NEUROFIT SAS

Pre-Clinical CRO

CNS & PNS preclinical Services

Distinct neural effects of psilocin, ketamine, and LSD compared to other psychedelics

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Introduction / Objectives

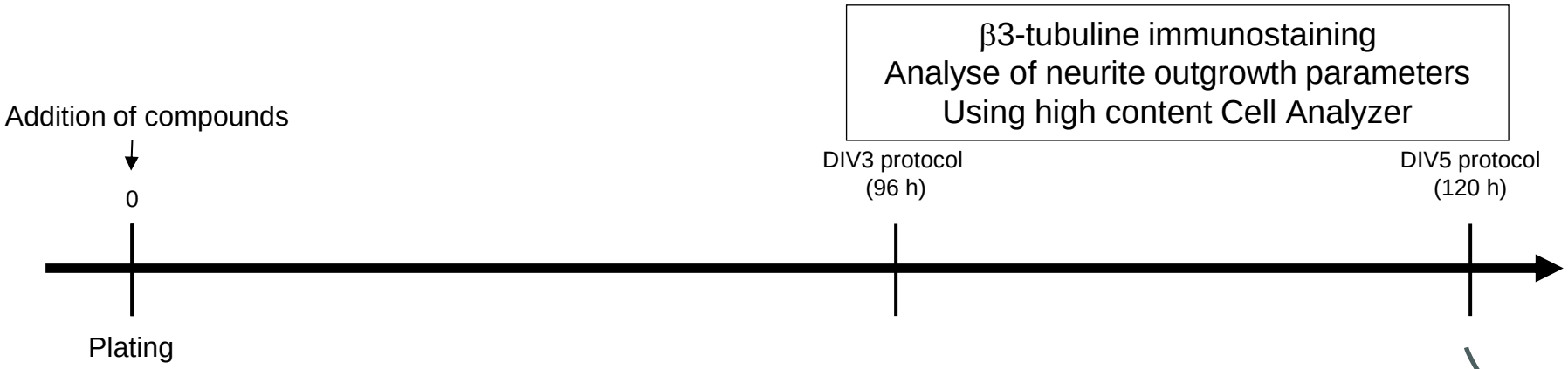
- **Increasing interest in using psychedelics to treat mental health conditions**
  - ✓ There is increasing interest in using psychedelics to treat mental health conditions like addiction and depression.
  - ✓ Clinical trials and animal studies suggest that psychedelics could offer a new avenue for the treatment of various mental health disorders

- **Their biological CNS effects remain poorly understood**
  - ✓ Despite the promising antidepressant, anxiolytic, and anti-addictive properties of some psychedelics, no neuronal morphological or structural correlation has been established.

- **Objectives**
  - ✓ Further examine the neuritogenic effect of several psychedelics (psilocin, low-dose ketamine (1 µM), LSD, DOI, MDMA, DMT, and 5-MeO-DMT) and conduct comparative analysis with the neurotrophin, BDNF, and the cognitive enhancer drug, donepezil.
  - ✓ In addition to the number and length of primary neurites, ramification and arborization profiles are also parameters of interest.

System setup and Experimental protocol

Fig. 1: Overview of the system setup and experimental protocol



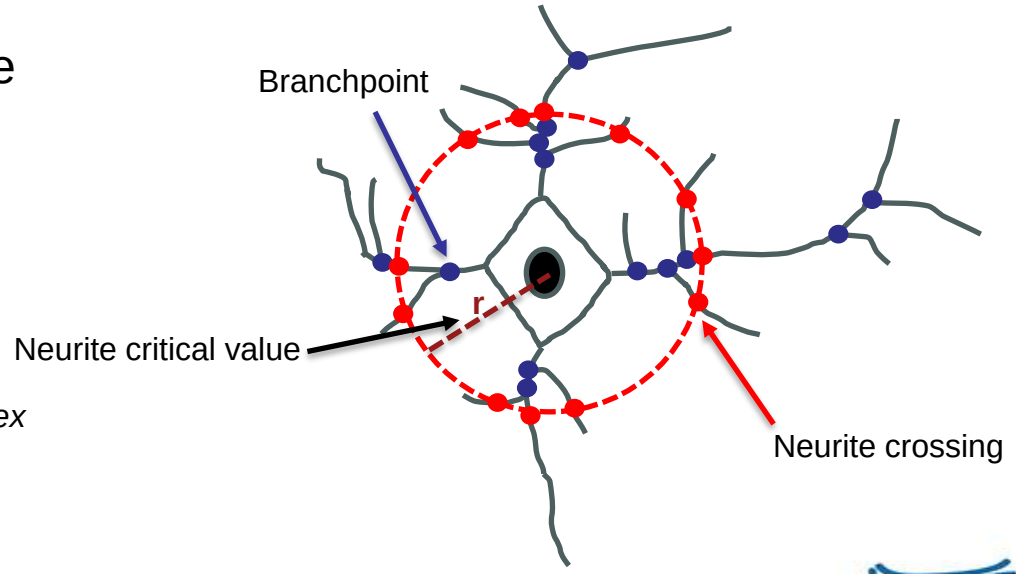
Primary culture of cortical neurons from rat embryos in 96 well plate

Parameters

Number of primary neurites
Length: total neurite length, length of the major neurite
} *Primary parameters*

Number of branchpoint (blue dots)

Neurite critical value "radius r" (distance from the soma at which there is a maximum number of neurite crossings (red dots))
} *Ramification and arborization index*



Psilocin, low-dose ketamine and LSD do not enhance neurite primary parameters either at DIV3 or at DIV5 (Number of primary neurites and neurite length)

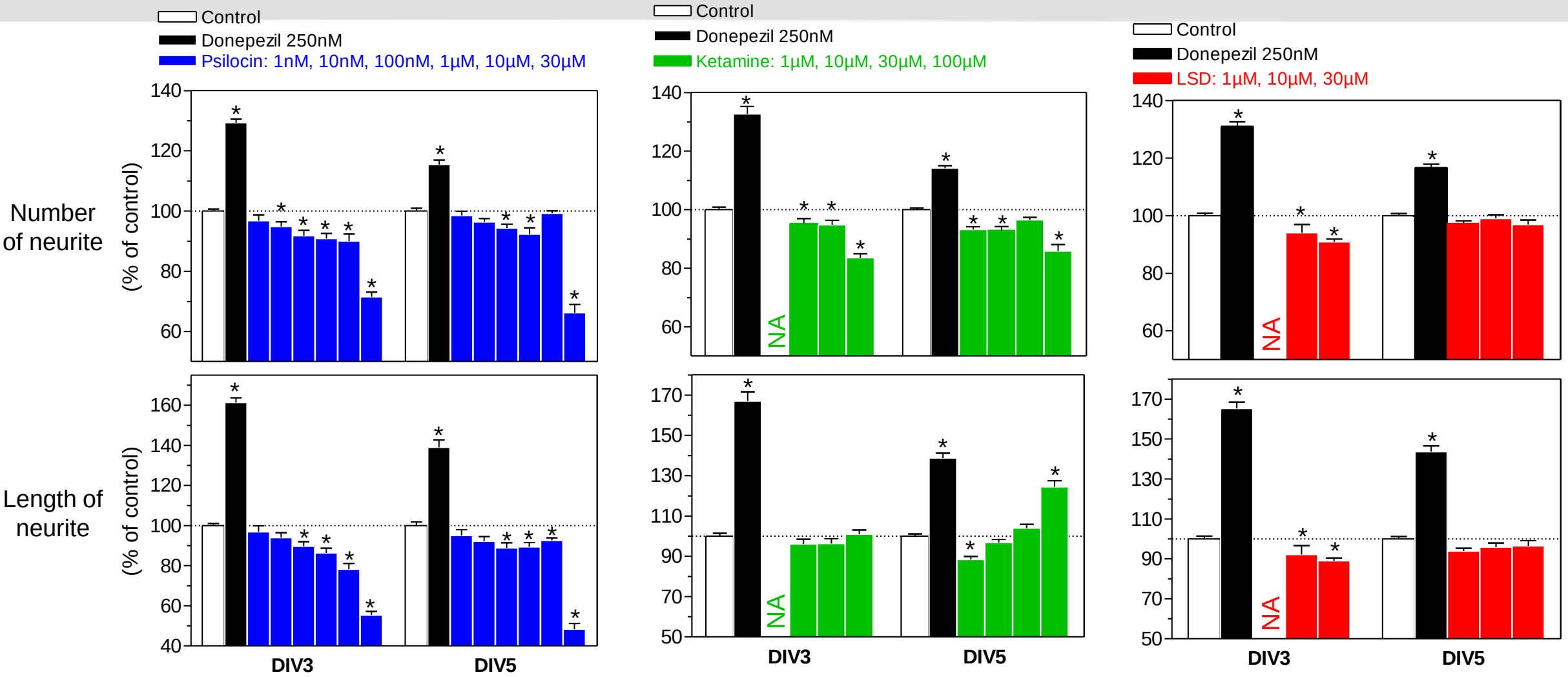


Fig. 2: Effect different concentrations of Psilocin, ketamine and LSD on neurite primary parameters (number and length) in cortical neuronal after 3 or 5 days of culture. NA denotes "not available"

Psilocin, low-dose ketamine and LSD increase neurite ramification and arborization at DIV5 but not DIV3 (Number of branchpoint and Neurite Critical value r)

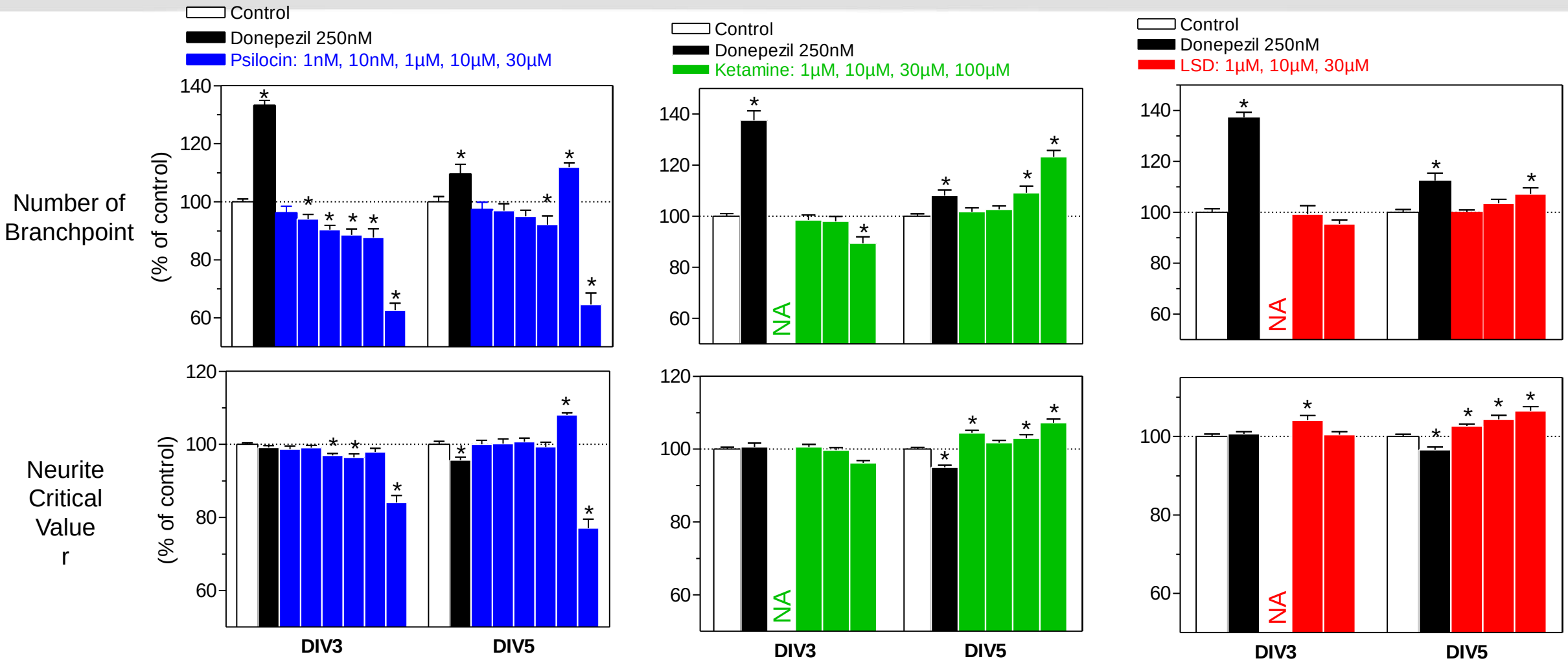


Fig. 3: Effect different concentrations of Psilocin, ketamine and LSD on neurite branchpoint and critical value r in cortical neuronal after 3 or 5 days of culture. NA denotes "not available"

DOI, MDMA, DMT and 5-MeO-DMT enhance neurite primary parameters either at DIV3 or at DIV5 (Number of primary neurites and neurite length)

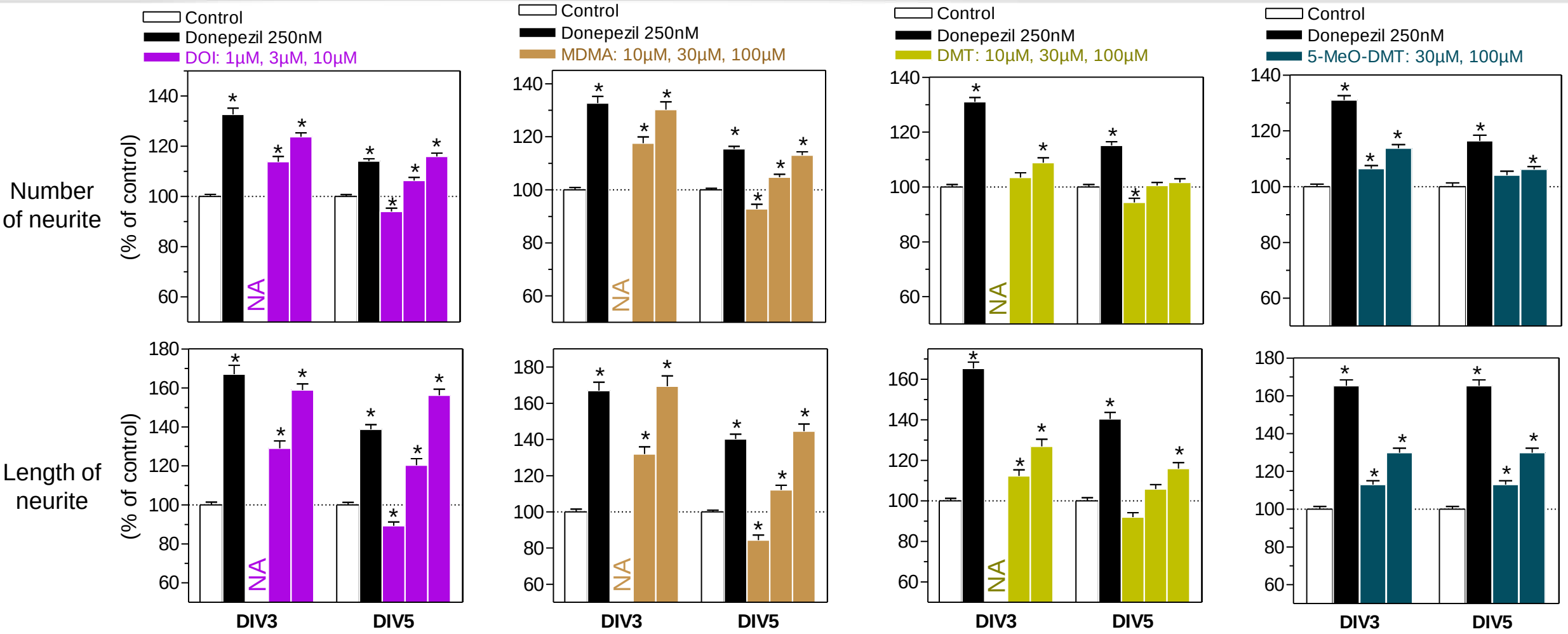


Fig. 4: Effect different concentrations of DOI, MDMA, DMT and 5-MeO-DMT on neurite primary parameters (number and length) in cortical neuronal after 3 or 5 days of culture. NA denotes "not available"

DOI, MDMA, DMT and 5-MeO-DMT increase neurite ramification but little to no effect on neurite arborization (Number of branchpoint and Neurite Critical value r)

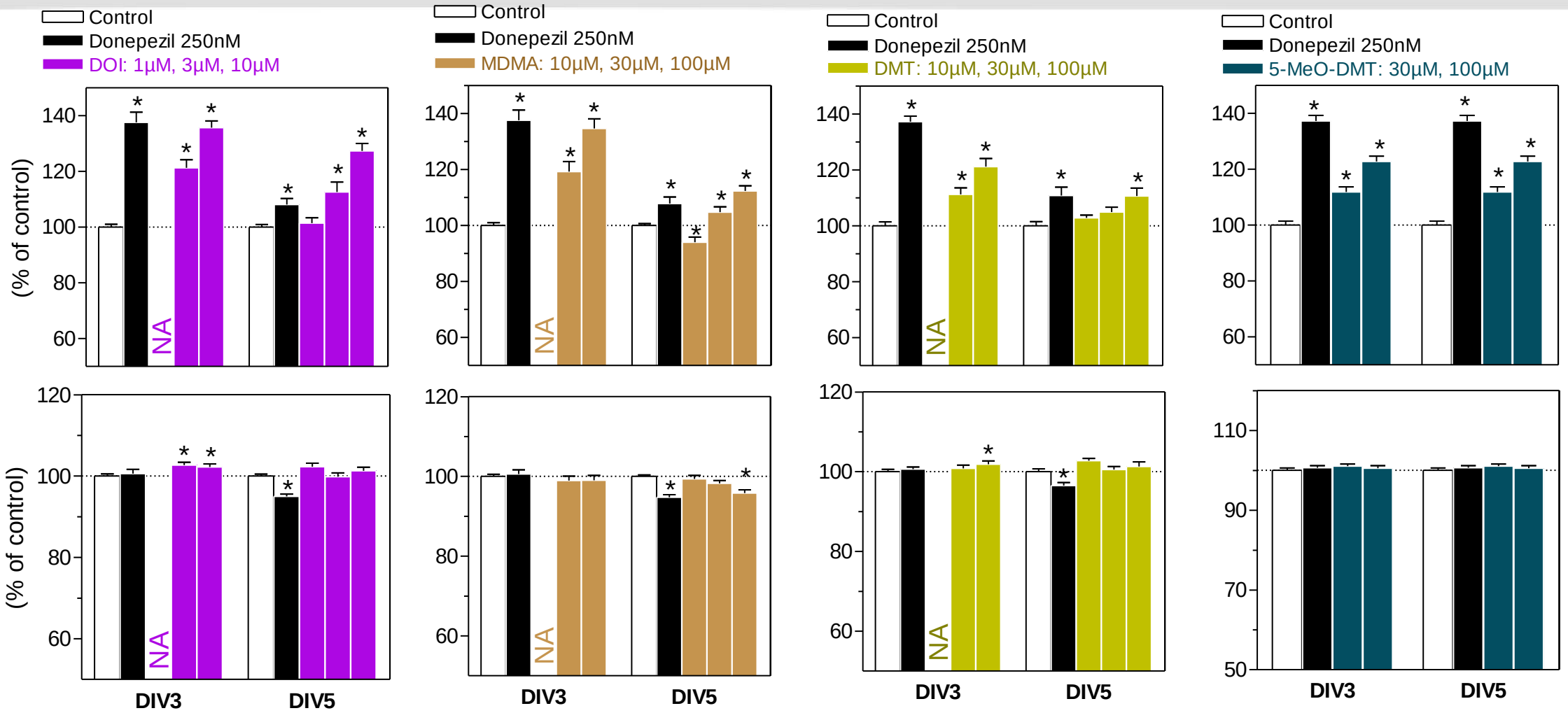


Fig. 5: Effect different concentrations of DOI, MDMA, DMT and 5-MeO-DMT on neurite branchpoint and neurite critical value r in cortical neuronal after 3 or 5 days of culture. NA denotes "not available"

The neurotrophin BDNF enhances all neurite parameters with a stronger effect at DIV5 compared to DIV3

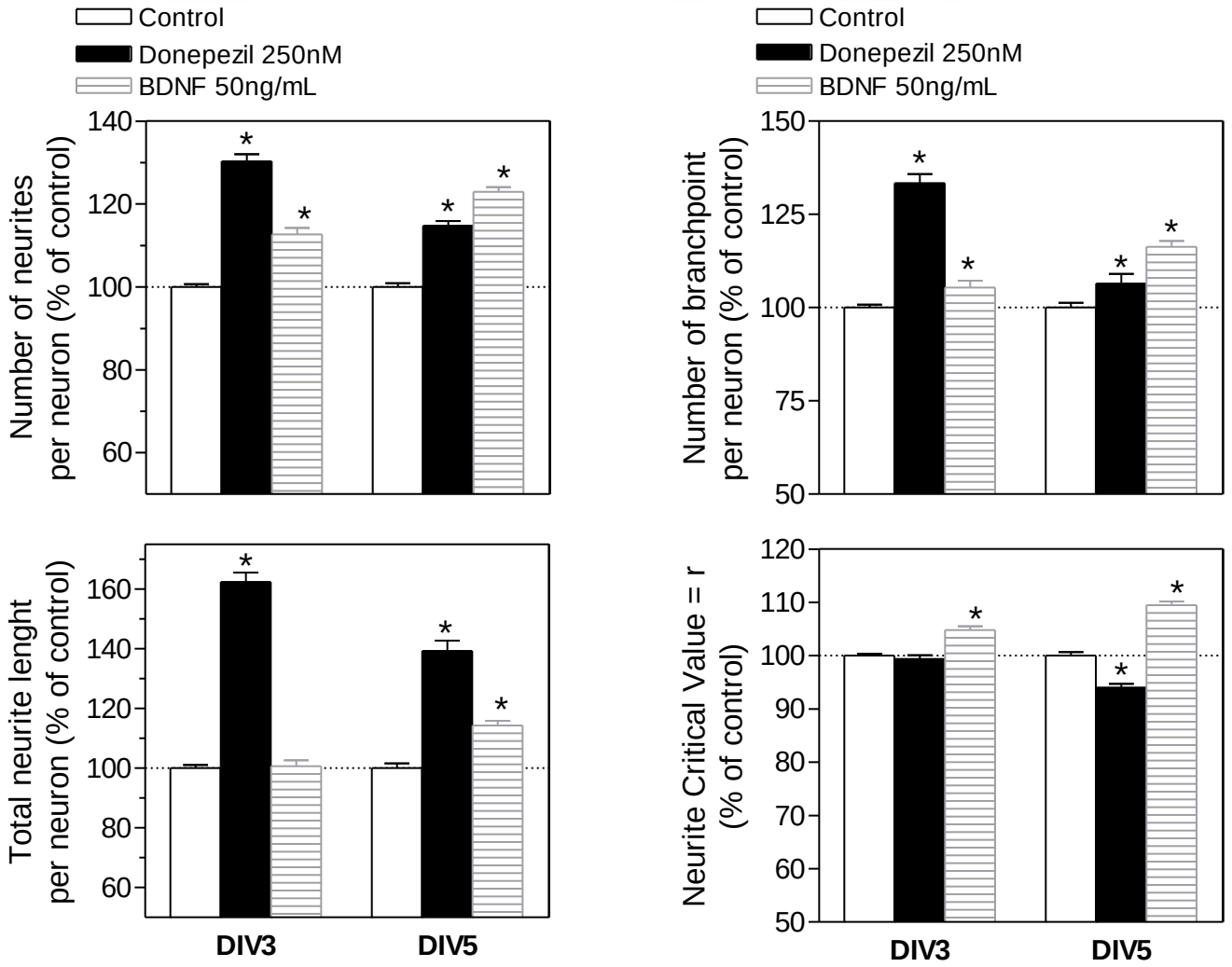


Fig. 6: Effect BDNF on different parameters of neurite outgrowth (number of primary neurites, length of neurites, number of branchpoint and neurite critical value r) in cortical neuronal after 3 or 5 days of culture.

Summary of findings

☞ 3 groups of compounds according to their impact on neurite outgrowth in primary cultures of cortical neurons

Psilocin, low-dose ketamine, LSD

Compounds that do not enhance primary neurite number and neurite length

But they increase branch points and neurite critical value "r"

The effect is observed at DIV5 but not at DIV3

DOI, MDMA, DMT, 5-MeO-DMT, Donepezil

Compounds that increase primary neurite number, neurite length, and branch points number

They are as effective at DIV3 as at DIV5

But they do not have enhance neurite critical value r

BDNF

Compound that stimulates all parameters of neurite outgrowth

The stimulatory effects become more pronounced at DIV5 compared to than at DIV3

Conclusion

Psilocin, low-dose ketamine and LSD uniquely diverge from psychedelics like DOI, MDMA, DMT, and 5-MeO-DMT by not increasing primary neurite count or length in rat cortical cultures. Instead, they modify neurite branching patterns and arborization profiles, suggesting a distinct neural circuit remodeling mechanism.