner et al. 1997). Pindolol (a 5HT<sub>1a</sub> autoreceptor blocker) enhanced antidepressant

response to total sleep deprivation in bipolars and blocked short term relapse (Smeraldi et al. 1999). Total sleep deprivation was facilitated by paroxetine in elderly depressed patients (Bump et al. 1997). SSRIs reduce anterior cingulate metabolism and this reduction was correlated with improvement in obsessive-compulsive symptom improvement.

Other studies, however, including metabolite, neuroendocrine effects, and human clinical studies, provide conflicting evidence for how the serotonergic system is affected by sleep deprivation. Rapid tryptophan depletion, which decreases brain serotonin concentration, had no acute effect on the antidepressant benefits sleep deprivation (Neumeister et al. 1998). Tryptophan depletion actually prevented depressive relapse suggesting that the serotonin system might actually contribute to depression. Sleep deprivation in rats resulted in reduced serotonin and 5HIAA in the frontal cortex (Borbely et al. 1980). Citalopram-stimulated prolactin release was blunted after sleep deprivation in healthy male subjects, suggesting downregulation of the serotonergic system with sleep deprivation. Fenfluramine increased metabolism in anterior cingulate in normal controls suggesting that the serotonin system activates anterior cingulate. If this relationship were true in depressed patients, then decrease in anterior cingulate metabolism with sleep deprivation would be associated with decrease in serotonin system.

Evidence from both animal and human studies suggests that sleep deprivation activates that the dopaminergic system (Ebert et al. 1996; Ebert and Berger 1998). Human psychophysiological studies have been conducted using blink rate in depressed patients, retinal pigment epithelial light adaptation in Parkinson's disease patient, and light adapted corneofundal potential in depressed responders which are suggestive of increased dopaminergic function. In a study of TSD in depressed and normal control subjects, concentrations of homovallic acid (HVA), a metabolite of dopamine, in spinal fluid increased from pre to post-sleep deprivation in responders but not in nonresponders or controls (Gerner et al. 1979). TSD also improved symptoms of rigidity, bradykinesia and gait in patients with Parkinson's disorder for two weeks; these intriguing findings suggestive that the dopamine system is activated by sleep deprivation. (DeMet et al. 1999)

Other studies challenge the role of the dopamine system in the antidepressant effects of sleep deprivation. Amineptine, a dopamine agonist, blocked rather than enhanced the antidepressant effect of sleep (Benedetti et al 1996). Nevertheless, the possibility that amineptine blocked an upregulation of D2 postsynaptic receptor in the responders has been suggested.

The role of the cholinergic system in the antidepressant effects of sleep deprivation are basically unknown. Cholinergic projections from brainstem initiate and

help to maintain cortical arousal during wakefulness and REM sleep. Prolonged wakefulness would presumably enhance duration of cholinergic neurotransmission. In addition to cerebral cortex, the cingulate gyrus receives cholinergic input from basal forebrain, but we are not aware of data implicating cholinergic mechanisms in sleep deprivation in depressed patients. Nevertheless, the cholinergic-aminergic imbalance hypothesis suggests that depression results from an increase ratio of cholinergic to aminergic neurotransmission in critical areas of the brain.

This review has focused on the role of dopamine and serotonin in the antidepressant effects of sleep deprivation, largely because these are the neurotransmitters which have been implicated in the mechanism of action of current antidepressant medications and by aminergic hypotheses for the pathophysiology of depression. These studies reviewed here provide some weak evidence suggesting that an underactivation of serotonergic and dopaminergic activity at baseline in the anterior cingulate cortex of depressed responders. Sleep deprivation could increase serotonergic and dopaminergic neurotransmission in the anterior cingulate of depressed responders and might be responsible for the antidepressant benefits. Nevertheless, this hypothesis is far from proven. Even if the evidence were compelling, it might be very surprising since the antidepressant effects of sleep deprivation occur much more rapidly than those of antidepressant drugs, ECT, bright light therapy, psychotherapy, or other established antidepressant treatments. It is not uncommon to see as much antidepressant improvement following 6–12 hours of sleep deprivation as that typically seen after 4–6 weeks of conventional antidepressant treatment. None of the established treatments, which presumably work through the aminergic systems, achieve significant antidepressant effects within hours or even days. Most treatments require 2–6 weeks for antidepressant benefits. The rapid, dramatic, and well established evidence-based antidepressant effect of sleep deprivation might reveal new mechanisms of action for novel treatments; drugs, for example, that act quickly.

Functional imaging studies of sleep deprivation first suggested in 1991–1992 (Ebert et al. 1991; Volk et al. 1992; Wu et al. 1992) that elevated cerebral metabolism in the anterior cingulate gyrus was a predictor of antidepressant response; furthermore, clinical improvement was associated with decreased metabolic activity there. As reviewed here and elsewhere (Gillin et al. 2001), all the functional brain imaging studies of sleep deprivation have shown these relatively consistent findings. As mentioned briefly, some but not all antidepressant medication studies with functional brain imaging have had results which are consistent with the sleep deprivation findings. Whether or not all antidepressant treatments should fit this model remains to be seen but it

should not necessarily do so since different therapies may have quite different mechanisms of action. These functional imaging studies of antidepressant therapies have identified localized areas within the medial orbital prefrontal cortex and anterior cingulate which are of great interest to understanding the pathophysiology and treatment of depression. Subtyping of depressed patients using functional brain imaging is just beginning. Further research could eventually lead to more rapid categorization of depressed patients with potentially beneficial enhancement of the appropriate selection of treatment.

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